CALCIPOTRIENE- calcipotriene solution
Novel Laboratories, Inc.

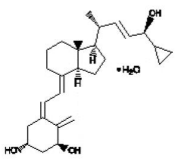
Calcipotriene Topical Solution, 0.005% (Scalp Solution)

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

DESCRIPTION

Calcipotriene Topical Solution, 0.005% (Scalp Solution) is a colorless topical solution containing 0.005% Calcipotriene in a vehicle of isopropanol (51% v/v), propylene glycol, hydroxypropyl cellulose, sodium citrate, menthol and water.

Chemically, calcipotriene monohydrate is (5*Z*,7*E*,22*E*,24*S*)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol monohydrate, with the empirical formula $C_{27}H_{40}O_3.H_2O$ a molecular weight of 430.6, and the following structural formula:



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 D_3 (cholecalciferol) in the skin. Calcipotriene is a synthetic analog of vitamin D_3.

Although the precise mechanism of calcipotriene's antipsoriatic action is not fully understood, *in vitro* evidence suggests that calcipotriene is roughly equipotent to the natural vitamin in its effects on proliferation and differentiation of a variety of cell types. Calcipotriene has also been shown, in animal studies, to be 100-200 times less potent in its effects on calcium utilization than the natural hormone.

Clinical studies with radiolabelled calcipotriene solution indicate that less than 1% of the applied dose of calcipotriene is absorbed through the scalp when the solution (2.0 mL) is applied topically to normal skin or psoriasis plaques (160 cm^2) for 12 hours, and that much of the absorbed calcipotriene 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 D_3 (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 D_3 (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 Calcipotriene Topical Solution, 0.005% (Scalp Solution), have demonstrated improvement usually beginning after 2 weeks of therapy. This improvement continued with approximately 31% of patients appearing either cleared (14%) or almost cleared (17%) after 8 weeks of therapy.

INDICATIONS AND USAGE

Calcipotriene Topical Solution, 0.005% (Scalp Solution) is indicated for the topical treatment of chronic, moderately severe psoriasis of the scalp. The safety and effectiveness of topical calcipotriene in dermatoses other than psoriasis have not been established.

CONTRAINDICATIONS

Calcipotriene Topical Solution, 0.005% (Scalp Solution) is contraindicated in those patients with acute psoriatic eruptions or 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.

WARNINGS

Avoid contact with the eyes or mucous membranes. Discontinue use if a sensitivity reaction occurs or if excessive irritation develops on uninvolved skin areas.

Drug product is flammable. Keep away from open flame.

PRECAUTIONS

General

Use of Calcipotriene Topical Solution, 0.005% (Scalp Solution) may cause transient irritation of both lesions and surrounding uninvolved skin. If irritation develops, Calcipotriene Topical Solution, 0.005% (Scalp Solution) 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 Calcipotriene Topical Solution, 0.005% (Scalp Solution) 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 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 µg/kg/day (corresponding to 9, 30 and 90 µg/m^2/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 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 Topical Solution, 0.005% (Scalp Solution).

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/m^2/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/m^2/day). Rabbits administered 36 µg/kg/day (396 µg/m^2 /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/m^2/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/m^2/day) and rabbit (17.6 µg/m^2/day) studies are greater than the expected human systemic exposure level (0.13 µg/m^2 /day) from dermal application. There are no adequate and well-controlled studies in pregnant women. Therefore, Calcipotriene Topical Solution, 0.005% (Scalp Solution) 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 D_3 (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 Calcipotriene Topical Solution, 0.005% (Scalp Solution), is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Calcipotriene Topical Solution, 0.005% (Scalp Solution) in pediatric patients have not been specifically 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 solution, approximately 16% were 65 or older, while approximately 4% were 75 and over. The results of an analysis of severity of skin-related adverse events showed no differences for subjects over 65 years compared to those under 65 years, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

In controlled clinical trials, the most frequent adverse reactions reported to be related to Calcipotriene Topical Solution, 0.005% (Scalp Solution), use were transient burning, stinging and tingling, which occurred in approximately 23% of patients. Rash was reported in about 11% of patients. Dry skin, irritation and worsening of psoriasis were reported in 1-5% of patients. Skin atrophy, hyperpigmentation, hypercalcemia, and folliculitis were not observed in these studies, but cannot be excluded.

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

Comb the hair to remove scaly debris and after suitably parting, apply Calcipotriene Topical Solution, 0.005% (Scalp Solution), twice daily, only to the lesions, and rub in gently and completely, taking care to prevent the solution spreading onto the forehead. The safety and efficacy of Calcipotriene Topical Solution, 0.005% (Scalp Solution), have been demonstrated in patients treated for eight weeks.

Keep Calcipotriene Topical Solution, 0.005% (Scalp Solution) well away from the eyes. Avoid application of the solution to uninvolved scalp margins. **Always wash hands thoroughly after use.**

HOW SUPPLIED

Calcipotriene Topical Solution, 0.005% (Scalp Solution) is available in 60 mL plastic bottles

NDC 40032-043-60

STORAGE

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

Manufactured by:

Novel Laboratories, Inc.

Somerset, NJ 08873

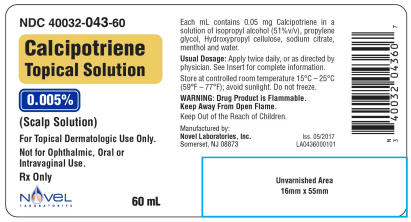
To report SUSPECTED ADVERSE REACTIONS, contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

PI0436000101

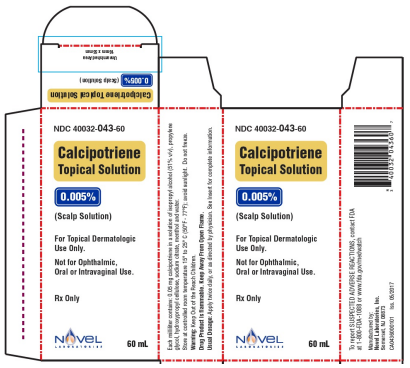
Rev. 05/2017

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

Container Label



Carton Label



CALCIPOTRIENE

calcipotriene solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:40032-043
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 mL

Inactive Ingredients	
Ingredient Name	**Strength**
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
ISOPROPYL ALCOHOL (UNII: ND2M416302)	
MENTHOL (UNII: L7T10EIP3A)	
HYDROXYPROPYL CELLULOSE, LOW SUBSTITUTED (UNII: 2165RE0K14)	
WATER (UNII: 059QF0KO0R)	
SODIUM CITRATE (UNII: 1Q73Q2JULR)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:40032-043-60	1 in 1 CARTON	12/26/2017	
1		60 mL in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	**Application Number or Monograph Citation**	**Marketing Start Date**	**Marketing End Date**
ANDA	ANDA207163	12/26/2017	

Labeler - Novel Laboratories, Inc. (793518643)

Registrant - Novel Laboratories, Inc. (793518643)

Establishment

Name	Address	ID/FEI	Business Operations
Novel Laboratories, Inc.		793518643	ANALYSIS(40032-043) , MANUFACTURE(40032-043) , PACK(40032-043)

Revised: 12/2018 Novel Laboratories, Inc.