

Pr DOVONEX*
(Calcipotriol)
Cream and Ointment 50 mcg/g
Scalp Solution 50 mcg/mL

Topical Non-Steroidal
Antipsoriatic Agent

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Control #074256

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PRODUCT MONOGRAPH

PRODUCT NAME

^{Pr} DOVONEX*

(Calcipotriol)

Cream and Ointment 50 mcg/g

Scalp Solution 50 mcg/mL

THERAPEUTIC CLASSIFICATION

Topical Non-Steroidal Antipsoriatic Agent

ACTION AND CLINICAL PHARMACOLOGY

Calcipotriol is a non-steroidal antipsoriatic agent, derived from the naturally occurring vitamin D. Calcipotriol exhibits a vitamin D-like effect by competing for the $1,25(\text{OH})_2\text{D}_3$ receptor. Calcipotriol is as potent as $1,25(\text{OH})_2\text{D}_3$, the naturally occurring active form of vitamin D, in regulating cell proliferation and cell differentiation, but much less active than $1,25(\text{OH})_2\text{D}_3$ in its effect on calcium metabolism. Calcipotriol induces differentiation and suppresses proliferation (without any evidence of a cytotoxic effect) of keratinocytes, thus reversing the abnormal keratinocyte changes in psoriasis. The therapeutic goal envisaged with calcipotriol is thus a normalization of epidermal growth.

Clinical trials have shown Dovonex cream and ointment (calcipotriol 50 mcg/g) and Dovonex scalp solution (calcipotriol 50 mcg/ml) to be efficacious and well-tolerated in the topical treatment of psoriasis vulgaris (plaque psoriasis). Clinical improvement usually occurred rapidly and was evident within 2 weeks of treatment. The symptoms of thickness, erythema and scaling, as well as extent of psoriasis, were all markedly improved. The efficacy and safety of Dovonex ointment and cream are similar with best results obtained at the end of up to 6 to 8 weeks of treatment. Long-term control of psoriasis has been demonstrated in clinical trials with Dovonex ointment lasting up to 12 months.

Clinical trials have demonstrated the efficacy and safety of once daily Dovonex administration in combination with once daily administration of a moderately potent to very potent topical corticosteroid. Twice daily application of Dovonex is safe and effective when combined with either systemic drug therapy (cyclosporin A or acitretin) or with phototherapy (PUVA or UVB). In clinical studies, Dovonex ointment was combined with either cyclosporin A (2 mg/kg/day) for up to 6 weeks or with acitretin (20-70 mg/day) for up to 12 weeks. Dovonex ointment was combined with PUVA phototherapy (3 times weekly) whereas Dovonex ointment and cream have been combined with UVB phototherapy (2 or 3 times weekly) for up to 12 weeks. Combination of Dovonex cream plus UVB 2 times weekly was shown to be equally effective as UVB monotherapy 3 times weekly while allowing a significant reduction in UVB exposure. Improved efficacy achieved through combination therapy allowed once daily steroid administration or reductions in the required dose of cyclosporin A, acitretin, UVA or UVB phototherapy, thereby reducing the potential for dose related adverse effects associated with these agents. Combination of Dovonex plus a moderately potent to very potent corticosteroid was also shown to reduce skin irritation due to calcipotriol. Combination of Dovonex with systemic drug therapy or phototherapy did not affect the incidence of short term adverse events compared to systemic drug or phototherapy alone.

The safety, efficacy and tolerability of Dovonex ointment in children (ages 2 to 14 years) has been demonstrated by an 8 week open-label trial as well as an 8 week double-blind vehicle controlled trial. Dovonex was significantly more effective than vehicle in reducing the symptoms of redness, thickness and scaliness, and in the overall assessment of efficacy. No significant effects on haematology, serum and urine biochemistry parameters (including calcium levels) and parameters of bone formation or resorption were observed after 8 weeks of treatment (maximum dose 50 g/week/m² body surface area).

Three pivotal trials to evaluate the safety and efficacy of Dovonex scalp solution were conducted in patients with scalp psoriasis. There was a statistically significant improvement in the scalp psoriasis with a positive effect on total sign score, redness, thickness, scaliness and extent of scalp psoriasis.

