CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-273/S008

Trade Name: Dovonex 0.005%

Generic Name: (calcipotriene ointment)

Sponsor: Bristol Myers Squibb Company

Approval Date: April 28, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-273/S008

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-273/S008

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-273/S-008

Bistol-Myers Squibb Company
Attention: David L. Silberstein
Associate Director, New Opportunities & Product Development
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Silberstein:

Please refer to your supplemental new drug application dated October 22, 2004, received October 28, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dovonex (calcipotriene ointment), 0.005%.

This supplemental new drug application provides language incorporating the results of the photocarcinogenicity study conducted as a Phase 4 commitment for Dovonex Ointment.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling (package insert).

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 20-273/S-008.**" Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Margo Owens, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Stanka Kukich
4/28/05 03:58:33 PM
sign off for Dr. Jonathan Wilkin, Division Director

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-273/S008

LABELING

Dovonex®
(calcipotriene ointment), 0.005%

Rx only

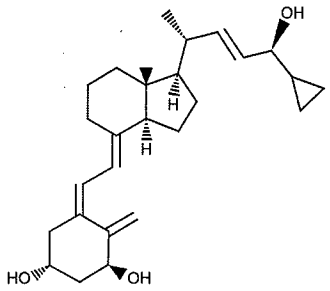
[Print Code TBD]

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

DESCRIPTION

Dovonex® (calcipotriene ointment), 0.005% contains the compound calcipotriene, a synthetic vitamin D_3 derivative for topical dermatological use.

Chemically, calcipotriene is (5Z,7E,22E,24S)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol-, with the empirical formula $C_{27}H_{40}O_3$, a molecular weight of 412.6, and the following structural formula:



Calcipotriene is a white or off-white crystalline substance. Dovonex ointment contains calcipotriene 50 µg/g in an ointment base of dibasic sodium phosphate, edetate disodium, mineral oil, petrolatum, propylene glycol, tocopherol, steareth-2 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 D_3 (cholecalciferol) in the skin. Calcipotriene is a synthetic analog of vitamin D_3.

Clinical studies with radiolabelled ointment indicate that approximately 6% (± 3%, SD) of the applied dose of calcipotriene is absorbed systemically when the ointment is applied topically to psoriasis

plaques or 5% (± 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 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 Dovonex ointment have demonstrated improvement usually beginning after two weeks of therapy. This improvement continued in patients using Dovonex once daily and twice daily. After 8 weeks of once daily Dovonex, 56.7% of patients showed at least marked improvements (6.4% showed complete clearing). After 8 weeks of twice daily Dovonex, 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 Dovonex 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 indicates 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 Dovonex for periods of up to one year. In half of these studies, patients who previously had not responded well to Dovonex 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 Dovonex by 16 weeks of treatment, because of satisfactory therapeutic results.

INDICATIONS AND USAGE

Dovonex (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

Dovonex 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 should not be used on the face.

PRECAUTIONS

General

Use of Dovonex may cause irritation of lesions and surrounding uninvolved skin. If irritation develops, Dovonex 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 Dovonex. 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 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 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

The potential of calcipotriene to induce carcinogenesis in standard long-term animal studies (in the absence of ultra-violet radiation (UVR)) has not been evaluated. 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 (318 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. In rabbits, increased maternal and fetal toxicity were noted at a dosage of 12 μg/kg/day (132 μg/m^2/day); a dosage of 36 μg/kg/day (396 μg/m^2/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 μg/kg/day (318 μg/m^2/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 μg/m^2/day) and rabbit (17.6 μg/m^2/day) studies are approximately equal to the expected human systemic exposure level (18.5 μg/m^2/day) from dermal application. There are no adequate and well-controlled studies in pregnant women. Therefore, Dovonex ointment 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 Dovonex (calcipotriene ointment), 0.005% is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Dovonex 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 ointment, 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 Dovonex 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 Dovonex can be absorbed in sufficient amounts to produce systemic effects. Elevated serum calcium has been observed with excessive use of Dovonex ointment.

DOSAGE AND ADMINISTRATION

Apply a thin layer of Dovonex ointment once or twice daily and rub in gently and completely.

HOW SUPPLIED

Dovonex® (calcipotriene ointment), 0.005% is available in:

60 gram aluminum tubes (NDC 0072-2540-06).
120 gram aluminum tubes (NDC 0072-2540-12).

