CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 90-633

Name: Calcipotriene Ointment, 0.005%

Sponsor: Glenmark Generics Inc., USA

Approval Date: March 24, 2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-633

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-633

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 090633

Glenmark Generics Inc., USA
Attention: William McIntyre, Ph.D.
Executive Vice President, Regulatory Affairs
750 Corporate Drive
Mahwah, NJ 07430

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated May 20, 2008, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Calcipotriene Ointment, 0.005%.

Reference is also made to your amendments dated December 11, 2008; January 9, January 23 and February 5, 2009; and March 11, and March 16, 2010.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Calcipotriene Ointment, 0.005%, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Dovonex Ointment, 0.005%, of Leo Pharmaceutical Products, Ltd. (Leo).

We note that the reference listed drug product (RLD) upon which you have based this ANDA, Leo's Dovonex Ointment, 0.005%, is no longer being marketed in the United States and currently appears in the Discontinued section of the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book". Reference is made to the Federal Register notice dated March 9, 2010 (Volume 75, No. 45) in which the agency announced its determination that Leo's Dovonex Ointment,

0.005%, was not withdrawn from sale for reasons of safety or effectiveness. This determination allows the agency to approve ANDAs for the discontinued drug product.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS, See 505-1(i).

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling. Upon receipt and verification, we will transmit that

version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as "***Miscellaneous Correspondence – SPL for Approved ANDA 090633***".

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90633	ORIG-1	GLENMARK GENERICS INC USA	CALCIPOTRIENE

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

/s/

ROBERT L WEST
03/24/2010
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-633

LABELING

SAME S ZE ARTWORK Calcipotriene Ointment 60 g S ZE D A 30 6 mm X145 mm LENGTH

glenmark

NDC 68462-310-65

Calcipotriene Ointment, 0.005%

For Topical Dermatologic Use Only. Not for Ophthalmic, Oral or Intravaginal Use.

Rx only **60 g**

Each gram contains 0.05 mg of calcipotriene in an ointment base of disodium phosphate dihydrate, edetate disodium, mineral oil, petrolatum, propylene glycol, α tocopherol, steareth 2 and water.

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

WARNING: Keep Out of Reach of Children.

Store at controlled room temperature 15°C 25°C (59°F 77°F).

Do not freeze.

Lot no. and expiration date on crimp of tube.

