CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-852

LABELING

TACLONEX®

(calcipotriene 0.005% and betamethasone dipropionate 0.064%)
OINTMENT

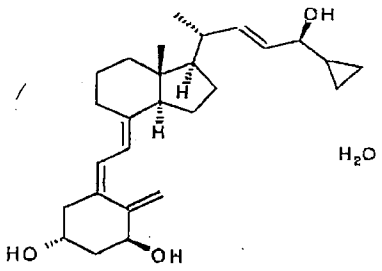
FOR TOPICAL USE ONLY.
Not for Ophthalmic, Oral or Intravaginal Use.

DESCRIPTION

Taclonex® Ointment contains calcipotriene hydrate and betamethasone dipropionate. It is intended for topical use.

Calcipotriene hydrate is a synthetic vitamin D_3 analogue.

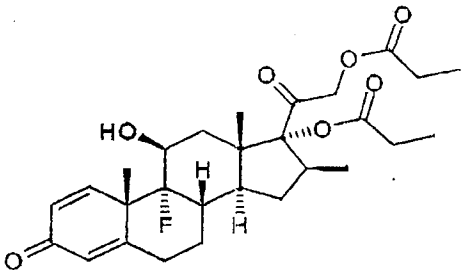
Chemically, calcipotriene hydrate is (5Z,7E,22E,24S)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1(α),3(β),24-triol,hydrate, with the empirical formula $C_{27}H_{40}O_3,H_2O$, a molecular weight of 430.6, and the following structural formula:



Calcipotriene hydrate is a white to almost white crystalline compound.

Betamethasone dipropionate is a synthetic corticosteroid.

Betamethasone dipropionate has the chemical name 9-fluoro-11(β),17,21-trihydroxy-16(β)-methylpregna-1,4-diene-3,20-dione17,21-dipropionate, with the empirical formula $C_{28}H_{37}FO_7$, a molecular weight of 504.6, and the following structural formula:



Betamethasone dipropionate is a white to almost white odorless powder.

Each gram of Taclonex® Ointment contains 52.18 mcg calcipotriene hydrate

(equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in an ointment base of mineral oil, PPG-15 stearyl ether, dl-alpha tocopherol and white petrolatum.

CLINICAL PHARMACOLOGY

Taclonex® Ointment:
Taclonex® Ointment combines the pharmacological effects of calcipotriene hydrate and betamethasone dipropionate as described below.

In a vasoconstrictor study, the skin blanching response of Taclonex® Ointment was consistent with that of a potent corticosteroid.

Calcipotriene

Pharmacokinetics: Calcipotriene metabolism following systemic uptake is rapid and occurs in the liver. The primary metabolites of calcipotriene are less potent than the parent compound.

Betamethasone dipropionate

Like other topical corticosteroids, betamethasone dipropionate has anti-inflammatory, antipruritic and vasoconstrictive properties. However, while the physiologic, pharmacologic, and clinical effects of the corticosteroids are well known, the exact mechanisms of their actions in psoriasis vulgaris are uncertain.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

There are no human data regarding the distribution of corticosteroids to body organs following topical application. Nevertheless, once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. In addition, some corticosteroids and their metabolites are also excreted in the bile.

Taclonex® Ointment was applied once daily for 4 weeks to adult patients (N = 12) with psoriasis vulgaris to study its effects on the hypothalamic-pituitary-adrenal (HPA) axis. Of eleven patients tested, none demonstrated adrenal suppression as indicated by a 30-minute post-stimulation cortisol level ≤ 18 mcg/dL.

However in another clinical study of Taclonex® Ointment, one subject (N = 19) demonstrated adrenal suppression.

CLINICAL STUDIES

In an international, multi-center, double-blind, vehicle- and active-controlled, parallel-group study, 1,603 patients with mild to very severe psoriasis vulgaris on trunk and limbs were treated once daily for 4 weeks. Patients were randomized to one of four treatment arms: Taclonex® Ointment, calcipotriene hydrate 50 mcg/g in the same vehicle, betamethasone dipropionate 0.64 mg/g in the same vehicle, and vehicle alone. The mean age of the patients was 48.4 years and 60.5% were male. Most patients had disease of moderate severity at baseline.

Efficacy was assessed as the proportion of patients with absent or very mild disease according to the Investigator's Global Assessment of Disease Severity at end of treatment (4 weeks). "Absent" disease was defined as no evidence of redness, thickness, or scaling. "Very mild disease" was defined as controlled disease, but not entirely cleared: lesions with some discoloration with absolutely minimal thickness, i.e. the edges to the lesion(s) could just be felt.

Percentage of Patients with Absent or Very Mild Disease According to the Investigator's Global Assessment of Disease Severity at End of Treatment (4 weeks).*

	Taclonex® Ointment N=490	Calcipotriene N=480	Betamethasone dipropionate N=476	Vehicle N=157
Absent or very mild disease	48.0%	16.5%	26.3%	7.6%

* Patients with mild disease at baseline were required to have "Absent" disease to be considered a success.

In addition to the pivotal study (N=490), four randomized, double-blind, vehicle- or active-controlled, parallel-group studies were conducted and provided supportive evidence of efficacy. These studies included a total of 1,058 patients treated with Taclonex® Ointment once daily for up to 4 weeks.

INDICATIONS AND USAGE

Taclonex® Ointment is indicated for the topical treatment of psoriasis vulgaris in adults 18 years of age and above for up to 4 weeks. The maximum weekly dose should not exceed 100 g. Treatment of more than 30% body surface area is not recommended.

