

CALCITRENE- calcipotriene ointment
Taro Pharmaceuticals U.S.A., Inc.

Calcitrene[®] (Calcipotriene) Ointment 0.005%

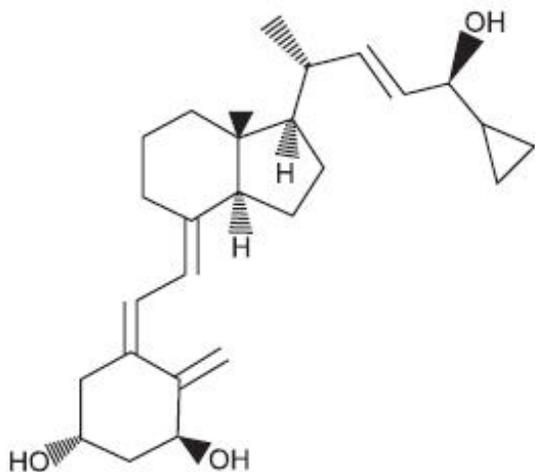
FOR TOPICAL DERMATOLOGIC USE ONLY.
Not for Ophthalmic, Oral or Intravaginal Use.

Rx Only

DESCRIPTION

Calcitrene[®] (calcipotriene) ointment, 0.005% contains the compound calcipotriene, a synthetic vitamin D₃ derivative for topical dermatological use.

Chemically, calcipotriene is (5Z,7E,22E,24S)-24-cyclopropyl-9,10-secocholela-5,7,10(19),22-tetraene-1 α ,3 β ,24-triol-, with the empirical formula C₂₇H₄₀O₃, a molecular weight of 412.6, and the following structural formula:



Calcipotriene is a white or off-white crystalline substance. Calcitrene[®] (calcipotriene) ointment, 0.005% contains calcipotriene 50 μ g/g in an ointment base of disodium phosphate dihydrate, edetate disodium, mineral oil, petrolatum, propylene glycol, α -tocopherol, steareth-2 and purified water.

CLINICAL PHARMACOLOGY

In humans, the natural supply of vitamin D depends mainly on exposure to the ultraviolet rays of the sun for conversion of 7-dehydrocholesterol to vitamin D₃ (cholecalciferol) in the skin. Calcipotriene is a synthetic analog of vitamin D₃.

Clinical studies with radiolabelled ointment indicate that approximately 6% (\pm 3%, SD) of the applied dose of calcipotriene is absorbed systemically when the ointment is applied topically to psoriasis plaques or 5% (\pm 2.6%, SD) when applied to normal skin, and much of the absorbed active is converted to inactive metabolites within 24 hours of application.

Vitamin D and its metabolites are transported in the blood, bound to specific plasma proteins. The active form of the vitamin, 1,25-dihydroxy vitamin D₃ (calcitriol), is known to be recycled via the liver and excreted in the bile. Calcipotriene metabolism following systemic uptake is rapid, and occurs via a

similar pathway to the natural hormone. The primary metabolites are much less potent than the parent compound.

There is evidence that maternal 1,25-dihydroxy vitamin D₃ (calcitriol) may enter the fetal circulation, but it is not known whether it is excreted in human milk. The systemic disposition of calcipotriene is expected to be similar to that of the naturally occurring vitamin.

CLINICAL STUDIES

Adequate and well-controlled trials of patients treated with Calcitrene[®] (calcipotriene) ointment, 0.005% have demonstrated improvement usually beginning after two weeks of therapy. This improvement continued in patients using calcipotriene once daily and twice daily. After 8 weeks of once daily calcipotriene, 56.7% of patients showed at least marked improvements (6.4% showed complete clearing). After 8 weeks of twice daily calcipotriene, 70.0% of patients showed at least marked improvement (11.3% showed complete clearing).

Subtracting percentages of patients using placebo (vehicle only) from percentages of patients using calcipotriene who had at least marked improvements after 8 weeks yields 39.9% for once daily and 49.6% for twice daily. This adjustment for placebo effect indicated that what might appear to be differences between once and twice daily use may reflect differences in the studies independent from the frequency of dosing. Although there was a numerical difference in comparison across studies, twice daily dosing has not been shown to be superior in efficacy to once daily dosing.

Over 400 patients have been treated in open label clinical studies of calcipotriene for periods of up to one year. In half of these studies, patients who previously had not responded well to calcipotriene were excluded. The adverse events in these extended studies included skin irritation in approximately 25% of patients and worsening of psoriasis in approximately 10% of patients. In one of these open label studies, half of the patients no longer required calcipotriene by 16 weeks of treatment, because of satisfactory therapeutic results.