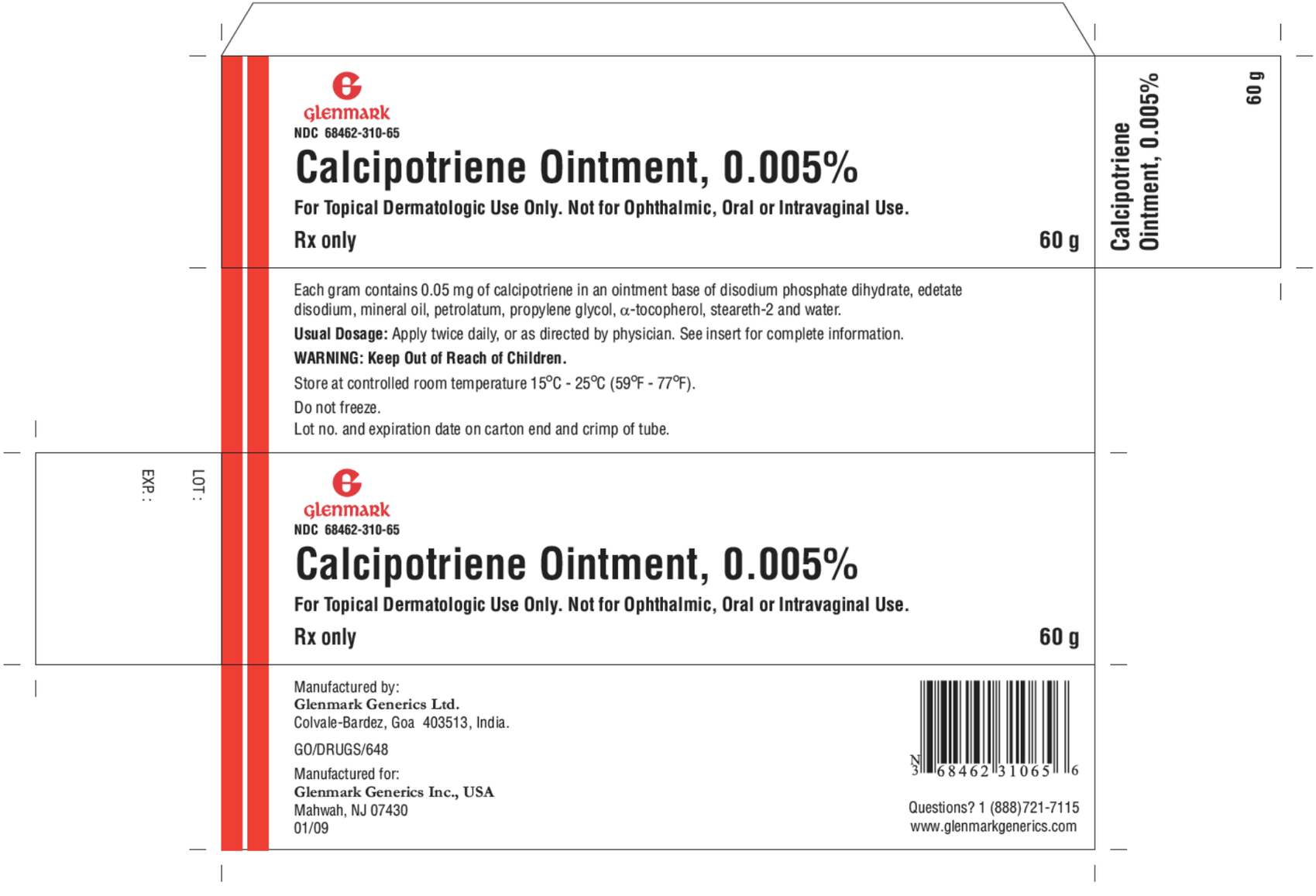
Manufactured by:
Glenmark Generics Ltd.
Colvale Bardez, Goa 403513, India.
GO/DRUGS/648
Manufactured for:
Glenmark Generics Inc., USA
Mahwah, NJ 07430
01/09

N 3 68462 31065 6

Questions? 1 (888)721 7115
www.glenmarkgenerics.com

145 mm

SAME SIZE ARTWORK
CARTON SIZE: 165 mm X 40 mm X 35 mm



Calcipotriene Ointment

0 004001 7

Calcipotriene Ointment

0 004001 7

Calcipotriene Ointment, 0.005%

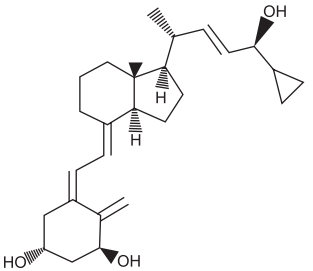
FOR TOPICAL DERMATOLOGIC USE ONLY.
Not for Ophthalmic, Oral or Intravaginal Use.

Rx Only

DESCRIPTION

Calcipotriene ointment, 0.005% contains he compound calcipotriene, a syn hetic vitamin D_3 derivative for topical dermatological use.

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



Calcipotriene is a white or off-white crystalline substance. Calcipotriene ointment contains calcipotriene 50 µg/g in an ointment base of disodium phosphate dihydrate, edetate disodium, mineral oil, pet olatum, p opylene glycol, α-tocophe ol, steareth-2 and purified 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-dehyd ocholesterol to vitamin D_3 (cholecalcife ol) in the skin. Calcipotriene is a syn hetic analog of vitamin D_3.

Clinical studies wi h radiolabelled ointment indicate hat approximately 6% (± 3%, SD) of he 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 he absorbed active is converted to inactive metabolites wi hin 24 hours of application.

Vitamin D and its metabolites are transported in he blood, bound to specific plasma p oteins. The active form of he vitamin, 1,25-dihy oxy vitamin D_3 (calcitriol), is known to be recycled via he liver and excreted in he bile. Calcipotriene metabolism following systemic uptake is rapid, and occurs via a similar pa hway to he natural hormone. The primary metabolites are much less potent than he parent compound.

There is evidence hat mate nal 1,25-d hydroxy vitamin D_3 (calcitriol) may enter the fetal circulation, but it is not known whe her it is excreted in human milk. The systemic disposition of calcipotriene is expected to be similar to hat of the naturally occurring vitamin.

