

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-087

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VECTICAL Ointment safely and effectively. See full prescribing information for VECTICAL Ointment.

VECTICAL (calcitriol) OINTMENT 3 mcg/g

For topical use only

Initial U.S. Approval: 1978

INDICATIONS AND USAGE

VECTICAL Ointment is a vitamin D analog indicated for the topical treatment of mild to moderate plaque psoriasis in adults 18 years and older.(1)

DOSAGE AND ADMINISTRATION

Apply VECTICAL Ointment to affected areas of the body twice daily (2). The maximum weekly dose should not exceed 200 g.

VECTICAL Ointment is not for oral, ophthalmic, or intravaginal use.

DOSAGE FORMS AND STRENGTHS

Each gram of ointment contains 3 micrograms of calcitriol (3)

CONTRAINDICATIONS

- None (4)

WARNINGS AND PRECAUTIONS

- If aberrations in parameters of calcium metabolism are noted discontinue VECTICAL Ointment until these normalize. (5.1)
- Avoid excessive exposure of VECTICAL Ointment treated areas to either natural or artificial sunlight. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 3\%$) were lab test abnormality, urine abnormality, psoriasis, hypercalciuria, and pruritus (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Galderma Laboratories, L.P. at

866-735-4137 or FDA at 1-800-FDA-1088 or

www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 1/2009

Appears This Way
On Original

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Indication

VECTICAL Ointment is indicated for the topical treatment of mild to moderate plaque psoriasis in adults 18 years and older.

1.2 Limitations of Use

VECTICAL Ointment should not be applied to the eyes, lips, or facial skin.

2 DOSAGE AND ADMINISTRATION

Apply VECTICAL Ointment to affected areas twice daily, morning and evening. The maximum weekly dose should not exceed 200 grams.

VECTICAL Ointment is not for oral, ophthalmic or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

Each gram of ointment contains 3 micrograms (mcg/g) of calcitriol.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Effects on Calcium Metabolism

In controlled clinical trials with VECTICAL Ointment, among subjects having laboratory monitoring, hypercalcemia was observed in 24% (18/74) of subjects exposed to active drug and

in 16% (13/79) of subjects exposed to vehicle. However, the increases in calcium and albumin-adjusted calcium levels were less than 10% above the upper limit of normal.

If aberrations in parameters of calcium metabolism occur, treatment should be discontinued until these parameters have normalized. The effects of VECTICAL Ointment on calcium metabolism following treatment durations greater than 52 weeks have not been evaluated. Increased absorption may occur with occlusive use.

5.2 Ultraviolet Light Exposure

Animal data suggest that the vehicle of VECTICAL Ointment may enhance the ability of ultraviolet radiation (UVR) to induce skin tumors [*see Carcinogenesis, Mutagenesis, Impairment of Fertility (13.1)*]

Subjects who apply VECTICAL Ointment to exposed skin should avoid excessive exposure of the treated areas to either natural or artificial sunlight, including tanning booths and sun lamps. Physicians may wish to limit or avoid use of phototherapy in patients who use VECTICAL Ointment.

5.3 Unevaluated Uses

The safety and effectiveness of VECTICAL Ointment in patients with known or suspected disorders of calcium metabolism have not been evaluated.

The safety and effectiveness of VECTICAL Ointment in patients with erythrodermic, exfoliative, or pustular psoriasis have not been evaluated.

6 ADVERSE REACTIONS

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

6.1 Clinical Studies Experience

VECTICAL Ointment was studied in two vehicle-controlled studies (419 subjects), and in one open label study (324 subjects). The table below describes exposure to VECTICAL Ointment in 743 subjects, including 239 exposed for 6 months and 116 exposed for one year.

Four hundred and nineteen subjects were treated with VECTICAL Ointment twice daily for 8 weeks. The population included subjects ages 13 to 87, males (284) and females (135), Caucasians (372) and non-Caucasians (47); with mild (105) to moderate (313) chronic plaque

psoriasis.