Taclonex® Ointment should not be applied to the face, axillae or groin.

CONTRAINDICATIONS

Taclonex® Ointment is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

Taclonex® Ointment is contraindicated in patients with known or suspected disorders of calcium metabolism.

Taclonex® Ointment is contraindicated in patients with erythrodermic, exfoliative and pustular psoriasis.

PRECAUTIONS

General:

Hypercalcemia has been observed with use of Taclonex® Ointment. If elevation of serum calcium outside the normal range occurs, discontinue treatment until normal calcium levels are restored. In the trials that included assessment of the effects of Taclonex® Ointment on calcium metabolism, such testing was done after 4 weeks of treatment. The effects of Taclonex® Ointment on calcium metabolism following treatment durations of longer than 4 weeks are not known.

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients. Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Use of more than one corticosteroid-containing product at the same time may increase total systemic glucocorticoid exposure. (See DOSAGE AND ADMINISTRATION).

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression by using the Cosyntropin Stimulation Test. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt and complete upon discontinuation of the topical corticosteroid.

The use of Taclonex® Ointment has not been studied in patients with severe renal insufficiency or severe hepatic disorders.

HPA axis suppression has been observed with Taclonex® Ointment.

If irritation develops, Taclonex® Ointment should be discontinued and appropriate therapy instituted.

Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than by noting any clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop after treatment initiations, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of Taclonex® Ointment should be discontinued until the infection has been adequately controlled.

Taclonex® Ointment should not be used in the presence of pre-existing skin atrophy at the treatment site.

Taclonex® Ointment should not be used on the face, axillae or groin.

Information for Patients:
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 Taclonex® 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 hands after application.
2) This medication should not be used for any disorder other than that for which it has been prescribed.
3) The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive, unless directed by the physician.
4) Patients should report any signs of adverse reactions to their physician.
5) Other products containing calcipotriene or a corticosteroid should not be used with Taclonex® Ointment without first talking to the physician.
6) Patients who apply Taclonex® 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 limit or avoid use of phototherapy in patients who use Taclonex® Ointment.

Laboratory Tests

See PRECAUTIONS, General.

Carcinogenesis, mutagenesis, impairment of fertility:
Long-term animal studies have not been performed to evaluate the carcinogenic potential of Taclonex® Ointment or any of the active constituents.

In a study in which albino hairless mice were exposed to both ultra-violet radiation (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 who apply Taclonex® 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 limit or avoid use of phototherapy in patients that use Taclonex® Ointment.

Calcipotriene did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, the human lymphocyte chromosome aberration test, or the mouse micronucleus test.

Betamethasone dipropionate did not elicit any genotoxic effects in the Ames mutagenicity assay, the mouse lymphoma TK locus assay, or in the rat micronucleus test.

Studies in rats with oral doses of up to 54 mcg/kg/day (324 mcg/m^2/day) of calcipotriene demonstrated no impairment of fertility or general reproductive performance.

Studies in rats with oral doses of up to 0.2 mg/kg/day (1,200 mcg/m^2/day) of betamethasone dipropionate demonstrated no impairment of male fertility.

Pregnancy:

Teratogenic Effects: Pregnancy Category C

Animal reproduction studies have not been conducted with Taclonex® Ointment. Taclonex® Ointment contains calcipotriene that has been shown to be fetotoxic and betamethasone dipropionate that has been shown to be teratogenic in animals when given systemically. There are no adequate and well-controlled studies in pregnant women. Taclonex® Ointment should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

Teratogenicity studies with calcipotriene were performed by the oral route in rats and rabbits. In rabbits, increased maternal and fetal toxicity were noted at dosage of 12 mcg/kg/day (144 mcg/m^2/day); a dosage of 36 mcg/kg/day (432 mcg/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 mcg/kg/day (324 mcg/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 levels in the rat (108 mcg/m^2/day) and rabbit (48 mcg/m^2/day) studies are lower than the estimated maximum topical dose in man (approximately 460 mcg/m^2/day). Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Betamethasone dipropionate has been shown to be teratogenic in mice and rabbits when given by the subcutaneous route at doses of 156 mcg/kg/day (468 mcg/m^2/day) and 2.5 mcg/kg/day (30 mcg/m^2/day), respectively. Those dose levels are lower than the estimated maximum topical dose in man (5,948 mcg/m^2/day). The abnormalities observed included umbilical hernia, exencephaly and cleft palates.

Pregnant women were excluded from the clinical trials conducted with Taclonex® Ointment.

Nursing mothers:

Safety of the use of Taclonex® Ointment during lactation has not been established.

Nursing women were excluded from the clinical trials conducted with Taclonex® Ointment.

It is not known whether topically administered calcipotriene is excreted in human milk.

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk.

Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant.

Because many drugs are excreted in human milk, caution should be exercised when Taclonex® Ointment is administered to a nursing woman.

Pediatric use:

Safety and effectiveness of Taclonex® 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 subjects in clinical studies of Taclonex® Ointment, approximately 14% were 65 years and older, while approximately 3% were 75 years and over.

No overall differences in safety or effectiveness of Taclonex® Ointment were observed between these subjects and younger subjects. All other reported clinical experience has not identified any differences in response between elderly and younger patients.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The data described below reflect exposure to Taclonex® Ointment in 2448 patients, including 1992 exposed for 4 weeks, and 289 exposed for 8 weeks. In the trials that included assessment of the effects of Taclonex® Ointment on calcium metabolism, such testing was done after 4 weeks of treatment. The effects of Taclonex® Ointment on calcium metabolism following treatment durations of longer than 4 weeks are not known (See PRECAUTIONS). The effects of Taclonex® Ointment on the HPA axis following treatment durations of longer than 4 weeks have not been adequately studied. Taclonex® Ointment was studied primarily in placebo- and active-controlled trials (N = 1176, and N = 1272, respectively). The population was 15-97 years old, 61% males and 39% females, mostly white (97%) and had a baseline disease severity ranging from mild to very severe. Most patients received once daily application, and the median weekly dose was 24.5 g.