A pharmacokinetic study of Dovonex ointment has demonstrated that the apparent systemic absorption of the applied dose of calcipotriol over 12 hours is approximately 5.5% of the dose in normal subjects and in psoriatic patients.

FOR DETAILS OF EFFICACY AND SAFETY DATA OBTAINED FROM VARIOUS CLINICAL TRIALS, SEE “CLINICAL PHARMACOLOGY - CLINICAL STUDIES” UNDER THE SECTION “PHARMACOLOGY”.

INDICATIONS AND CLINICAL USES

Dovonex cream and ointment are indicated for the topical treatment of psoriasis. Dovonex may be used in combination with a moderate to very potent topical corticosteroid, cyclosporin A, acitretin, or phototherapy. Dovonex scalp solution is indicated for the topical treatment of scalp psoriasis.

FOR DETAILS OF EFFICACY AND SAFETY DATA OBTAINED FROM VARIOUS CLINICAL TRIALS, SEE “CLINICAL PHARMACOLOGY - CLINICAL STUDIES” UNDER THE SECTION “PHARMACOLOGY”.

See also information under the section “WARNINGS”.

CONTRAINDICATIONS

Hypersensitivity to any constituent of calcipotriol cream, ointment or scalp solution. NOT FOR OPHTHALMIC USE.

When Dovonex is used in combination with other antipsoriatic therapies, all available information on “CONTRAINDICATIONS” for the other antipsoriatic therapy/therapies apply and should be considered.

WARNINGS

Dovonex (calcipotriol) cream, ointment and scalp solution are not generally recommended for severe extensive psoriasis. If calcipotriol is used for severe extensive psoriasis it is important to monitor the serum calcium levels at regular intervals due to the risk of hypercalcemia secondary to excessive absorption of calcipotriol when there is extensive skin involvement. If the serum calcium level becomes elevated, calcipotriol therapy should be discontinued and the serum calcium level monitored in these patients until it returns to normal.

When Dovonex is used in combination with other antipsoriatic therapies, all available information on “WARNINGS” for the other antipsoriatic therapy/therapies apply and should be considered.

Topical calcipotriol is not recommended for use on the face since this may give rise to itching and erythema of the facial skin. Patients should be instructed to wash their hands after using calcipotriol to avoid inadvertent transfer to the face from other body parts. Should facial dermatitis develop in spite of these precautions, calcipotriol therapy should be discontinued (See Patient Package Insert).

Use During Pregnancy and Lactation: Safety for use during pregnancy has not yet been established, although studies in experimental animals have not shown teratogenic effects. It is not known whether calcipotriol could be excreted in breast milk. Calcipotriol should be used in women during pregnancy or breast feeding only if the anticipated benefit clearly outweighs the potential risk.

Infants: There is inadequate experience with the use of calcipotriol in infants under 2 years of age to recommend use in this age group. Use beneath diapers has not been investigated and should be avoided as diapers may be occlusive.

Children: Administration to children should be supervised by a responsible individual to ensure proper administration and dosage. There is no experience in children with the use of Dovonex in combination with other antipsoriatic therapies.

PRECAUTIONS

Calcipotriol should be used cautiously in skin folds, where the natural occlusion may give rise to an increase of the irritant effect of calcipotriol.

When Dovonex is used in combination with other antipsoriatic therapies, all available information on “PRECAUTIONS” for the other antipsoriatic therapy/therapies apply and should be considered.

Treatment with Dovonex in the recommended amounts (See Dosage and Administration) does not generally result in changes in laboratory values. However, it is recommended that baseline serum calcium levels be obtained in all patients before starting treatment with calcipotriol, with subsequent monitoring of these serum calcium levels at suitable intervals. The monitoring of serum calcium levels is particularly important if the total dose of calcipotriol exceeds the recommended amount or if calcipotriol is used for severe psoriasis with extensive skin involvement. If the serum calcium becomes elevated, calcipotriol treatment should be discontinued and the levels of serum calcium should be measured once weekly until the serum calcium levels return to normal values. Patients with marginally elevated serum calcium may be treated with calcipotriol, provided that the serum calcium is monitored at suitable intervals.