CLINICAL STUDIES

Adequate and well-cont olled trials of patients treated wi h calcipotriene ointment have demonstrated imp ovement usually beginning after two weeks of therapy. This imp ovement continued in patients using calcipotriene once daily and twice daily. After 8 weeks of once daily calcipotriene, 56.7% of patients showed at least marked imp ovements (6.4% showed complete clearing). After 8 weeks of twice daily calcipotriene, 70.0% of patients showed at least marked imp ovement (11.3% showed complete clearing).

Subtracting percentages of patients using placebo (vehicle only) f om percentages of patients using calcipotriene who had at least marked imp ovements after 8 weeks yields 39.9% for once daily and 49.6% for twice daily. This adjustment for placebo effect indicated hat what might appear to be differences between once and twice daily use may reflect differences in he studies independent f om he frequency of dosing. Al hough there was a numerical difference in comparison ac oss 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 calcipotriene for periods of up to one year. In half of hese studies, patients who previously had not responded well to calcipotriene were excluded. The adverse events in hese extended studies included skin irritation in app oximately 25% of patients and worsening of psoriasis in app oximately 10% of patients. In one of these open label studies, half of he patients no longer required calcipotriene by 16 weeks of treatment, because of satisfactory herapeutic results.

INDICATIONS AND USAGE

Calcipotriene ointment, 0.005%, is indicated for he treatment of plaque psoriasis in adults. The safety and effectiveness of topical calcipotriene in dermatoses o her than psoriasis have not been established.

CONTRAINDICATIONS

Calcipotriene is contraindicated in hose patients with a history of hypersensitivity to any of he components of he preparation. It should not be used by patients with demonstrated hypercalcemia or evidence of vitamin D toxicity. Calcipotriene should not be used on he face.

PRECAUTIONS

General

Use of calcipotriene may cause irritation of lesions and sur ounding uninvolved skin. If irritation develops, calcipotriene should be discontinued.

For exte nal use only. Keep out of he reach of children. Always wash hands ho oughly after use.

Transient, rapidly reversible elevation of serum calcium has occurred with use of calcipotriene. If elevation in serum calcium outside he normal range should occur, discontinue treatment until normal calcium levels are restored.

Information for Patients

Patients using calcipotriene should receive he following information and instructions:

1. This medication is to be used as directed by he physician. It is for exte nal use only. Avoid contact wi h he face or eyes. As with any topical medication, patients should wash hands after application.
2. This medication should not be used for any disorder o her than that for which it was prescribed.
3. Patients should report to heir physician any signs of local adverse reactions.
4. Patients hat apply calcipotriene to exposed portions of he body should avoid excessive exposure to ei her natural or artificial sunlight (including tanning boo hs, sun lamps, etc.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

When calcipotriene was applied topically to mice for up to 24 mon hs 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 cont ol. In a study in which albino hairless mice were exposed to bo h UVR and topically applied calcipotriene, a reduction in the time required for UVR to indicate the formation of skin tumors was observed (statistically significant in males only), suggesting hat calcipotriene may enhance he effect of UVR to induce skin tumors. Patients that apply calcipotriene to exposed portions of the body should avoid excessive exposure to either natural or artificial sunlight (including tanning boo hs, sun lamps, etc.). Physicians may wish to limit or avoid use of phototherapy in patients that use calcipotriene.

Calcipotriene did not elicit any mutagenic effects in an Ames mutagenicity assay, a mouse lymphoma TK locus assay, a human lymphocyte ch omosome aberration assay, or in a mic onucleus 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 rep oductive performance.

Pregnancy

Teratogenic Effects: Pregnancy Category C

Studies of teratogenicity were done by he oral oute where bioavailability is expected to be app oximately 40-60% of he administered dose. In rabbits, increased mate nal 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 he 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 mate nal and fetal no-effect exposure levels in he rat (43.2 µg/m^2/day) and rabbit (17.6 µg/m^2/day) studies are app oximately equal to he expected human systemic exposure level (18.5 µg/m^2/day) f om dermal application. There are no adequate and well-controlled studies in pregnant women. Therefore, calcipotriene ointment should be used during pregnancy only if the potential benefit justifies he potential risk to the fetus.

Nursing Mothers

It is not known whe her calcipotriene is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when calcipotriene ointment, 0.005% is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of calcipotriene 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 han adults of systemic adverse effects when hey are treated with topical medication.