The percentage of subjects reporting at least one adverse event was 27.1% in the Taclonex® Ointment group, 33.0% in the calcipotriene group, 28.3% in the betamethasone group, and 33.4% in the vehicle group.

Adverse Events Reported by ≥ 1% of Subjects by Preferred Term

	Taclonex® Ointment N=2448	Calcipotriene N=3197	Betamethasone dipropionate N=1164	Vehicle N=470
Any Adverse Event	663 (27.1)	1055 (33.0)	329 (28.3)	157 (33.4)
Preferred Term	**#of subjects (%)**			
Pruritus	75 (3.1)	183 (5.7)	38 (3.3)	43 (9.1)
Headache	69 (2.8)	75 (2.3)	44 (3.8)	12 (2.6)
Nasopharyngitis	56 (2.3)	77 (2.4)	34 (2.9)	9 (1.9)
Psoriasis	30 (1.2)	47 (1.5)	14 (1.2)	5 (1.1)
Rash scaly	30 (1.2)	40 (1.3)	0 (0.0)	1 (0.2)
Influenza	23 (0.9)	34 (1.1)	14 (1.2)	6 (1.3)
Upper respiratory tract infection	20 (0.8)	19 (0.6)	12 (1.0)	3 (0.6)
Erythema	15 (0.6)	54 (1.7)	3 (0.3)	5 (1.1)
Application site pruritus	13 (0.5)	24 (0.8)	10 (0.9)	6 (1.3)
Skin Irritation	11 (0.4)	60 (1.9)	8 (0.7)	5 (1.1)
Pain	7 (0.3)	12 (0.4)	3 (0.3)	5 (1.1)
Burning sensation	6 (0.2)	30 (0.9)	3 (0.3)	6 (1.3)

A lesional/perilesional adverse event was generally defined as an adverse event located ≤ 2 cm from the lesional border.

Lesional/Perilesional Adverse Events Reported by ≥ 1% of Subjects

	Taclonex® Ointment N=2448	Calcipotriene N=3197	Betamethasone dipropionate N=1164	Vehicle N=470
Any Adverse Event	213 (8.7)	419 (13.1)	85 (7.3)	76 (16.2)
Preferred Term	**# of subjects (%)**			
Pruritus	69 (2.8)	170 (5.3)	31 (2.7)	41 (8.7)
Rash scaly	29 (1.2)	38 (1.2)	0 (0.0)	0 (0.0)
Application site pruritus	12 (0.5)	24 (0.8)	10 (0.9)	6 (1.3)
Erythema	9 (0.4)	36 (1.1)	2 (0.2)	4 (0.9)
Skin Irritation	9 (0.4)	51 (1.6)	8 (0.7)	5 (1.1)
Burning sensation	6 (0.2)	25 (0.8)	3 (0.3)	5 (1.1)

For subjects who reported lesional/perilesional adverse events, the median time to onset was 7 days for Taclonex® Ointment, 7 days for calcipotriene, 5 days for betamethasone dipropionate, and 3 days for vehicle.

Other less common reactions (less than 1% but more than 0.1%) were, in decreasing order of incidence, folliculitis, rash papular, rash pustular, and skin hypopigmentation. Skin atrophy, telangiectasia and skin hyperpigmentation were reported infrequently (0.1%).

In a separate study, patients (N=207) with at least moderate disease severity were given Taclonex® Ointment intermittently on an "as needed" basis for up to 52 weeks. The median use was 15.4 g per week. **The effects of Taclonex® Ointment on calcium metabolism were not studied and the effects on the HPA axis were not adequately studied.** The following adverse reactions were reported by 1% or more of the patients: pruritus (7.2%), psoriasis (3.4%), skin atrophy (1.9%), folliculitis (1.4%), burning sensation (1.4%), skin depigmentation (1.4%), ecchymosis (1.0%), erythema (1.0%) and hand dermatitis (1.0%). One case of a serious flare-up of psoriasis was reported.

Development of pustular psoriasis has been reported as an adverse reaction during and following use of Taclonex® Ointment.

OVERDOSAGE

Topically applied Taclonex® Ointment can be absorbed in sufficient amounts to produce systemic effects. (See PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Apply an adequate layer of Taclonex® Ointment to the affected area(s) once daily for up to 4 weeks. Taclonex® Ointment should be rubbed in gently and completely. The maximum weekly dose should not exceed 100 g. Treatment of more than 30% body surface area is not recommended. Taclonex® Ointment should not be applied to the face, axillae or groin.

HOW SUPPLIED

Taclonex® Ointment (calcipotriene 0.005% and betamethasone dipropionate 0.064%) is available in 15 gram collapsible tubes (NDC 0430-3230-11), 30 gram collapsible tubes (NDC 0430-3230-13), and 60 gram collapsible tubes (NDC 0430-3230-15).

Store Taclonex® Ointment between 20-25°C (68-77°F); excursions permitted between 15-30°C (59-86°F).

Keep out of reach of children.

Rx only.

U.S. Patent Nos.: 4,866,048 and 6,753,013.