Drug Interactions: With the exception of topical corticosteroids (See Dosage and Administration), there is no experience of concomitant therapy with other antipsoriatic drugs applied to the same skin area.

ADVERSE REACTIONS

In clinical trials reported to-date, the most common adverse reactions have been related to lesional and perilesional irritation. Some patients develop face and scalp irritation which is likely related to the inadvertent transfer of Dovonex cream or ointment from other body parts. Facial irritation may also occur with the use of Dovonex scalp solution from inadvertent transfer of the scalp solution to the face. One unconfirmed case of Koebner phenomenon and three unconfirmed cases of hypersensitivity reaction to calcipotriol have been reported. Occasionally hypercalcemia has been reported usually related to excessive (greater than the recommended weekly amount - See Dosage and Administration) use of topical calcipotriol or when excessive absorption of calcipotriol has occurred when used for severe psoriasis with extensive skin involvement (see Warnings).

Clinical studies have shown that combination of Dovonex once daily plus a moderately potent to very potent topical corticosteroid once daily reduces skin irritation due to calcipotriol. Combination of Dovonex plus cyclosporin A (2 mg/kg/day) or Dovonex plus acitretin (20-70 mg/day) did not affect the incidence of short term adverse effects compared to cyclosporin or acitretin plus placebo ointment. The combination of Dovonex plus PUVA or UVB phototherapy did not affect the incidence of short term adverse effects compared to PUVA or UVB plus placebo ointment/cream.

FOR FURTHER DETAILS SEE “CLINICAL PHARMACOLOGY - CLINICAL STUDIES” UNDER THE SECTION “PHARMACOLOGY”.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Hypercalcemia does not occur at the usual dose of calcipotriol (See Dosage and Administration). Excessive use (i.e. more than the recommended weekly amount) may cause elevated serum calcium, which rapidly subsides when treatment is discontinued; in such cases the monitoring of serum calcium levels once weekly until the serum calcium returns to normal levels is recommended.

DOSAGE AND ADMINISTRATION

DOVONEX (calcipotriol) is available in an ointment or a cream formulation at a concentration of 50 mcg/g for use on the body and scalp solution at a concentration of 50 mcg/mL for hairy areas. Calcipotriol is indicated FOR TOPICAL USE ONLY and NOT FOR OPHTHALMIC USE.

Dovonex Used as Monotherapy

Dovonex should be applied topically to the affected areas twice daily (i.e., in the morning and in the evening). Application can be reduced to once daily (ie., in the morning or in the evening) for maintenance treatment when appropriate. After satisfactory improvement has occurred, the drug can be discontinued. If recurrence takes place after discontinuation, the treatment may be reinstated.

The maximum recommended weekly dosage of Dovonex cream and/or ointment is:

<u>Age (years)</u>	<u>Dose (g/week)</u>
2 - 5	25
6 - 10	50
11 - 14	75
Adults (over 14)	100

The maximum weekly dose of Dovonex cream and/or ointment for children is based on the adult dose of 100 g/week adjusted for body surface area (maximum 50 g/week/m²). The dosage regimen is based on the following expected body surface area: age 2-5 years - 0.5 m² (25% of adult), age 6-10 years - 1.0 m² (50% of adult) and age 11-14 years - 1.5 m² (75% of adult).

The maximum recommended adult weekly dose of calcipotriol scalp solution is 60 mL. There is no clinical trial experience with use of Dovonex scalp solution in children. **When cream, ointment or scalp solution are used together, the total dose of calcipotriol should not exceed the recommended weekly amount for each age group (ie. 2-5 years - 1.25 mg; 6-10 years - 2.5 mg; 11-14 years - 3.75 mg; Adults - 5 mg in any week).**

Dovonex Used As Combination Therapies

Dovonex can be used in combination with a moderately potent to very potent topical corticosteroid (See Action and Clinical Pharmacology). Dovonex and the steroid should be applied once daily at alternate times (ie. morning versus evening application).

