

DOVONEX - calcipotriene cream
Physicians Total Care, Inc.

Dovonex[®]
(calcipotriene cream)
Cream, 0.005%

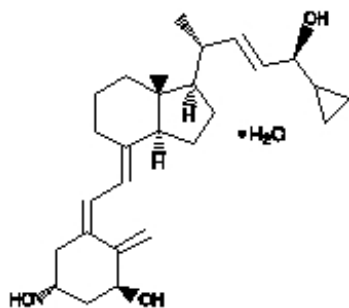
Rx only

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

DESCRIPTION

Dovonex[®] (calcipotriene cream) Cream, 0.005% contains calcipotriene monohydrate, a synthetic vitamin D₃ derivative, for topical dermatological use.

Chemically, calcipotriene monohydrate is (5Z,7E,22E,24S)-24-cyclopropyl-9,10-secochole-5,7,10(19),22-tetraene-1 α ,3 β ,24-triol monohydrate, with the empirical formula C₂₇H₄₀O₃•H₂O, a molecular weight of 430.6, and the following structural formula:



Calcipotriene monohydrate is a white or off-white crystalline substance. Dovonex[®] Cream contains calcipotriene monohydrate equivalent to 50 μ g/g anhydrous calcipotriene in a cream base of cetearyl alcohol, ceteth-20, diazolidinyl urea, dichlorobenzyl alcohol, dibasic sodium phosphate, edetate disodium, glycerin, mineral oil, petrolatum, and 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 calcipotriene 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. Systemic absorption of the cream has not been studied.

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.

CLINICAL STUDIES

Adequate and well-controlled trials of patients treated with Dovonex[®] Cream have demonstrated improvement usually beginning after 2 weeks of therapy. This improvement continued with approximately 50% of patients showing at least marked improvement in the signs and symptoms of psoriasis after 8 weeks of therapy, but only approximately 4% showed complete clearing.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Dovonex[®] Cream 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. Dovonex[®] Cream should not be used on the face.

PRECAUTIONS

General

Use of Dovonex[®] Cream may cause transient irritation of both lesions and surrounding uninvolved skin. If irritation develops, Dovonex[®] Cream should be discontinued.

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

Reversible elevation of serum calcium has occurred with use of topical 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 Dovonex[®] Cream should receive the following information and instructions:

1. This medication is to be used only 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 their 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 adverse reactions.
4. Patients that apply Dovonex[®] 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 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. Patients that apply Dovonex[®] 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 Dovonex[®].

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 µg/kg/day (324 µg/m²/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. Increased rabbit maternal and fetal toxicity was noted at 12 µg/kg/day (132 µg/m²/day). Rabbits administered 36 µg/kg/day (396 µg/m²/day) resulted in fetuses with a significant increase in the incidences of pubic bones, forelimb phalanges, and incomplete bone ossification. In a rat study, oral doses of 54 µg/kg/day (318 µg/m²/day) resulted in a significantly higher incidence of skeletal abnormalities consisting primarily of enlarged fontanelles and extra ribs. The enlarged fontanelles are most likely due to calcipotriene's effect upon calcium metabolism. The maternal and fetal calculated no-effect exposures in the rat (43.2 µg/m²/day) and rabbit (17.6 µg/m²/day) studies are approximately equal to the expected human systemic exposure level (18.5 µg/m²/day) from dermal application. There are no adequate and well-controlled studies in pregnant women. Therefore, Dovonex[®] Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

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. Because many drugs are excreted in human milk, caution should be exercised when Dovonex[®] Cream is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Dovonex[®] Cream 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 calcipotriene cream, approximately 15% were 65 or older, while approximately 3% were 75 and over. There were no significant differences in adverse events for subjects over 65 years compared to those under 65 years of age. However, the greater sensitivity of older individuals cannot be ruled out.

ADVERSE REACTIONS

In controlled clinical trials, the most frequent adverse experiences reported for Dovonex[®] (calcipotriene cream) Cream, 0.005% were cases of skin irritation, which occurred in approximately 10-15% of patients. Rash, pruritus, dermatitis and worsening of psoriasis were reported in 1 to 10% of patients.