Manufactured by:
LEO Laboratories Ltd. (LEO Pharma)
Dublin, Ireland

Marketed by:
Warner Chilcott (US), Inc.
Rockaway, NJ 07866
USA

Patient Information

Taclonex® Ointment
(calcipotriene, 0.005% and betamethasone dipropionate, 0.064%)

Read the Patient Information that comes with Taclonex® Ointment before you start using it and each time you use the ointment. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment.

What is Taclonex® Ointment and what is it used for?
Taclonex® Ointment is a prescription medicine called a topical (skin-use only).
Taclonex® Ointment is used on the skin to treat psoriasis vulgaris in adults.
Taclonex® Ointment contains

- calcipotriene hydrate, which is somewhat similar to vitamin D, but not the same as vitamin D, and
- betamethasone dipropionate, which is a strong (potent) corticosteroid.

It is very important that you use Taclonex® Ointment only as directed, in order to avoid serious side effects.

Taclonex® Ointment is not recommended for use in children. Taclonex® Ointment has not been studied in patients under the age of 18.

Who should not use Taclonex® Ointment?
Do not use Taclonex® Ointment if you:

- **have a calcium metabolism disorder**
- **have one of the following types of psoriasis:**
    - erythrodermic psoriasis
    - exfoliative psoriasis
    - pustular psoriasis
- **are allergic to anything in Taclonex® Ointment**. See the end of this leaflet for a complete list of ingredients.

What should I tell my doctor before using Taclonex® Ointment?
Tell your doctor about all of your health conditions, including if you:

- **have a skin infection**. Your skin infection should be treated before starting Taclonex® Ointment
- **have thin-skin (atrophy) at the site to be treated**. You should not use Taclonex® Ointment

- **are getting phototherapy treatments for your psoriasis**
- **are pregnant or planning to become pregnant.** It is not known if Taclonex® Ointment can harm your unborn baby. You and your doctor will have to decide if Taclonex® Ointment is right for you while pregnant
- **are breastfeeding.** It is not known if Taclonex® Ointment passes into your milk and if it can harm your baby

Tell your doctor about all the medicines you take, including prescription, and nonprescription medicines, vitamins and herbal supplements. Taclonex® Ointment and some other medicines can interact with each other. Especially tell your doctor if you use:

- other corticosteroid medicines
- other medicines for your psoriasis

How should I use Taclonex® Ointment?

- **Use Taclonex® Ointment exactly as directed by your doctor.** Do not use more than the recommended weekly amount of 100 grams of Taclonex® Ointment.
- **Do not use Taclonex® Ointment on your face, under your arms or on your groin. Do not get any Taclonex® Ointment in your eyes.** Wash your face or eyes right away if you get Taclonex® Ointment on them.

Using Taclonex® Ointment:

- Remove the cap and check that the aluminum seal covers the tube, before the first use. To break the seal, turn the cap over and push through the seal.
- Apply Taclonex® Ointment once a day to the areas of your skin affected by psoriasis. Gently rub Taclonex® Ointment into your affected skin areas.
- Do not bandage or tightly cover or wrap the treated skin area. Wear your usual clothes.
- Only use Taclonex® Ointment as directed by your doctor. Taclonex® Ointment is recommended for up to 4 weeks of treatment. Do not use Taclonex® Ointment for more than 4 weeks unless prescribed by your doctor.
- If you forget to use your Taclonex® Ointment, use it as soon as you remember. Then go on as before.
- Wash your hands well after using Taclonex® Ointment.

What are the possible side effects of Taclonex® Ointment?

The most common side effects are:

- itching
- rash
- skin burning

Other less common side effects with Taclonex® Ointment include:

- redness of the skin
- inflamed hair pores (folliculitis)
- psoriasis
- skin irritation
- change of skin color (at the site of application)
- thinning of the skin (atrophy)
- swollen fine blood vessels (this makes your skin appear red at the site of application)

Taclonex® Ointment may cause serious side effects if you use too much or use it for too long. Taclonex® Ointment can pass through your skin. Serious side effects may include:

- **too much calcium in your blood**
- **adrenal gland problems**

Your doctor may do special blood and urine tests to check your calcium levels and adrenal gland function while you are using Taclonex® Ointment.

Call your doctor about any side effect that bothers you or that does not go away.

These are not all of the side effects with Taclonex® Ointment. Ask your doctor or pharmacist for more information.

How should I store Taclonex® Ointment?

- Taclonex® Ointment should be stored between 68-77°F (20-25°C); excursions permitted between 59-86°F (15-30°C). Make sure the cap on the tube is tightly closed.
- Taclonex® Ointment has an expiry date marked on the tube. Do not use the ointment after this date.
- **Keep Taclonex® Ointment out of the reach of children and pets.**

General information about Taclonex® Ointment

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Taclonex® Ointment for a condition for which it was not prescribed. Do not give ointment to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about Taclonex® Ointment. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Taclonex® Ointment that is written for health professionals.

Additional consumer information is available on (800) 521-8813.

What are the ingredients in Taclonex® Ointment?

Active Ingredients: calcipotriene hydrate, betamethasone diproplonate
Inactive ingredients: mineral oil, PPG-15 stearyl ether, dl-alpha tocopherol, white petrolatum.