Geriatric Use

Of he total number of patients in clinical studies of calcipotriene ointment, approximately 12% were 65 or older, while app oximately 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 hose under 65 years (less severe).

ADVERSE REACTIONS

In cont olled clinical trials, the most frequent adverse reactions reported for calcipotriene were bu ning, 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. O her experiences reported in less han 1% of patients included skin at ophy, hyperpigmentation, hypercalcemia, and folliculitis. Once daily dosing has not been shown to be superior in safety to twice daily dosing.

OVERDOSAGE

Topically applied calcipotriene can be absorbed in sufficient amounts to p oduce systemic effects. Elevated serum calcium has been observed wi h excessive use of calcipotriene ointment.

DOSAGE AND ADMINISTRATION

Apply a hin layer of calcipotriene ointment once or twice daily and rub in gently and completely.

HOW SUPPLIED

Calcipotriene ointment, 0.005% is available in:

60 gram aluminum tube **NDC (68462-310-65)**

STORAGE

Store at cont olled oom temperature 15°C-25°C (59°F-77°F). Do not freeze.

Manufactured by:
Glenmark Generics Ltd.
Colvale-Bardez, Goa 403 513, India

Manufactured for:

Glenmark Generics Inc., USA
Mahwah, NJ 07430

Questions? 1 (888)721-7115
www.glenmarkgenerics.com

December 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-633

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 90-633

Date of Submission: May 20, 2008

Applicant's Name: Glenmark Pharmaceuticals

Established Name: Calcipotriene Ointment 0.005%

Labeling Deficiencies:

1. **CONTAINER:** (60 gram): Satisfactory in DRAFT

2. **CARTON:** (60 gram): Satisfactory in DRAFT

3. **INSERT:** DESCRIPTION: Inactives: Revise water to read as “purified water”

Revise your labeling, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with that of your last submission with all differences annotated and explained.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have Final Printed Labels and Labeling? Yes

Container

60 g – Satisfactory in FPL as of electronic submission.

Carton

60 g – Satisfactory in FPL as of electronic submission.

Package Insert: Satisfactory in FPL as of electronic submission.

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form:
- NDA Number: 20-273
- NDA Drug Name: Dovonex Ointment
- NDA Firm: Schering Corporation
- Date of Approval of NDA Insert and supplement: 20-273/S-009: Approved September 26, 2007
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side-by-side comparison
- Basis of Approval for the Carton Labeling: Side-by-side comparison
- Revisions needed post-approval: NO
- Patents/Exclusivities: Refer to chart below.

Patent Data – NDA 20-273

No	Expiration	Use Code	Use	File
		There is no unexpired patents for this product		II

Exclusivity Data - NDA 20-273

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There is no unexpired exclusivity for this product		NONE

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. MODEL LABELING

Review based on the labeling for the reference listed drug, Dovonex ointment, 0.005%, (NDA 20-273/S-009): Approved September 26, 2007.

2. PATIENTS/EXCLUSIVTIES:

Patent Data – NDA 20-273

No	Expiration	Use Code	Use	File
		There is no unexpired patents for this product		II

Exclusivity Data – NDA 20-273

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There is no unexpired exclusivity for this product		NONE

3. INACTIVE INGREDIENTS

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

Calcipotriene Ointment, 0.005% Glenmark Generics Ltd.	Dovonex® Ointment, 0.005% manufactured by Leo Laboratories Ltd
Calcipotriene (b) (4)	Calcipotriene (b) (4)
Dibasic sodium phosphate USP	Dibasic sodium phosphate
Edetate disodium USP	Edetate disodium
Mineral Oil USP (b) (4)	Mineral Oil
Propylene glycol USP	Propylene glycol
(b) (4) α-tocopherol USP-NF	Tocopherol
(b) (4) (b) (4) (Steareth 2)	Steareth 2
(b) (4) petrolatum USP (b) (4)	Petrolatum
Purified water USP	Water

4. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**
   - USP: None
   - RLD: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]
   - ANDA: (b) (4)

5. **DISPENSING STATEMENT COMPARISON**
   - USP: Preserve in well closed containers
   - RLD: None.
   - ANDA: None.

6. **PACKAGE CONFIGURATION**
   - RLD: 60 and 120 gram aluminum tubes
   - ANDA: 60 gram aluminum tube.