OVERDOSAGE

Topically applied calcipotriene can be absorbed in sufficient amounts to produce systemic effects. Elevated serum calcium has been observed with excessive use of topical calcipotriene. If elevation in serum calcium should occur, discontinue treatment until normal calcium levels are restored. (See PRECAUTIONS.)

DOSAGE AND ADMINISTRATION

Apply a thin layer of Dovonex[®] Cream to the affected skin twice daily and rub in gently and completely. The safety and efficacy of Dovonex[®] Cream have been demonstrated in patients treated for eight weeks.

HOW SUPPLIED

Dovonex[®] (calcipotriene cream) Cream, 0.005% is available in:
60 gram aluminum tubes **NDC 54868-4725-0**

STORAGE

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



LEO[®]

Manufactured by LEO Laboratories Ltd.
Dublin, Ireland



Marketed by:
Warner Chilcott (US), LLC
Rockaway, NJ 07866 USA
1-800-521-8813

U.S. Patent No. RE39,706 E

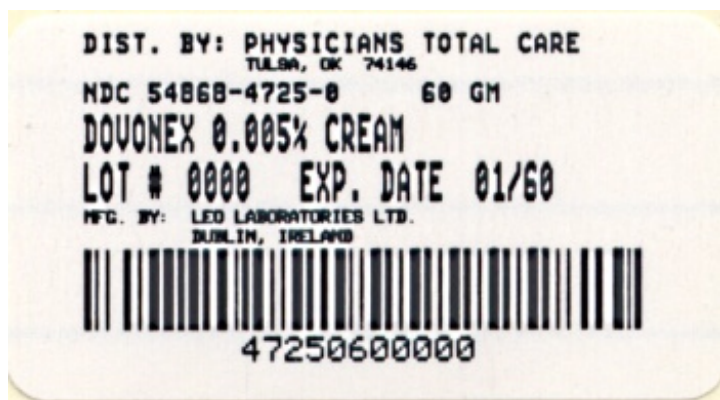
3020G062

3020G012

Revised February 2008

Relabeling of "Additional" barcode label by:
Physicians Total Care, Inc.
Tulsa, OK 74146

PRINCIPAL DISPLAY PANEL



Dovonex[®]
(calcipotriene cream),
0.005% Cream

Rx only

WARNING: Keep Out of Reach of Children

Each gram contains 0.05 mg of calcipotriene in a cream base of cetearyl alcohol, ceteth-20, diazolidinyl urea, dichlorobenzyl alcohol, dibasic sodium phosphate, edetate disodium, glycerin, mineral oil, petrolatum, and water.

For Topical Dermatologic Use Only.
Not for Ophthalmic, Oral, or
Intravaginal Use.

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

Read all Panels.

NET WT. 60 g

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.

DOVONEX

calcipotriene cream

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:54868-4725(NDC:0430-3020)
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
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CALCIPO TRIENE (UNII: 143NQ3779B) (CALCIPOTRIENE - UNII:143NQ3779B)		CALCIPOTRIENE	50 ug in 1 g	
Inactive Ingredients				
Ingredient Name				Strength
CETOSTEARYL ALCOHOL (UNII: 2DMT128M1S)				
CETETH-20 (UNII: I835H2IHHX)				
DICHLOROBENZYL ALCOHOL (UNII: 1NKX3648J9)				
SODIUM PHOSPHATE, DIBASIC (UNII: GR686LBA74)				
EDETATE DISODIUM (UNII: 7FLD91C86K)				
GLYCERIN (UNII: PDC6A3C0OX)				
MINERAL OIL (UNII: T5L8T28FGP)				
PETROLATUM (UNII: 4T6H12BN9U)				
WATER (UNII: 059QF0K00R)				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-4725-0	1 in 1 CARTON		
1		60 g in 1 TUBE		
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NDA	NDA020554	09/15/2006		

Labeler - Physicians Total Care, Inc. (194123980)

Establishment

Name	Address	ID/FEI	Business Operations
Physicians Total Care, Inc.		194123980	relabel

Revised: 11/2009

Physicians Total Care, Inc.