Manufactured by:
LEO Laboratories Ltd. (LEO Pharma)
Dublin, Ireland

Marketed by:
Warner Chilcott (US), Inc.
Rockaway, NJ 07866
USA

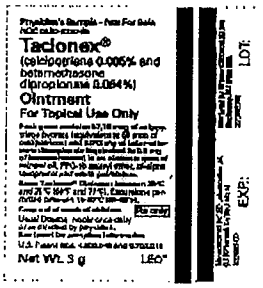
ARTWORK

Please return to:
LEO Pharma A/S
Internal Market Access
Industriparken 55 – DK-2750 – Ballerup

Scale	Get-up	Item No.	Rev. No.	Sent by e-mail	
100%	US / WC	022605	00	▼	
Subject: TBA 13,5 x 65 mm			Date: 29/12/05	Date	Date
Colour: PMS 485 + black			Sign.: OM	Sign.	Sign.

Preparation / Strength	Supplier / Place of production
Tacionex® ointment 3 g	Ireland

Comments: Pharmacode XXX Mock-up



5. PROOF PR FROM — Artwork Approval Stamp (AAS)

Date 06/01/06

New proof requested ☐

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Sign.:

Date:

Graphical Design		Editorial Proof		Market Regulatory Approval	
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Size/Ratio	☐	Dosage form	☐	Marketing Authorisation	☐
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ARTWORK

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Industriparken 55 – DK-2750 – Ballerup

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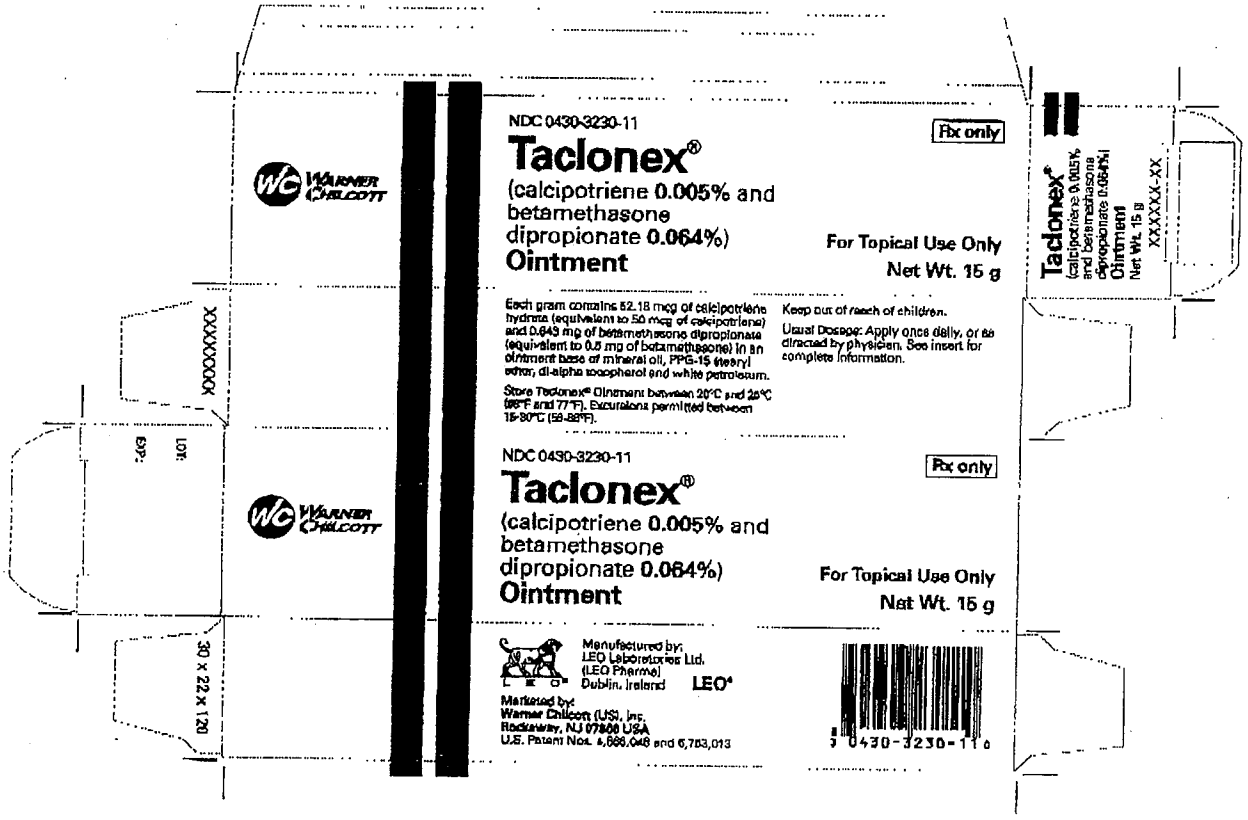
Subject: CRT 30 x 22 x 120 mm			Date: 04/01/06	Date	Date
Colour: PMS 485 + 301 + black			Sign.: OM	Sign.	Sign.

Preparation Strength: Taclonex® ointment 15 g
Supplier / Place of production: Ireland
Comments: Pharmacode XXX Mock-up



Artwork Approval Stamp (AAS)