STORAGE

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

Manufactured by Leo Laboratories Ltd., Dublin, Ireland

Bristol-Myers Squibb Company

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

U.S. Patent No. 4,866,048

[Print Code TBD] Revised TBD

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-273/S008

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 20-273
Review number: NA
Sequence number/date/type of submission: SLR-008/22-OCT-2004

Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Bristol-Myers Squibb
Manufacturer for drug substance: NA

Reviewer name: Norman A. See, PhD
Division name: DDDDP
HFD #: 540
Review completion date: 29-DEC-2004

Drug:

Trade name: Dovonex Ointment
Generic name (list alphabetically): Calcipotriene
Code name: BMS-181161
Chemical name: NA
CAS registry number: 112965-21-6
Mole file number: NA
Molecular formula/molecular weight: $C_{27}H_{40}O_3$/412.60
Structure: NA

Relevant INDs/NDAs/DMFs: IND 35,560; IND 44,261; IND 45,007; NDA 20-273; NDA 20-554; NDA 20-611 (same drug substance and sponsor, available in ointment, cream, and solution formulations).

Drug class: Vitamin D agonist

Indication: Treatment of psoriasis

Clinical formulations: Dovonex is available as a solution (NDA 20-611), cream (NDA 20-554), or ointment (NDA 20-273). The formulations of the Dovonex drug products are:

Ingredient	Soln. (mg/ml)	Cream (mg/g)	Ointment (mg/g)
Calcipotriene	0.05	0.05	0.05
Propylene Glycol			
Hydroxypropyl Cellulose			
Sodium Citrate			
Menthol			
Mineral Oil			
Disodium Phosphate			

Edetate Disodium	0	0.5	0.065
Petrolatum	0	150.0	0
tocopherol	0	0	0.02
stearyl ether	0	0	50.0
Water	qs	qs	26.0

Route of administration: Topical to skin

Proposed clinical protocol: NA

Previous clinical experience: The products are currently marketed under NDA 20-273 (Dovonex ointment, AP 29-DEC-1993), NDA 20-554 (Dovonex cream, AP 22-JUL-1996), and NDA 20-611 (Dovonex solution, AP 03-MAR-1997).

Disclaimer: Tabular and graphical information was generated by the reviewer unless stated otherwise.

Introduction and drug history: The products are currently marketed under NDA 20-273 (Dovonex ointment, AP 29-DEC-1993), NDA 20-554 (Dovonex cream, AP 22-JUL-1996), and NDA 20-611 (Dovonex solution, AP 03-MAR-1997). This submission contained the final report of a photocarcinogenesis study that was conducted with Dovonex solution as a post-approval commitment. The submission also contained proposed revised labeling, intended to reflect data from the photocarcinogenesis study.

Studies reviewed within this submission:

1. Twelve-month photocarcinogenesis study with ultraviolet radiation in hairless mice, study No. DN01098.

Studies not reviewed within this submission: None.

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Please see prior reviews associated with the applications listed above.

II. SAFETY PHARMACOLOGY:

Please see prior reviews associated with the applications listed above.

III. PHARMACOKINETICS/TOXICOKINETICS:

Please see prior reviews associated with the applications listed above.

IV. GENERAL TOXICOLOGY:

Please see prior reviews associated with the applications listed above.

V. GENETIC TOXICOLOGY:

Please see prior reviews associated with the applications listed above.

VI. CARCINOGENICITY:

1. Study title: Twelve-month photocarcinogenesis study with ultraviolet radiation in hairless mice

Key study findings: The median number of weeks on study at which the first tumor (for a given animal) greater than or equal to 1.0 mm in diameter was observed was significantly reduced for males that received the greatest exposure to calcipotriene (30 µg/kg/day). No other statistically significant effects on UV-induced skin tumor formation were observed. The vehicle of Dovonex solution did not influence UV-induced skin tumor formation.

Study No.: DN01098
Document #, Volume #, and Page #: Electronic submission
Conducting laboratory and location: /
Date of study initiation: 15-NOV-2001
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: Calcipotriol solution vehicle (control), batch 012541601; calcipotriol solution 0.75 µg/mL, batch No. 012541901; calcipotriol solution 2.5 µg/mL, batch No. 012541801; calcipotriol solution 7.5 µg/mL, batch No. 012541701. / / / potency.
Formulation/vehicle: See page one of this review.