Dovonex can be used twice daily in combination with low dose cyclosporin A (ie. 2 mg/kg/day) or in combination with acitretin (20-70 mg/day) (See Action and Clinical Pharmacology).

Dovonex can be used twice daily in combination with PUVA phototherapy (3 times weekly) or UVB phototherapy (2 times weekly) (See Action and Clinical Pharmacology). When used in combination with PUVA, the dose of Dovonex immediately prior to UVA should be skipped. When used in combination with UVB, Dovonex should not be applied within 2 hours of phototherapy.

The use of Dovonex in combination with other treatments (ie., topical steroids, cyclosporin, acitretin, PUVA phototherapy or UVB phototherapy) improves efficacy allowing for dosage reduction of the other treatments.

There is no experience in children with the use of Dovonex in combination with other antipsoriatic therapies.

FOR DETAILS OF EFFICACY AND SAFETY DATA OBTAINED FROM VARIOUS CLINICAL TRIALS, SEE “CLINICAL PHARMACOLOGY - CLINICAL STUDIES” UNDER THE SECTION “PHARMACOLOGY”.

SEE ALSO INFORMATION UNDER “CONTRAINDICATIONS”, “WARNINGS”, AND “PRECAUTIONS”.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

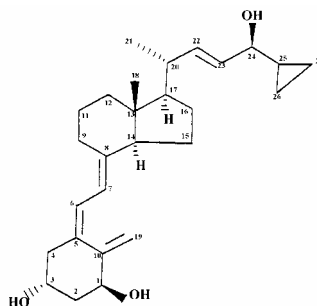
Common Name (I.N.N.): Calcipotriol

Chemical Abstracts Name: 9,10-Secochola-5,7,10(19),22-tetraene-1,3,24-triol,
24-cyclo-propyl-,(1 α ,3 β ,5Z,7E,22E,24S)

Alternative Chemical Name: 20(R)-(3'(S)-Cyclopropyl-3'-hydroxyprop-1'(E)-enyl)-
1(S),3(R)-dihydroxy-9,10-secopregna-5(Z),7(E),10(19)-triene

Laboratory Code Name: MC 903 or MC 903-000

Structural Formula:



Molecular Formula: C₂₇ H₄₀ O₃

Molecular Weight: 412.6

Chirality: The calcipotriol molecule is one single stereoisomer. The absolute configuration of the chiral centers at carbon atoms nos. 1, 3, 13, 14, 17, 20 and 24 is indicated in the structural formula above.

Physical Form: Calcipotriol is a white or almost white crystalline substance.

Solubility at Room Temperature: Freely soluble in ethanol, soluble in chloroform and propylene glycol, practically insoluble in liquid paraffin. Solubility in water is 0.6 mcg/mL.

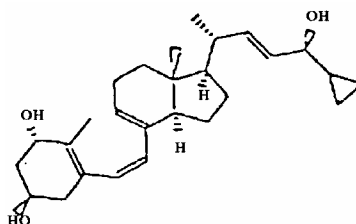
Melting Point: 166-168°C

Polymorphism:

So far no signs have indicated the existence of polymorphic forms.

Other Characteristics:

Calcipotriol is a vitamin D derivative. It is well-known that vitamin D in solution forms a reversible temperature dependent equilibrium between vitamin D and pre-vitamin D (described in (i.e.) J Pharm Sci 1968; 57:1326). In the same way, solutions of calcipotriol establish an equilibrium with "pre-calcipotriol". The structural formula of "pre-calcipotriol" is shown below.



COMPOSITION:

Non-Medicinal Ingredients:

OINTMENT

white soft paraffin
propylene glycol
liquid paraffin
polyoxyethylene-(2)-stearyl ether
purified water
disodium phosphate dihydrate
disodium edetate
DL- α -tocopherol

CREAM

white soft paraffin
cetostearyl alcohol
liquid paraffin
glycerol 85%
cetomacrogol 1000
disodium phosphate dihydrate
disodium edetate
chloroallylhexaminium
(dowicil 200)
purified water

SCALP SOLUTION

hydroxypropyl cellulose
isopropanol
levomenthol
sodium citrate
propylene glycol
purified water

STABILITY AND STORAGE RECOMMENDATIONS:

Cream and Ointment: Store at room temperature (15°C to 25°C).