4. PROOF FROM: OM
Date: 06/01/06
New proof requested ☐
PLEASE RETURN TO: INTERNAL MARKET ACCESS DEPT. 898
Sign.:
Date:

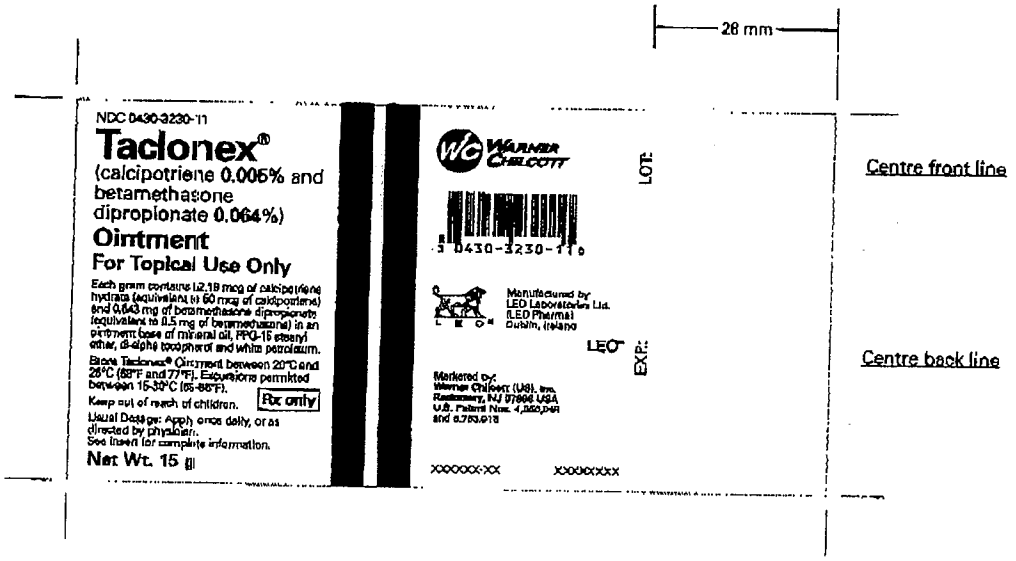
Graphical Design		Editorial Proof		Market Regulatory Approval	
Design/Colour	☐	Product name	☐	National Legislation	☐
Size/Ratio	☐	Dosage form	☐	Marketing Authorisation	☐
Imprinting	☐	Strength	☐	Relevant languages	☐
Strength/Stripes	☐	Pack size	☐	Sign.: Date:	
Sign.: Date:		Prompts	☐		
		Item No./N. Vnr.	☐		
Colour-/Blueprint	☐	Sign.: Date:		Printed name:	
New C-/B request	☐				
Sign.: Date:				Artwork Case Report Issued	☐
				Sign. Date:	

ARTWORK

Please return to:
LEO Pharma A/S
Internal Market Access
Industriparken 55 - DK-2750 - Ballerup

Scale	Set-up	Item No.	Rev. No.	Sent by e-mail	
100%	US / WC	XXXXXX	XX	▼	
Subject: TBA 60,1 x 115 mm			Date: 04/01/06	Date	Date
Colour: PMS 485 + 301 + black			Sign.: OM	Sign.	Sign.

Preparation/Strength: Taclonex® ointment 15 g
Supplier / Place of production: Ireland
Comments: Pharmacode XXX Mock-up



4. PROOF OM FROM	Artwork Approval Stamp (AAS)		
Date 06/01/06	**Graphical Design**	**Editorial Proof**	**Market Regulatory Approval**
New proof requested ☐	Design/Colour ☐	Product name ☐	National Legislation ☐
PLEASE RETURN TO: INTERNAL MARKET ACCESS DEPT. 898	Size/Ratio ☐	Dosage form ☐	Marketing Authorisation ☐
	Imprinting ☐	Strength ☐	Relevant languages ☐
Sign.:	Strength/Stripes ☐	Pack size ☐	Sign.: Date:
Date:	Sign.: Date:	Prompts ☐	Printed name:
	Colour-/Blueprint ☐	Item No./N. Vnr. ☐	Artwork Case Report issued ☐
	New C-/B request, ☐	Sign.: Date:	Sign. Date:
	Sign.: Date:		

ARTWORK

Please return to:
LEO Pharma A/S
(Internal) Market Access
Industriparken 55 – DK-2750 – Ballerup

Scale	Set-up	Item No.	Batch no.	Sent by e-mail
100%	US / WC	XXXXXX	XX	▼

Subject	Date	Date	Date
CRT 35 x 28 x 135 mm	04/01/06		

Colour	Sign.	Sign.	Sign.
PMS 485 + black	OM		

Preparation Strength: Taclonex® ointment 30 g

Supplier / Place of production: Ireland

Comments: Pharmacode XXX

Mock-up

Red PMS 485

NDC 0430-3230-13

Taclonex®

(calcipotriene 0.005% and betamethasone dipropionate 0.064%)

Ointment

Rx only

For Topical Use Only

Net Wt. 30 g

Each gram contains 52.18 mcg of calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in an ointment base of mineral oil, PPG-15 stearyl ether, dl-alpha tocopherol and white petroleum.

Store Taclonex® Ointment between 20°C and 25°C (68°F and 77°F). Excursions permitted between 15-30°C (59-86°F).

Keep out of reach of children.

Usual Dosage: Apply once daily or as directed by physician. See insert for complete information.