7. **CONTAINER/CLOSURE -** Calcipotriene Ointment, 0.005% is packed in a closed end nozzle, Collapsible (b) (4) Aluminum Tube with white cap having piercing point. The tube is crimped after the desired quantity of ointment is filled into the tube.

8. **FNISHED DOSAGE FORM**
   - RLD: Ointment
   - ANDA: Ointment

9. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**
   Glenmark Pharmaceuticals Limited
   Plot No. S-7, Colvale Industrial Estate,
   Colvale, Bardez, Goa 403513, India

Date of Submission: May 20, 2008

Primary Reviewer: **B. Weitzman** **Date:**

Team Leader: **J. Grace** **Date:**

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/s/

Beverly Weitzman
11/19/2008 04:03:33 PM
LABELING REVIEWER

John Grace
11/24/2008 10:35:01 AM
LABELING REVIEWER

APPROVAL SUMMARY #1

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 90-633

Date of Submission: December 11, 2008 and January 23, 2009

Applicant's Name: Glenmark Pharmaceuticals

Established Name: Calcipotriene Ointment 0.005%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have Final Printed Labels and Labeling? Yes

Container

60 g – Satisfactory in FPL as of **January 23, 2009** electronic submission.

\\Fdswa150\nonectd\N90633\N_000\2009-01-23\Container Labels\Tube\Calcipotriene ointment tube 60 g.pdf

Carton

60 g – Satisfactory in FPL as of **January 23, 2009** electronic submission.

\\Fdswa150\nonectd\N90633\N_000\2009-01-23\Container Labels\Carton\Calcipotriene ointment carton 60 g.pdf

Package Insert: Satisfactory in FPL as of **December 11, 2008** electronic submission.

\\Fdswa150\nonectd\N90633\N_000\2008-12-11\Package Insert\FPL\Calcipotriene Ointment FPL.pdf

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form:
- NDA Number: 20-273
- NDA Drug Name: Dovonex Ointment
- NDA Firm: Schering Corporation
- Date of Approval of NDA Insert and supplement: 20-273/S-009: Approved September 26, 2007
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side-by-side comparison
- Basis of Approval for the Carton Labeling: Side-by-side comparison
- Revisions needed post-approval: NO
- Patents/Exclusivities: Refer to chart below.

Patent Data – NDA 20-273

No	Expiration	Use Code	Use	File
		There is no unexpired patents for this product		II

Exclusivity Data - NDA 20-273

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There is no unexpired exclusivity for this product		NONE

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. MODEL LABELING

Review based on the labeling for the reference listed drug, Dovonex ointment, 0.005%, (NDA 20-273/S-009): Approved September 26, 2007.

2. PATIENTS/EXCLUSIVTIES:

Patent Data – NDA 20-273

No	Expiration	Use Code	Use	File
		There is no unexpired patents for this product		II

Exclusivity Data – NDA 20-273

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There is no unexpired exclusivity for this product		NONE

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There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

Calcipotriene Ointment, 0.005% Glenmark Generics Ltd.	Dovonex® Ointment, 0.005% manufactured by Leo Laboratories Ltd
Calcipotriene (b) (4)	Calcipotriene (b) (4)
Dibasic sodium phosphate USP	Dibasic sodium phosphate
Edetate disodium USP	Edetate disodium
Mineral Oil USP (b) (4)	Mineral Oil
Propylene glycol USP	Propylene glycol
(b) (4) α-tocopherol USP-NF	Tocopherol
(b) (4) (b) (4) (Steareth 2)	Steareth 2
(b) (4) petrolatum USP (b) (4)	Petrolatum
Purified water USP	Water

4. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**

- USP: None
- RLD: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]
- ANDA: (b) (4)

5. DISPENSING STATEMENT COMPARISON

- USP: Preserve in well closed containers
- RLD: None.
- ANDA: None.

6. PACKAGE CONFIGURATION

- RLD: 60 and 120 gram aluminum tubes
- ANDA: 60 gram aluminum tube.

7. CONTAINER/CLOSURE - Calcipotriene Ointment, 0.005% is packed in a closed end nozzle, Collapsible (b) (4) Aluminum Tube with white cap having piercing point. The tube is crimped after the desired quantity of ointment is filled into the tube.