Scalp Solution: Store below 25°C.

For easy application: do not refrigerate (this is to prevent rubbing and pulling of delicate skin).

AVAILABILITY OF DOSAGE FORMS

Dosage Form: Ointment (faintly translucent white to yellowish ointment)
Cream (white, soft cream)
Scalp solution (colourless, slightly viscous solution)

Strength: Cream and ointment: 50 mcg calcipotriol per gram
Scalp solution: 50 mcg calcipotriol per mL

Recommended Route of Administration: For topical use only.

Containers: Cream and ointment: available in 15g, 60g and 120g lacquered aluminium tubes and 240g laminate tubes (equipped with an aluminium membrane).
Scalp solution: 30 mL and 60 mL, and 120 mL polyethylene bottles.

PATIENT PACKAGE INSERT

DOVONEX Cream and Ointment

DOVONEX:

This leaflet is intended to give you some important information about using Dovonex in the treatment of your psoriasis. If you have any questions please talk to your doctor or pharmacist.

What is Dovonex?

Dovonex contains calcipotriol (50 mcg/g). Calcipotriol is a vitamin D derivative designed to control the excessive production of skin cells in areas affected by psoriasis and has proven benefits in the treatment of this condition.

Dovonex has been developed as a smooth preparation, making it easy to use.

BEFORE USING YOUR CREAM OR OINTMENT

Tell your doctor:

- If you are pregnant or breast feeding or if you become pregnant during your treatment.

USING YOUR CREAM OR OINTMENT

How should I use Dovonex?

- Remove the cap and check that the aluminium seal is intact before first use. To break the seal, reverse the cap and pierce.
- Dovonex should be applied to the areas of your skin affected by psoriasis and gently rubbed in. Wash your hands after using Dovonex to avoid inadvertent transfer to your face from other body parts. Your usual clothes may then be worn as Dovonex need not be specially covered. Do not worry if you accidentally get some Dovonex on the surrounding normal skin but wash it off if it spreads too far.
- Dovonex should not be used on the face as it may cause skin irritation. If it accidentally gets on your face, wash it off.
- Dovonex is not recommended for use in infants under 2 years of age. Use beneath diapers has

not been investigated and should be avoided as diapers may be occlusive.

- You must not use more than the recommended weekly amount of Dovonex:

<u>Age (years)</u>	<u>Dose (g/week)</u>
2 - 5	25
6 - 10	50
11 - 14	75
Adults (over 14)	100

The maximum weekly dose of Dovonex cream and/or ointment for children is based on the adult dose of 100 g/week adjusted for body surface area (maximum 50 g/week/m²). The dosage regimen is based on the following expected body surface area: age 2-5 years - 0.5 m² (25% of adult), age 6-10 years - 1.0 m² (50% of adult) and age 11-14 years - 1.5 m² (75% of adult).

When cream, ointment or scalp solution are used together, the total dose of calcipotriol should not exceed the recommended weekly amount for each age group (ie. 2-5 years - 1.25 mg; 6-10 years - 2.5 mg; 11-14 years - 3.75 mg; Adults - 5 mg in any week). As an example, adults should not use more than one 30 mL bottle of scalp solution plus one 60 g tube of ointment or cream per week.

- Administration to children should be supervised by a responsible individual to ensure proper administration and dosage.
- Dovonex is usually applied twice daily (morning and night) when first starting treatment. Most patients will begin to see an improvement within 2 weeks. Best results are seen within 6-8 weeks. When satisfactory improvement has been achieved, application may be reduced to once daily in order to maintain control of psoriasis. Follow your doctor's instructions carefully.
- Dovonex can be used in combination with a moderately potent to very potent topical corticosteroid if recommended by your doctor. Apply each medication once daily at alternate times of the day (ie. morning versus evening).