Methods (unique aspects):

Dosing:

Species/strain: Mouse/ (albino hairless)
#/sex/group or time point (main study): 36/sex/group; housed 1 per cage
Satellite groups used for toxicokinetics or recovery: No
Age: Approximately 60 days at initiation
Weight: At start of dosing: males, 22-36 g, females, 20-30 g
Doses in administered units:

Group	Calcipotriol Exposure (µg/kg/day)*	Calcipotriol Solution Concentration (µg/mL)	Volume of Test Material Applied Per Day (µL/mouse)
1	0	0	100
2	3	0.75	100
3	10	2.5	100
4	30	7.5	100
5	0	NA**	0
6	0	NA**	0

*Approximate, based upon assumed BW of 25 g.
**No test material applied to these animals.

The test materials were applied, and the mice irradiated, five days per week (M-F) for 40 weeks. The test materials were applied approximately 70 minutes prior to UVR exposure on Mondays, Wednesdays, and Fridays, and approximately 70 minutes following UVR exposure on Tuesdays and Thursdays. The UVR exposure was 120 RBU per day (600 RBU per week) for all groups except group 6, which received 240 RBU per day (1200 RBU per week). UV light was generated by a / / xenon long arc lamp with a 1 mm / filter and with definitive output in both the UVA (320 nm to 400 nm) and UVB (280 nm to 320 nm) ranges.

All surviving animals were maintained for 12 weeks without treatment following 40 weeks of treatment, with sacrifice during week 52. Mice were sacrificed prematurely if a skin tumor ≥ 10 mm diameter was present. All mice in a given dosage/gender group were killed: a) when survival in that group reached 50%; and b) if more than 50% of the surviving mice had tumors ≥ 4 mm diameter.

Route, form, volume, and infusion rate: Topical, 100 µL/day (see above), once per day M-F for 40 consecutive weeks. The assigned material was applied to the back and sides (approximately 25 cm^2) of the mice.

Observations and times:

Clinical signs: Animals observed twice daily for viability and weekly for general appearance. Clinical signs and local skin reactions (including skin tumors) weekly.
Body weights: Weekly
Food consumption: No
Ophthalmology: No

EKG: No
Hematology: NA
Clinical chemistry: No
Urinalysis: No
Gross pathology: All animals
Organs weighed: None
Histopathology: No
Toxicokinetics: No

Results:

- Survival: No drug-related effects on survival were observed. Increased exposure to UVR resulted in an increased rate of mortality.

Numbers of Animals Surviving to Scheduled Sacrifice

Group	Calcipotriol Exposure (µg/kg/day)*	UVR Exposure (RBU/Week)	Number of Males Killed at Scheduled Sacrifice, Week 53	Number of Females Killed at Scheduled Sacrifice, Week 53
1	0 (Vehicle)	600	20/36	21/36
2	3	600	16/36	18/36
3	10	600	19/36	21/36
4	30	600	19/36	23/36
5	0 (No treatment)	600	19/36	15/36
6	0 (No treatment)	1200	0/36	0/36

*Approximate, based upon assumed BW of 25 g.

- Clinical signs: All test materials were well tolerated, although some edema was observed, particularly in group 4 animals.
- Body weights: Mean body weights and weight gains tended to be slightly reduced with increased exposure to calcipotriene, particularly in males:

Body weight gains (mean±SD):

Group	Calcipotriol Exposure (µg/kg/day)*	UVR Exposure (RBU/Week)	Mean BW Change for Males, Weeks 1-53	Mean BW Change for Females, Weeks 1-53
1	0 (Vehicle)	600	10.3±3.1	9.1±2.3
2	3	600	8.6±2.6	8.4±2.5
3	10	600	7.7±2.3**	8.2±2.7
4	30	600	7.6±2.3**	8.6±2.5
5	0 (No treatment)	600	10.0±2.6	10.9±3.3
6	0 (No treatment)	1200	NA	NA

*Approximate, based upon assumed BW of 25 g.
**$p<0.01$

- Gross pathology: No remarkable observations, with exception of skin tumors (see below).
- Tumor data analysis: The median number of weeks on study at which the first tumor (for a given animal) greater than or equal to 1.0 mm in diameter was observed was significantly reduced for males in group 4 (30 µg/kg/day) and for animals of both genders in group 6 (1200 RBU per day).