8. FNISHED DOSAGE FORM

- RLD: Ointment
- ANDA: Ointment

9. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Glenmark Pharmaceuticals Limited
Plot No. S-7, Colvale Industrial Estate,
Colvale, Bardez, Goa 403513, India

Date of Submission: December 11, 2008 and January 23, 2009

Primary Reviewer: B. Weitzman **Date:**

Team Leader: J. Grace **Date:**

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/s/

Beverly Weitzman
2/4/2009 02:15:44 PM
LABELING REVIEWER

John Grace
2/6/2009 12:23:56 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-633

CHEMISTRY REVIEWS

ANDA 90 - 633

CALCIPOTRIENE Ointment, 0.005%

Glenmark Generics Inc., U.S.A.

Nashed E. Nashed, Ph.D.

Chemistry Division 1

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Chemistry Assessment **8**

Chemistry Review Data Sheet

1. ANDA: 90 - 633

2. REVIEW #: 1 (QbR.QOS)

3. REVIEW DATE: 9/30/08

4. REVIEWER: Nashed E. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	5/20/08
Acceptable for filing	5/23/08
Citizen Petition	8/6/08
Telephone Amendment (CMC/Commitment for USP <467>)	9/8/08

7. NAME & ADDRESS OF APPLICANT:

Name: Glenmark Generics Inc., USA

Address: 750 Corporate Drive, Mahwah, NJ 07430

Representative: William Mclntyre, Ph.D.

Telephone: 201-684-8017

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): CALCIPOTRIENE Ointment

9. LEGAL BASIS FOR SUBMISSION:

Paragraph II Patent Certification

Pursuant to § 505(j)(2)(A)(vii)(II) of the Food, Drug and Cosmetic ("FD&C") Act, Glenmark Generics Inc., USA ("Glenmark") hereby certifies that to the best of our knowledge there is no unexpired United States Patent(s) for Calcipotriene Ointment 0.005%.

Pursuant to 21 CFR §314.94(a)(3)(ii), information published in "Approved Drug Products with Therapeutic Equivalence Evaluations," Electronic Version published by the Food and Drug Administration as of the date of this filing, there is no unexpired exclusivity for Calcipotriene Ointment 0.005%.

Reference Listed Drug DOVONEX® (Calcipotriene) ointment, 0.005%, manufactured by Leo Laboratories Limited, holder of NDA 20-273

10. PHARMACOL CATEGORY:

PSORIASIS AGENT

11. DOSAGE FORM:

Ointment

12. STRENGTH/POTENCY:

0.005%

13. ROUTE OF ADMINISTRATION:

Topical

14. Rx/OTC DISPENSED: __XX_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

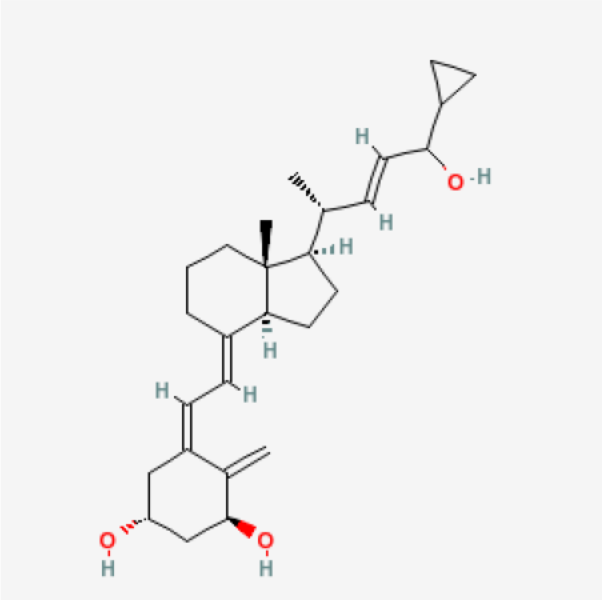
_____SPOTS product – Form Completed

__XX___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(5Z,7E,22E,24S)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol-

$C_{27}H_{40}O_3$ M.W. 412.6



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	9/19/07	By L. Huang
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application

5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	Not required		
Labeling	Pending		
Bioequivalence	Pending		
EA	Not required		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _XX___ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 90 - 633

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is not approvable due to minor deficiencies.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product Calcipotriene ointment, 0.005% will be marketed in 60 g tubes.