Selected Adverse Events Occurring in at least 1% of Subjects in the Two Pooled
Vehicle-Controlled Studies

	Vectical Ointment (n=419)	Vehicle Ointment (n=420)
Discomfort skin	3%	2%
Pruritus	1%	1%

Among subjects having laboratory monitoring, hypercalcemia was observed in 24% (18/74) of subjects exposed to active drug and in 16% (13/79) of subjects exposed to vehicle, however the elevations were less than 10% above the upper limit of normal [*see WARNINGS AND PRECAUTIONS (5.1)*]

The open label study enrolled 324 subjects with psoriasis who were then treated for up to 52 weeks. Adverse events reported at a rate of greater than or equal to 3% of subjects treated with VECTICAL Ointment were lab test abnormality (8%), urine abnormality (4%), psoriasis (4%), hypercalciuria (3%), and pruritus (3%). Kidney stones were reported in 3 subjects and confirmed in two.

6.2 Postmarketing Experience

The following adverse reactions have been identified during world-wide post-approval use of VECTICAL Ointment: acute blistering dermatitis, erythema, pruritus, skin burning sensation, and skin discomfort. 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.

7 DRUG INTERACTIONS

VECTICAL Ointment should be used with caution in patients receiving medications known to increase the serum calcium level, such as thiazide diuretics. Caution should also be exercised in patients receiving calcium supplements or high doses of vitamin D [*see WARNINGS AND PRECAUTIONS (5.1)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

VECTICAL Ointment contains calcitriol which has been shown to be fetotoxic. There are no adequate and well-controlled studies for VECTICAL Ointment in pregnant women. VECTICAL Ointment should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

Teratogenicity studies with calcitriol were performed in which rats were treated orally at dosages up to 0.9 mcg/kg/day (5.4 mcg/m²/day) and in which rabbits received topical application of calcitriol ointment (3 ppm) to 6.4% of the body surface area. No effects on reproductive or fetal parameters were observed in rats. In rabbits, topically applied calcitriol induced a significantly elevated mean post-implantation loss and an increased incidence of minor skeletal abnormalities due to retarded ossification of the pubic bones. A slightly increased incidence of skeletal variation (extra 13th rib, reduced ossification of epiphyses) was also observed. These effects may have been secondary to maternal toxicity. Based on the recommended human dose and instructions for use, it is not possible to calculate human dose equivalents for animal exposures in these studies.

8.3 Nursing Mothers

It is not known whether calcitriol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VECTICAL Ointment is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

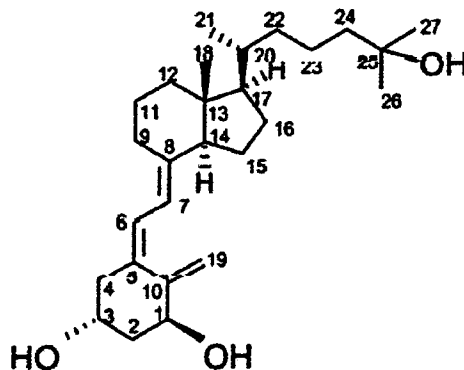
Clinical studies of VECTICAL Ointment did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported experience has not identified differences in responses between the elderly and younger patients.

10 OVERDOSAGE

Topically applied calcitriol can be absorbed in sufficient amounts to produce systemic effects [*see WARNINGS AND PRECAUTIONS (5.1)*]

11 DESCRIPTION

VECTICAL (calcitriol) Ointment 3 mcg/g is a vitamin D analog intended for topical application to the skin. The chemical name of the active ingredient is (5Z,7E)-9,10-secocholesta-5,7,10(19)-triene-1 α ,3 β ,25-triol. The structural formula is:



Calcitriol is a white or almost white crystalline solid. It is practically insoluble in water, soluble in alcohol and in fatty oils. The molecular formula is $C_{27}H_{44}O_3$, and the molecular weight is 416.64.

VECTICAL Ointment is a translucent ointment containing 3 mcg/g (0.0003% w/w) of calcitriol, packaged in aluminum tubes with screw caps. Other components of the ointment are mineral oil, dl- α -tocopherol, and white petrolatum.

12 CLINICAL PHARMACOLOGY

The contribution to efficacy of individual components of the vehicle has not been established.

12.1 Mechanism of Action

The mechanism of action of calcitriol in the treatment of psoriasis has not been established.

