CALCITRIOL- calcitriol ointment
Perrigo New York Inc
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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Calcitriol Ointment safely and effectively. See full prescribing information for Calcitriol Ointment, 3 mcg/g.

For topical use only
Initial U.S. Approval: 1978

INDICATIONS AND USAGE
Calcitriol 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 Calcitriol Ointment to affected areas of the body twice daily (2). The maximum weekly dose should not exceed 200 g.
Calcitriol 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

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

ADVERSE REACTIONS
Most common adverse reactions (incidence >3%) were lab test abnormality, urine abnormality, psoriasis, hypercalciuria, and pruritus (6.1). To report SUSPECTED ADVERSE REACTIONS, contact Perrigo at 1-866-634-9120 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION.

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Revised: 1/2019
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

1.2 Limitations of Use
Calcitriol Ointment should not be applied to the eyes, lips, or facial skin.

2 DOSAGE AND ADMINISTRATION
Apply Calcitriol Ointment to affected areas twice daily, morning and evening. The maximum weekly dose should not exceed 200 grams. Calcitriol 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 Calcitriol 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 Calcitriol Ointment on calcium metabolism following treatment durations greater than 52 weeks have not been evaluated. Increase absorption may occur with occlusive use.

5.2 Ultraviolet Light Exposure

Animal data suggest that the vehicle of calcitriol Ointment may enhance the ability of ultraviolet radiation (UVR) to induce skin tumors [see Carcinogenesis, Mutagenesis, Impairment of Fertility (13.1)] Subjects who apply Calcitriol Ointment to exposed skin should avoid excessive exposure to 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 Calcitriol Ointment.

5.3 Unevaluated Uses

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

6.1 Clinical Studies Experience

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

Four hundred and nineteen subjects were treated with Calcitriol 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

<table>
<thead>
<tr>
<th></th>
<th>Calcitriol Ointment (n=419)</th>
<th>Vehicle Ointment (n=420)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discomfort Skin</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

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 elevation 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 Calcitriol Ointment were lab test abnormality (8%), urine abnormality (4%), psoriasis (4%), hyperciuria (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 the world-wide post-approval use of Calcitriol Ointment: acute blistering dermatitis, erythema, pruritus, skin burning sensation, and skin discomfort. Because these reactions were 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
Calcitriol 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
Pregnancy
Teratogenic Effects: Pregnancy Category C.
Calcitriol Ointment contains calcitriol which has been shown to be fetotoxic. There are no adequate and well-controlled studies for Calcitriol Ointment in pregnant women. Calcitriol 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 Calcitriol 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 Calcitriol 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
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-1α, 3β,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.

Calcitriol 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 increased by 44%. There was no correlation between the elevated calcitriol levels and the pharmacodynamic parameters or 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/m^{2}/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 ultraviolet 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 Calcitriol 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 performances.

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 tested twice daily for 8 weeks. Subjects were randomized in a 1:1 ratio to receive either Calcitriol Ointment or vehicle ointment. The mean age of 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 coloration, surface dryness with some white coloration, and slight elevation above normal skin) with at least 2-grade change from baseline. The success rates are displayed in the table.

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitriol Ointment</td>
<td>23.4%</td>
<td>20.5%</td>
</tr>
<tr>
<td>Vehicle Ointment</td>
<td>14.4%</td>
<td>6.6%</td>
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</tbody>
</table>

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
Calcitriol Ointment 3 mcg/g is available in collapsible aluminum tubes of the following package sizes:
- 100 g tube (NDC 45802-608-01)

16.2 Storage
Store at controlled room temperature 68° - 77°F (20° - 25°C) with excursions permitted between 59° - 86°F (15° - 30°C). [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 Calcitriol 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.

**To report SUSPECTED ADVERSE REACTIONS,** contact Perrigo at 1-866-634-9120 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Marketed by:
Perrigo
Allegan, MI 49010

Manufactured by:
G Production Inc.
Baie d’Urfé, QC, H9X 3S4 Canada

Made in Canada.
P51947-2
6Z300 RC J3

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL
Rx Only
NDC 45802-608-01
Calcitriol Ointment, 3 mcg/g
For Topical Use Only
NET WT 100g
Perrigo
For topical use only. Not for ophthalmic, oral or intravaginal use.

Usual Dosage: Apply to affected areas twice daily. See package insert for complete prescribing information.

Each gram contains: calcitriol 3 mcg in an ointment base consisting of mineral oil, dl-α-tocopherol, and white petrolatum.

Storage: Store at controlled room temperature 68°-77°F (20°-25°C) with excursions permitted between 59°-86°F (15°-30°C). Do not freeze or refrigerate.

Made in Canada
Marketed by: Perrigo
Allegan, MI 49010 • www.perrigo.com Rev. 01/17
P51946-2
:6Z3C1 RC C3

CALCITRIOL
calcitriol ointment

Product Information

Product Type | HUMAN PRESCRIPTION DRUG | Item Code (Source) | NDC:45802-608
--- | --- | --- | ---
Route of Administration | TOPICAL | --- | ---

Active Ingredient/Active Moiety

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<th>Ingredient Name</th>
<th>Basis of Strength</th>
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Inactive Ingredients

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<tr>
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<td>MINERAL OIL (UNII: T5L8T28FGP)</td>
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<tr>
<td>PETROLATUM (UNII: 4T6H12BN9U)</td>
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Packaging

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<td>NDC:45802-608-01</td>
<td>1 in 1 CARTON</td>
<td>03/08/2012</td>
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<td>1</td>
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<td>100 g in 1 TUBE; Type 0: Not a Combination Product</td>
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## Marketing Information

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**Labeler** - Perrigo New York Inc (078846912)

## Establishment

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<td>manufacture(45802-608)</td>
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Revised: 1/2019