NDC 0430-3230-13

Taclonex®

(calcipotriene 0.005% and betamethasone dipropionate 0.064%)

Ointment

Rx only

For Topical Use Only

Net Wt. 30 g

Manufactured by:
LEO Laboratories Ltd
(LEO Pharma)
Dublin, Ireland

LEO®

Marketed by:
Warner Chilcott (US), Inc.
Rockaway, NJ 07866 USA
U.S. Patent Nos. 4,866,048 and 5,753,013

1 0430-3230-13 1

Taclonex® (calcipotriene 0.005% and betamethasone dipropionate 0.064%) Ointment Net Wt. 30 g XXXXX-XX

XXXXXXXX

LOT

551 X 82 X 82

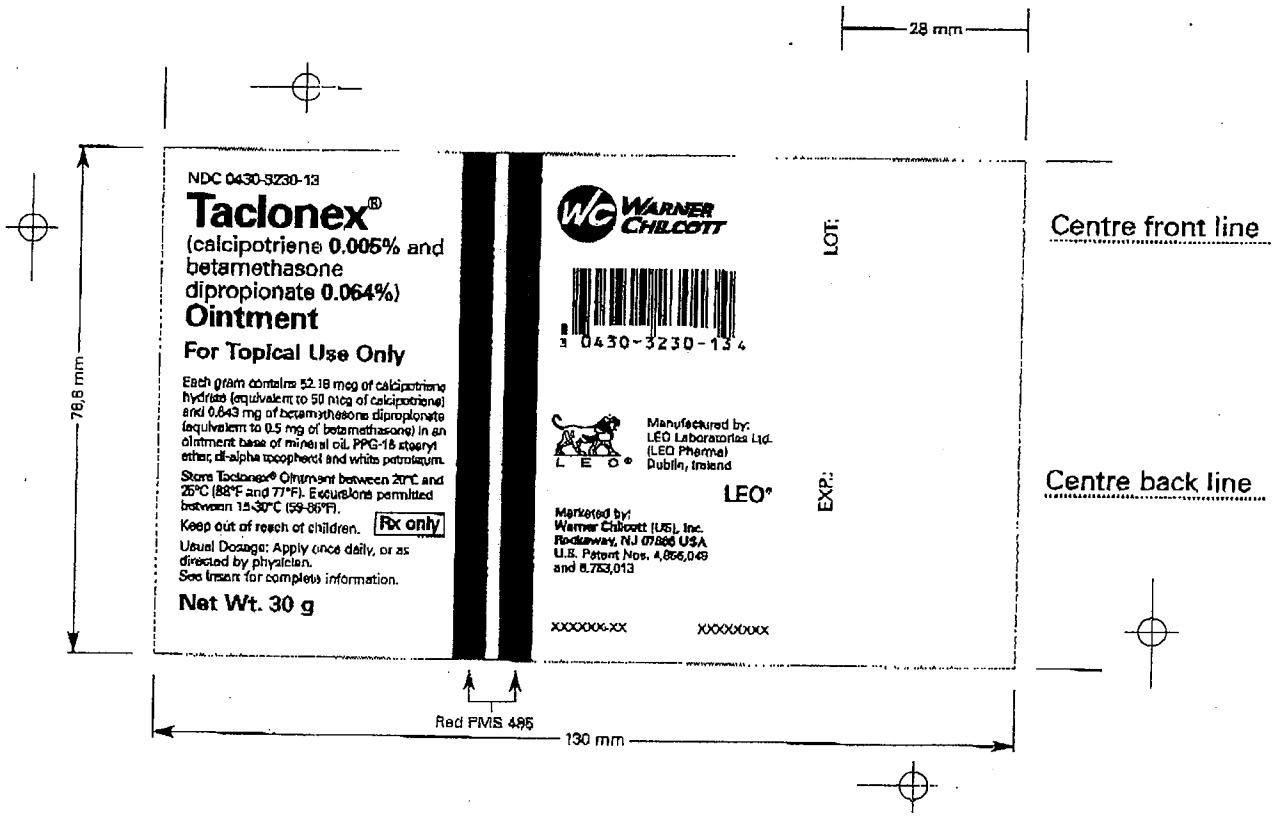
4. PROOF OM FROM	Artwork Approval Stamp (AAS)		
Date: 06/01/06	Graphical Design	Editorial Proof	Market Regulatory Approval
New proof requested ☐	Design/Colour ☐	Product name ☐	National Legislation ☐
PLEASE RETURN TO: LEO INTERNAL PRINT ADDRESS DEPT. 856	Size/Ratio ☐	Dosage form ☐	Marketing Authorisation ☐
Sign.:	Imprinting ☐	Strength ☐	Relevant languages ☐
Date:	Strength/Stripes ☐	Pack size ☐	Sign.: Date:
	Sign.: Date:	Prompts ☐	Printed name:
	Colour-/B'eprint ☐	Item No./N.Vnr. ☐	Artwork Case Report issued ☐
	New C-/B request. ☐	Sign.: Date:	Sign.: Date:
	Sign.: Date:		

ARTWORK

Please return to:
LEO Pharma A/S
Internal Market Access
Industriparken 55 – DK-2750 – Ballerup

Scale	Get-up	Item No.	Rev. No.	Sent by e-mail	
100%	US / WC	XXXXXX	XX	▼	
Subject: TBA 25 x 130 mm			Date: 04/01/06	Date:	Date:
Colour: PMS 485 + 301 + black			Sign.: OM	Sign.:	Sign.:

Preparation Strength: Taclonex® ointment 30 g
Supplier / Place of production: Ireland
Comments: Pharmacode XXX — Mock-up



Artwork Approval Stamp (AAS)

6. PROOF PR FROM	Graphical Design	Editorial Proof	Market Regulatory Approval
Date 06/01/06	Design/Colour ☐	Product name ☐	National Legislation ☐
New proof requested ☐	Size/Ratio ☐	Dosage form ☐	Marketing Authorisation ☐
PLEASE RETURN TO: INTERNAL MARKET ACCESS DEPT. 898	Imprinting ☐	Strength ☐	Relevant languages ☐
Sign.:	Strength/Stripes ☐	Pack size ☐	Sign.: Date:
Date:	Sign.: Date:	Prompts ☐	
	Colour-/Blueprint ☐	Item No./N. Vnr. ☐	Printed name:
	New C-/B request ☐	Sign.: Date:	Artwork Case Report issued ☐
	Sign.: Date:		Sign. Date:

ARTWORK

LEO

Please return to:
LEO Pharma A/S
Internal Market Access
Industriparken 55 – DK-2750 – Ballerup

Scale: 100%	Call-up: US / WC	Folder No.: 022606	Rev. No.: 00	Sent by e-mail ▼	
Subject: CRT 40 x 35 x 165 mm			Date: 29/12/05	Date	Date
Colour: PMS 485 + 301 + black			Sign: OM	Sign	Sign
Preparation: Taclonex® ointment 60 g			Supplied / Place of production: Ireland		
Comments: Pharmacode XXX	Mock-up				

NDC 0430-3230-15

Rx only

Taclonex®
(calcipotriene 0.005% and betamethasone dipropionate 0.064%)
Ointment

For Topical Use Only
Net Wt. 60 g

Warner Chilcott

Taclonex®
(calcipotriene 0.005% and betamethasone dipropionate 0.064%)
Ointment
Net Wt. 60 g
022606-00

Each gram contains 52.18 mcg of calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in an ointment base of mineral oil, PPG-15 stearyl ether, dl-alpha tocopherol and white petrolatum.

Store Taclonex® Ointment between 20°C and 25°C (68°F and 77°F). Excursions permitted between 15-30°C (59-86°F).

Keep out of reach of children.

Usual Dosage: Apply once daily, or as directed by physician. See insert for complete information.

LOT:
EXP:

NDC 0430-3230-15

Rx only

Taclonex®
(calcipotriene 0.005% and betamethasone dipropionate 0.064%)
Ointment

For Topical Use Only
Net Wt. 60 g

Warner Chilcott

Manufactured by:
LEO Laboratories Ltd.
(LEO Pharma)
Dublin, Ireland
LEO®

Marketed by:
Warner Chilcott (US), Inc.
Rockaway, NJ 07866 USA
U.S. Patent Nos. 4,866,048 and 6,753,013

3 0430-3230-15 8

40 x 35 x 165

Artwork Approval Stamp (AAS)

5. Proof from: OM
Date: 05/01/06
New proof requested ☐
Please return to: Internal Market Access Dept. 095
Sign:
Date:

Graphical Design	Editorial Proof	Market Regulatory Approval
Design/Colour ☐	Product name ☐	National Legislation ☐
Size/Ratio ☐	Dosage form ☐	Marketing Authorisation ☐
Imprinting ☐	Strength ☐	Relevant languages ☐
Strength/Stripes ☐	Pack size ☐	Sign: Date:
Sign: Date:	Prompts ☐	Printed name:
Colour-/Blueprint ☐	Item No./N. Vnr. ☐	Artwork Case Report Issued ☐
New C-/B request ☐	Sign: Date:	Sign: Date:
Sign: Date:		

ARTWORK

L E O

Please return to:
LEO Pharma A/S
Internal Market Access
Industriparken 55 - DK-2750 - Ballerup

Scale	Cut-up	Item No.	Rev. No.	Sent by e-mail
100%	US / WC	022606	00	▼
Subject: CRT 40 x 35 x 165 mm			Date: 29/12/05	Date
Colour: PMS 485 + 301 + black			Sign: OM	Sign

Preparation (Strength): Taclonex® ointment 60 g — Supplier / Place of production: Ireland

Comments: Pharmacode XXX Mock-up

NDC 0430-3230-15

Taclonex®
(calcipotriene 0.005% and betamethasone dipropionate 0.064%)
Ointment

Rx only

For Topical Use Only
Net Wt. 60 g

Each gram contains 52.18 mcg of calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in an ointment base of mineral oil, PPG-15 stearyl ether, dl-alpha tocopherol and white petrolatum.

Store Taclonex® Ointment between 20°C and 25°C (68°F and 77°F). Excursions permitted between 15-30°C (59-86°F).

Keep out of reach of children.

Usual Dosage: Apply once daily, or as directed by physician. See insert for complete information.

Taclonex®
(calcipotriene 0.005% and betamethasone dipropionate 0.064%)
Ointment
Net Wt. 60 g
022608-00

3230C05a

LOT:
EXP:

NDC 0430-3230-15

Taclonex®
(calcipotriene 0.005% and betamethasone dipropionate 0.064%)
Ointment

Rx only

For Topical Use Only
Net Wt. 60 g

Manufactured by:
LEO Laboratories Ltd.
(LEO Pharma)
Dublin, Ireland
LEO®

Marketed by:
Warner Chilcott (US), Inc.
Rockaway, NJ 07866 USA
U.S. Patent Nos. 4,866,048 and 6,753,013

3 0430-3230-15 8

40 x 35 x 165

Artwork Approval Stamp (AAS)

5. From: OM
Date: 06/01/06
New proof requested ☐
Please return to: Internal Market Access Dept. 6M
Sign:
Date

Graphical Design		Editorial Proof		Market Regulatory Approval	
Design/Colour	☐	Product name	☐	National Legislation	☐
Size/Ratio	☐	Dosage form	☐	Marketing Authorisation	☐
Imprinting	☐	Strength	☐	Relevant languages	☐
Strength/Stripes	☐	Pack size	☐	Sign: Date:	
Sign: Date:		Prompts	☐	Printed name:	
Colour-/Blueprint	☐	Item No./N. Vnr.	☐		
New C-/B request	☐	Sign: Date:		Artwork Case Report issued	☐
Sign: Date:				Sign: Date:	