INDICATIONS AND USAGE

Calcitrene[®] (calcipotriene) ointment, 0.005%, is indicated for the treatment of plaque psoriasis in adults. The safety and effectiveness of topical calcipotriene in dermatoses other than psoriasis have not been established.

CONTRAINDICATIONS

Calcitrene[®] (calcipotriene) ointment, 0.005%, is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation. It should not be used by patients with demonstrated hypercalcemia or evidence of vitamin D toxicity. Calcipotriene should not be used on the face.

PRECAUTIONS

General

Use of calcipotriene may cause irritation of lesions and surrounding uninvolved skin. If irritation develops, calcipotriene should be discontinued.

For external use only. Keep out of the reach of children. Always wash hands thoroughly after use.

Transient, rapidly reversible elevation of serum calcium has occurred with use of calcipotriene. If elevation in serum calcium outside the normal range should occur, discontinue treatment until normal calcium levels are restored.

Information for Patients

Patients using calcipotriene should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the face or eyes. As with any topical medication, patients should wash hands after application.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. Patients should report to their physician any signs of local adverse reactions.
4. Patients that apply calcipotriene to exposed portions of the body should avoid excessive exposure to either natural or artificial sunlight (including tanning booths, sun lamps, etc.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

When calcipotriene was applied topically to mice for up to 24 months at dosages of 3, 10 and 30 $\mu\text{g}/\text{kg}/\text{day}$ (corresponding to 9, 30 and 90 $\mu\text{g}/\text{m}^2/\text{day}$), no significant changes in tumor incidence were observed when compared to control. In a study in which albino hairless mice were exposed to both UVR and topically applied calcipotriene, a reduction in the time required for UVR to indicate 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. Patients that apply calcipotriene to exposed portions of the body 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 that use calcipotriene.

Calcipotriene did not elicit any mutagenic effects in an Ames mutagenicity assay, a mouse lymphoma TK locus assay, a human lymphocyte chromosome aberration assay, or in a micronucleus assay conducted in mice.

Studies in rats at doses up to 54 $\mu\text{g}/\text{kg}/\text{day}$ (324 $\mu\text{g}/\text{m}^2/\text{day}$) of calcipotriene indicated no impairment of fertility or general reproductive performance.

Pregnancy

Teratogenic Effects

Pregnancy Category C

Studies of teratogenicity were done by the oral route where bioavailability is expected to be approximately 40-60% of the administered dose. In rabbits, increased maternal and fetal toxicity were noted at a dosage of 12 $\mu\text{g}/\text{kg}/\text{day}$ (132 $\mu\text{g}/\text{m}^2/\text{day}$); a dosage of 36 $\mu\text{g}/\text{kg}/\text{day}$ (396 $\mu\text{g}/\text{m}^2/\text{day}$) 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 $\mu\text{g}/\text{kg}/\text{day}$ (318 $\mu\text{g}/\text{m}^2/\text{day}$) resulted in a significantly increased incidence of skeletal abnormalities (enlarged fontanelles and extra ribs). The enlarged fontanelles are most likely due to calcipotriene's effect upon calcium metabolism. The estimated maternal and fetal no-effect exposure levels in the rat (43.2 $\mu\text{g}/\text{m}^2/\text{day}$) and rabbit (17.6 $\mu\text{g}/\text{m}^2/\text{day}$) studies are approximately equal to the expected human systemic exposure level (18.5 $\mu\text{g}/\text{m}^2/\text{day}$) from dermal application. There are no adequate and well-controlled studies in pregnant women. Therefore, Calcitrene[®] (calcipotriene) ointment, 0.005% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether calcipotriene is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Calcitrene[®] (calcipotriene) ointment, 0.005% is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of calcipotriene in pediatric patients have not been established. Because of a

higher ratio of skin surface area to body mass, pediatric patients are at greater risk than adults of systemic adverse effects when they are treated with topical medication.

Geriatric Use

Of the total number of patients in clinical studies of Calcitrene[®] (calcipotriene) ointment, 0.005%, approximately 12% were 65 or older, while approximately 4% were 75 and over. The results of an analysis of severity of skin-related adverse events showed a statistically significant difference for subjects over 65 years (more severe) compared to those under 65 years (less severe).

ADVERSE REACTIONS

In controlled clinical trials, the most frequent adverse reactions reported for calcipotriene were burning, itching and skin irritation, which occurred in approximately 10-15% of patients. Erythema, dry skin, peeling, rash, dermatitis, worsening of psoriasis including development of facial/scalp psoriasis were reported in 1 to 10% of patients. Other experiences reported in less than 1% of patients included skin atrophy, hyperpigmentation, hypercalcemia, and folliculitis. Once daily dosing has not been shown to be superior in safety to twice daily dosing.

