Dovonex® (calcipotriene) Ointment, 0.005%

Rx only

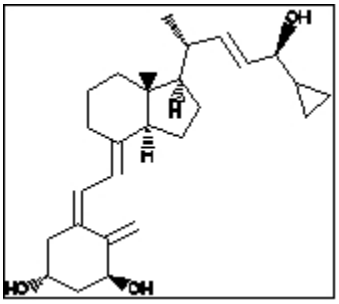
FOR TOPICAL DERMATOLOGIC USE ONLY.

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 calcipotriene 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 2 weeks of therapy. This improvement continued in patients using Dovonex Ointment once daily and twice daily. After 8 weeks

of once daily Dovonex Ointment, 56.7% of patients showed at least marked improvements (6.4% showed complete clearing). After 8 weeks of twice daily Dovonex Ointment, 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 Ointment 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 Ointment for periods of up to one year. In half of these studies, patients who previously had not responded well to Dovonex Ointment were excluded. The adverse reactions 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 Ointment 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 Ointment 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 Ointment should not be used on the face.

WARNINGS

Contact dermatitis, including allergic contact dermatitis, has been observed with the use of Dovonex Ointment.

PRECAUTIONS

General

Use of Dovonex Ointment may cause irritation of lesions and surrounding uninvolved skin. If irritation develops, Dovonex Ointment 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 Dovonex Ointment. 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 Ointment 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 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 local adverse reactions.

4. Patients that apply Dovonex Ointment 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 Dovonex Ointment 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 avoid use of phototherapy in patients that use Dovonex Ointment.

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

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 (calcipotrience) Ointment, 0.005% is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of Dovonex Ointment 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

Clinical Trials Experience

In controlled clinical trials, the most frequent adverse reactions reported for Dovonex Ointment 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.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of Dovonex Ointment. 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.

Renal and urinary disorders: hypercalciuria

Skin and subcutaneous tissue disorders: application site edema, application site pain, contact dermatitis (including allergic contact dermatitis), depigmentation, hypopigmentation, photosensitivity, rash (including erythematous, maculo-papular, and pustular), and urticaria.

OVERDOSAGE

Topically applied Dovonex Ointment 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** 0430-3010-15

120 gram aluminum tubes **NDC** 0430-3010-17

STORAGE

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

LEO®

Manufactured by: LEO Laboratories Ltd.

Dublin 12, Ireland

To report SUSPECTED ADVERSE REACTIONS, contact LEO Pharma Inc. at 1-877-494-4536 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DOVONEX®
(calcipotriene) Cream, 0.005%

Rx only

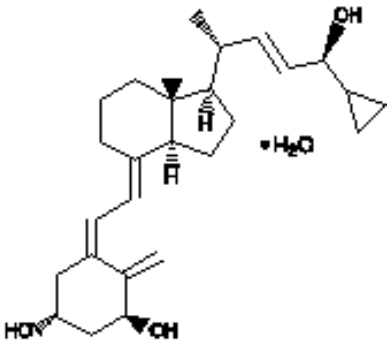
FOR TOPICAL DERMATOLOGIC USE ONLY.

Not for Ophthalmic, Oral or Intravaginal Use.

DESCRIPTION

Dovonex (calcipotriene) Cream, 0.005% contains calcipotriene monohydrate, a synthetic vitamin D_3 derivative, for topical dermatological use.

Chemically, calcipotriene monohydrate is (5Z,7E,22E,24S)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,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 µg/g anhydrous calcipotriene in a cream base of cetearyl alcohol, ceteth-20, diazolidinyl urea, dichlorobenzyl alcohol, dibasic sodium phosphate, edetate disodium, dl-alpha tocopherol, 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 D_3 (cholecalciferol) in the skin. Calcipotriene is a synthetic analog of vitamin D_3.

Clinical studies with radiolabelled calcipotriene 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. 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 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.

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, 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.

WARNINGS

Contact dermatitis, including allergic contact dermatitis, has been observed with the use of Dovonex Cream.

PRECAUTIONS

General

Use of Dovonex Cream may cause 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 Cream 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 Dovonex Cream 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 Cream.

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

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 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 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

Clinical Trials Experience

In controlled clinical trials, the most frequent adverse experiences reported for Dovonex (calcipotriene) 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.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Dovonex Cream. 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.

Metabolism and nutrition disorders: hypercalcemia

Renal and urinary disorders: hypercalciuria

Skin and subcutaneous tissue disorder: application site edema, application site pain, contact dermatitis (including allergic contact dermatitis), depigmentation, dry skin, erythema, hyperpigmentation, hypopigmentation, photosensitivity, rash (including erythematous, maculo-papular, and pustular), skin burning sensation, skin exfoliation, and urticaria.

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, 0.005% is available in:

60 gram aluminum tubes (NDC 50222-260-06)

120 gram aluminum tubes (NDC 50222-260-12)

STORAGE

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

LEO®

Manufactured by:

LEO Laboratories Ltd.

Dublin 12, Ireland

Distributed by:

LEO Pharma Inc.

Seven Giralda Farms

Madison, NJ 07940 USA

To report SUSPECTED ADVERSE REACTIONS, contact
LEO Pharma Inc. at 1-877-494-4536 or FDA at 1-800-FDA-1088
or www.fda.gov/medwatch.

Revises 10/2025