12.3 Pharmacokinetics

The systemic exposure of calcitriol was assessed in subjects with chronic, plaque psoriasis. In the pivotal pharmacokinetic/pharmacodynamic study, calcitriol ointment 3 mcg/g, was applied twice daily for 21 days (for a total dose of 30 g/day) to 35% of the body surface area (psoriatic + surrounding healthy skin) of subjects with at least 25% of body surface area involvement. At Day 21, the geometric mean plasma concentration values of C_{max} increased by approximately 36% over baseline and the geometric mean value of $AUC_{(0-12\text{ hr})}$ increased by 44%. There was no correlation between the elevated calcitriol levels and the pharmacodynamic

parameters of serum albumin adjusted calcium, serum phosphorus, urinary calcium and urinary phosphorus.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

When calcitriol was applied topically to mice for up to 24 months, no significant changes in tumor incidence were observed. Concentrations of calcitriol in ointment base of 0 (vehicle control), 0.3, 0.6 and 1.0 ppm were evaluated.

A two-year carcinogenicity study was conducted in which calcitriol was orally administered to rats at dosages of approximately 0.005, 0.03, and 0.1 mcg/kg/day (0.03, 0.18, and 0.6 mcg/m²/day, respectively). The incidence of benign pheochromocytomas was significantly increased in female rats. No other significant differences in tumor incidence data were observed.

In a study in which albino hairless mice were exposed to both ultra-violet radiation (UVR) and topically applied calcitriol ointment, a reduction in the time required for UVR to induce the formation of skin tumors was observed in all groups that received the ointment base, including the vehicle-treated control group, relative to animals that received no ointment but which were exposed to UVR. The time required for UVR to induce the formation of skin tumors did not differ between animals that received plain vehicle and those that received vehicle that contained calcitriol. Concentrations of calcitriol in ointment base of 0 (vehicle control), 0.3, 0.6 and 1.0 ppm were evaluated. These data suggest that the vehicle of VECTICAL Ointment may enhance the ability of UVR to induce skin tumors.

Calcitriol did not elicit genotoxic effects in the mouse lymphoma TK locus assay. Studies in which male and female rats received oral doses of calcitriol of up to 0.6 mcg/kg/day (3.6 mcg/m²/day) indicated no impairment of fertility or general reproductive performance. Based upon the recommended human dose and instructions for use, it is not possible to calculate human dose equivalents for animal exposure in these studies.

14 CLINICAL STUDIES

In two, multicenter, double-blind, vehicle-controlled studies, a total of 839 subjects with psoriasis rated "mild" or "moderate" using an investigator global assessment scale were treated twice daily for 8 weeks. Subjects were randomized in a 1:1 ratio to receive either VECTICAL

Ointment or vehicle ointment. The mean age of the subjects was 48 years and 66% were male; most subjects were rated "moderate" at baseline.

Success was defined as "Clear or Minimal" (up to light red or pink in coloration, surface dryness with some white coloration, and slight elevation above normal skin) with at least a 2-grade change from baseline. The success rates are displayed in the table.

Percentage of Subjects with Clear or Minimal Disease AND Two Grade Improvement at End of Treatment (8 weeks)

Study 1		Study 2	
VECTICAL Ointment (N=209)	Vehicle Ointment (N=209)	VECTICAL Ointment (N=210)	Vehicle Ointment (N=211)
23.4%	14.4%	20.5%	6.6%

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

VECTICAL Ointment 3 mcg/g is available in collapsible aluminum tubes of the following package sizes:

- 5 g tube (NDC 0299-2012-05)
- 100 g tube (NDC 0299-2012-10)

16.2 Storage

Store at 25° C (77° F); excursions permitted to 15° - 30° C (59° - 86° F) [See USP Controlled Room Temperature.] Do not freeze or refrigerate.

17 PATIENT COUNSELING INFORMATION

This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients using VECTICAL Ointment should receive the following information:

17.1 Instructions for Use

This medication is to be used as directed by the physician. It is for external use only. This medication is to be applied only to areas of the skin affected by psoriasis, as directed. It should be gently rubbed into the skin so that no medication remains visible.

17.2 Adverse Reactions

Patients should report any signs of adverse reactions to their physician.

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