OVERDOSAGE

Topically applied calcipotriene can be absorbed in sufficient amounts to produce systemic effects. Elevated serum calcium has been observed with excessive use of Calcitrene[®] (calcipotriene) ointment, 0.005%.

DOSAGE AND ADMINISTRATION

Apply a thin layer of Calcitrene[®] (calcipotriene) ointment, 0.005% once or twice daily and rub in gently and completely.

HOW SUPPLIED

Calcitrene[®] (calcipotriene) ointment, 0.005% is available in:

60 gram aluminum tube **NDC (51672-5278-3)**

120 gram aluminum tube **NDC (51672-5278-4)**

STORAGE

Store at controlled room temperature 15°C-25°C (59°F-77°F). Do not freeze.

Manufactured by:

Glenmark Generics Ltd.

Colvale-Bardez, Goa 403 513, India

Distributed by:

TaroPharma a division of Taro Pharmaceuticals U.S.A., Inc.

Hawthorne, NY 10532

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November 2011

PPE150010710-1

PRINCIPAL DISPLAY PANEL - 120 g Tube Carton

NDC 51672-5278-4

120 g

Calcitrene[®]
Calcipotriene Ointment
0.005%

Rx only

TaroPharma[®]

*FOR TOPICAL DERMATOLOGIC USE ONLY.
NOT FOR OPHTHALMIC, ORAL OR INTRAVAGINAL USE.*

Keep this and all medications out of the reach of children.

TaroPharma[®]

The image shows a detailed product label for Calcitrene Calcipotriene Ointment 0.005%. The label is rectangular with a white background and a decorative border of diagonal lines. On the left side, there are three vertical bars: a pink one at the top, a blue one in the middle, and another pink one at the bottom. The text on the label includes the product name 'Calcitrene[®] Calcipotriene Ointment 0.005%' in large, bold, blue and pink fonts. Below this, it states 'FOR TOPICAL DERMATOLOGIC USE ONLY. NOT FOR OPHTHALMIC, ORAL OR INTRAVAGINAL USE.' and 'Keep this and all medications out of the reach of children.' in bold black text. The NDC number '51672-5278-4' and weight '120 g' are printed in the top right corner. The 'Rx only' designation is in red. The TaroPharma logo is repeated vertically on the right side. A barcode is located at the bottom right, with the number '3 51672 52784 6' below it. The bottom left section contains manufacturing and distribution information: 'Manufactured by: Glenmark Generics Ltd, Colvale-Bardez, Goa 403 513, India, GO/DRUGS/648' and 'Distributed by: TaroPharma a division of Taro Pharmaceuticals U.S.A., Inc, Hawthorne, NY 10532 11/11 PE166971111-1'. The bottom right section contains the text 'Each gram contains 0,05 mg of calcipotriene in an ointment base of disodium phosphate dihydrate, edetate disodium, mineral oil, petrolatum, propylene glycol, α-tocopherol, steareth-2 and purified water.' followed by 'Usual Dosage: Apply twice daily, or as directed by physician. See insert for complete information.' and a 'WARNING: Keep Out of Reach of Children.' section with storage instructions: 'Store at controlled room temperature 15°C - 25°C (59°F - 77°F). Do not freeze. Lot no. and expiration date on carton end and crimp of tube.'

CALCITRENE

calcipotriene ointment

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:51672-5278
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Calcipotriene (UNII: 143NQ3779B) (Calcipotriene - UNII:143NQ3779B)	Calcipotriene	0.05 mg in 1 g

Inactive Ingredients

Ingredient Name	Strength
sodium phosphate, dibasic, dihydrate (UNII: 9425516E2T)	
edetate disodium (UNII: 7FLD91C86K)	
mineral oil (UNII: T5L8T28FGP)	
petrolatum (UNII: 4T6H12BN9U)	
propylene glycol (UNII: 6DC9Q167V3)	
.alpha.-tocopherol (UNII: H4N855PNZ1)	
steareth-2 (UNII: V56DFE46J5)	
water (UNII: 059QF0K00R)	

Product Characteristics

Color	WHITE	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51672-5278-5	10 in 1 CARTON	03/24/2010	
1		5 g in 1 TUBE; Type 0: Not a Combination Product		
2	NDC:51672-5278-3	1 in 1 CARTON	03/24/2010	
2		60 g in 1 TUBE; Type 0: Not a Combination Product		
3	NDC:51672-5278-4	1 in 1 CARTON	03/24/2010	
3		120 g in 1 TUBE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090633	03/24/2010	

Labeler - Taro Pharmaceuticals U.S.A., Inc. (145186370)**Establishment**

Name	Address	ID/FEI	Business Operations
Glenmark Generics Ltd.		677318665	MANUFACTURE(51672-5278)