- Dovonex can be used in combination with oral drug therapies (eg., cyclosporin A or acitretin) or in combination with phototherapy (PUVA or UVB), if recommended by your doctor. When used in combination with PUVA, the dose of Dovonex immediately prior to UVA phototherapy should be skipped. Dovonex should not be applied within 2 hours of UVB phototherapy.
- There is no experience in children with the use of Dovonex in combination with other antipsoriatic therapies.

What should I do if I forget to use my cream or ointment?

- If you forget to use your Dovonex at the right time, use it as soon as you remember. Then go on as before.

AFTER USING YOUR DOVONEX

- Dovonex may cause irritation of your skin for a short while after you have applied it. Try not to scratch the area.
- See your doctor if the irritation persists, if you get a facial rash or if the Dovonex upsets you in any other way.

STORING YOUR DOVONEX

- Keep Dovonex in a safe place where children cannot reach it.
- Keep Dovonex out of reach of pets. Dogs enjoy the taste of Dovonex but ingestion can be fatal to dogs. If your dog eats Dovonex contact a veterinarian immediately.
- Cream and ointment: Store at room temperature (15°C to 25°C).
- Dovonex has an expiry date marked on the bottom of each tube. Please do not use the contents of the tube after this date.

PATIENT PACKAGE INSERT

DOVONEX Scalp Solution

DOVONEX:

This leaflet is intended to give you some important information about using Dovonex in the treatment of your psoriasis. If you have any questions please talk to your doctor or pharmacist.

What is Dovonex?

Dovonex contains calcipotriol (50 mcg/mL). Calcipotriol is a vitamin D derivative designed to control the excessive production of skin cells in areas affected by psoriasis on your scalp and has proven benefits in the treatment of this condition.

Dovonex scalp solution is a colourless, slightly viscous solution.

BEFORE USING YOUR DOVONEX SCALP SOLUTION

Tell your doctor:

- If you are pregnant or breast feeding or if you become pregnant during your treatment.

USING YOUR DOVONEX SCALP SOLUTION

How should I use Dovonex?

- Remove the cap and place the nozzle through the hair next to the scalp. Squeeze the bottle gently and apply a few drops on to the affected area. Rub in gently with your fingertips. One or two drops should cover the area of a postage stamp.
- Wash your hands after using Dovonex to avoid inadvertent transfer to your face. Do not worry if you accidentally get some Dovonex on the surrounding normal skin but wash it off if it spreads too far.
- Dovonex scalp solution should not be used on the face as it may cause skin irritation. If it accidentally gets on your face, wash it off. If you get the scalp solution in your eye, bathe the eye with water.
- After washing your hair, dry it thoroughly before using the scalp solution. Do not wash your hair just after using Dovonex scalp solution or it will wash out.
- You must not use more than 60 mL of Dovonex in one week. If you are using the cream or ointment with the scalp solution, the total adult dose of calcipotriol should not exceed 5 mg in one week (ie.) one 30 mL bottle of scalp solution plus one 60 g tube of cream or ointment per week. There is no clinical trial experience with use of Dovonex scalp solution in children.
- Dovonex scalp solution is usually used twice a day (morning and night). Most patients will begin to see an improvement within two weeks. Follow your doctor's instructions carefully.

What should I do if I forget to use my Dovonex scalp solution?

- If you forget to use your Dovonex at the right time, use it as soon as you remember. Then go on as before.

AFTER USING YOUR DOVONEX SCALP SOLUTION

- Dovonex may cause irritation of your scalp for a short time after you have applied it. Try not to scratch the area.
- See your doctor if the irritation persists, if you get a facial rash or if the Dovonex upsets you in any other way.

STORING YOUR DOVONEX SCALP SOLUTION

- Keep Dovonex in a safe place where children cannot reach it.
- Keep Dovonex out of reach of pets. Dogs enjoy the taste of Dovonex but ingestion can be fatal to dogs. If your dog eats Dovonex contact a veterinarian immediately.
- Scalp solution: Store below 25°C.
- Dovonex has an expiry date marked on the bottle. Please do not use the contents of the bottle after this date.