Median Number of Weeks on Study at Which First Tumor ≥ 1 mm Diameter was Observed:

Group	Calcipotriol Exposure (µg/kg/day)*	UVR Exposure (RBU/Week)	Median Week to Tumor ≥ 1 mm, Males	Median Week to Tumor ≥ 1 mm, Females
1	0 (Vehicle)	600	42.0	40.0
2	3	600	39.0	36.5
3	10	600	39.5	42.0
4	30	600	37.0**	35.5
5	0 (No treatment)	600	43.0	37
6	0 (No treatment)	1200	24.0***	23.5***

*Approximate, based upon assumed BW of 25 g.
**p<0.01 compared to group 1.
***p<0.001 compared to group 5.

The median time to first tumor greater than or equal to 1 mm for groups 1 and 5 did not differ statistically. The only difference between groups 1 and 5 was that group 1 animals received vehicle plus 600 RBU per week, while group 5 animals received only 600 RBU per week. These data suggest that the product vehicle did not impact UV-induced tumor formation.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Please see prior reviews associated with the applications listed above.

VIII. SPECIAL TOXICOLOGY STUDIES:

Please see prior reviews associated with the applications listed above.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

NDAs for three formulations of Dovonex have been approved (see above for dates of approval). This submission contained the final report of a photocarcinogenesis study that was conducted with calcipotriene in the vehicle for Dovonex solution as a "Phase 4" commitment. The key finding of this study was that the median number of weeks on study at which the first tumor (for a given animal) greater than or equal to 1.0 mm in diameter was observed was

significantly reduced for males that received the greatest exposure to calcipotriene (30 μg/kg/day). No other statistically significant effects on UVR-induced skin tumor formation were observed. The vehicle of Dovonex solution did not influence UVR-induced skin tumor formation. In my opinion, these data indicate cause for concern, since they suggest the risk for UVR-induced carcinogenesis increases with increasing concentration, or quantity, of calcipotriene in and on the skin. Enhancement of carcinogenesis was observed in animals treated with solution that contained calcipotriene at a concentration of 7.5 μg/mL, but not at lower concentrations. The clinical formulations contain a much higher concentration of calcipotriene (50 μg/mL), which suggests that they may promote UVR-induced carcinogenesis to a greater extent than did any of the materials that were evaluated in this mouse study (calcipotriene concentrations of 0, 0.75, 2.5, and 7.5 μg/mL were evaluated). Note that it was impossible to evaluate the clinical formulation because mice would not have tolerated such a high concentration of calcipotriene under the conditions of this study. I recommend that the label of the Dovonex products be modified to reflect the data from the mouse photocarcinogenesis study (see below for specific wording).

General Toxicology Issues: The label of the Dovonex products should be modified to reflect the data from the mouse photocarcinogenesis study.

Recommendations: The label of the Dovonex products should be modified to reflect the data from the mouse photocarcinogenesis study.

Labeling with basis for findings: The "Carcinogenesis" and the "Information for Patients" sections of the labels of Dovonex solution (NDA 20-611), Dovonex ointment (NDA 20-273), and Dovonex cream (NDA 20-554) should be modified as indicated below. Note that separate (but essentially identical) reviews of this mouse photocarcinogenesis study will be filed with each NDA.

The "Precautions" section of the labels of the products should be modified to state:

Information for Patients

Patients using Dovonex 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 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: The potential of calcipotriene to induce carcinogenesis in standard long-term animal studies (in the absence of ultra-violet radiation (UVR)) has not been evaluated. 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 (318 $\mu g/m^2$/day) of calcipotriene indicated no impairment of fertility or general reproductive performance.

Comments to be communicated to the sponsor:

1. The "Information for Patients" and "Carcinogenesis" portions of the "Precautions" section of the label of Dovonex ointment should be modified to state:

Information for Patients

Patients using Dovonex 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.

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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 (318 $\mu g/m^2$/day) of calcipotriene indicated no impairment of fertility or general reproductive performance.

Reviewer signature: _____

Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

cc: list:
M. Owens, PM

X. APPENDIX/ATTACHMENTS:

Addendum to review: None

Other relevant materials (Studies not reviewed, appended consults, etc.): None

Any compliance issues: None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman See
1/21/05 01:09:28 PM
PHARMACOLOGIST

Paul Brown
1/21/05 05:38:25 PM
PHARMACOLOGIST