The drug substance is a white or almost white crystalline powder with empirical formula $C_{27}H_{40}O_3$ and molecular weight of 412.6

Calcipotriene ointment contains calcipotriene 50 µg/g in an ointment base of disodium phosphate dehydrate, edentate disodium, mineral oil, petrolatum, propylene glycol, α-tocopherol, stearate-2 and water.

B. Description of How the Drug Product is Intended to be Used

Calcipotriene ointment, 0.005% is indicated for the treatment of plaque psoriasis in adults.

Calcipotriene ointment is applied to the affected skin once or twice daily and rub in gently and completely.

How Supplied:

Calcipotriene ointment, 0.005% supplied in 60 gram aluminum tube

Storage Condition:

Store at controlled room temperature 15ºC – 25ºC (59ºF-77ºF). Do not freeze.

C. Basis or Approvability or Not-Approval Recommendation

This application is not approvable due to minor deficiencies.

Following this page,105 pages withheld in full - (b)(4)

30. MICROBIOLOGY:

N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS:

Not required.

32. LABELING:

Labeling is pending

33. ESTABLISHMENT INSPECTION:

EER is pending

34. BIOEQUIVALENCE:

Bio is pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Satisfactory

GLENMARK claims a categorical exclusion under 21 CFR 25.31(a).
GLENMARK certifies that in their opinion and to the best of its knowledge they are in compliance with all federal, state and local environmental rules and regulations.

ANDA: 90 - 633 APPLICANT: Glenmark Generics Inc., USA

DRUG PRODUCT: Calcipotriene Ointment, 0.005%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please provide an additional (b) (4)

2. Please revise your proposed (b) (4) revisions.

3. Please provide a list of the (b) (4) for example:

   - (b) (4)
   -
   -
   -
   -

   Additionally, the (b) (4)

4. Please provide (b) (4) requirements.

5. Please revise your (b) (4) .

6. Please revise (b) (4)

7. Please revise the (b) (4) [redacted]

8. Please provide (b) (4) [redacted]

9. Please provide a statements from the (b) (4) [redacted].

10 Please revise your (b) (4) [redacted].

11. Please provide (b) (4) [redacted]

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The firms referenced in your application should be in compliance with cGMP at the time of approval.

2. Please provide all available drug product room temperature stability data.

3. The Bioequivalence information you have provided is pending review by our Division of Bioequivalence. After the review is completed, any deficiencies found will be communicated to you under a separate cover.

4. The labeling information you have provided is pending review. After the review is completed, any deficiencies found will be communicated to you under a separate cover.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 90-633
ANDA DUP
Division File
Field Copy

Endorsements:

HFD-627/N.Nashed
HFD-620/P.Schwartz
HFD-617/R.Adigun

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

/s/

Nashed Nashed
10/16/2008 06:47:57 AM
CHEMIST

Rosalyn Adigun
10/17/2008 01:17:20 PM
CSO

Paul Schwartz
10/17/2008 05:37:45 PM
CHEMIST

ANDA 90 - 633

CALCIPOTRIENE Ointment, 0.005%

Glenmark Generics Inc., U.S.A.

Nashed E. Nashed, Ph.D.

Chemistry Division 1

Table of Contents

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Chemistry Review Data Sheet **3**

The Executive Summary **7**

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A. Recommendation and Conclusion on Approvability 7

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 7

II. Summary of Chemistry Assessments 7

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B. Description of How the Drug Product is Intended to be Used 7

C. Basis for Approvability or Not-Approval Recommendation 8

Chemistry Assessment **8**

Chemistry Review Data Sheet

1. ANDA: 90 - 633

2. REVIEW #: 2 (QbR.QOS)

3. REVIEW DATE: 2/10/09

4. REVIEWER: Nashed E. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	5/20/08
Acceptable for filing	5/23/08
Citizen Petition	8/6/08
Telephone Amendment (CMC/Commitment for USP <467>)	9/8/08
Labeling Amendment	12/11/08
Minor Amendment (CMC)	1/9/09
Labeling Amendment	1/23/09
Telephone Amendment (CMC)	2/5/09

7. NAME & ADDRESS OF APPLICANT:

Name: Glenmark Generics Inc., USA

Address: 750 Corporate Drive, Mahwah, NJ 07430

Representative: William Mclntyre, Ph.D.

Telephone: 201-684-8017

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): CALCIPOTRIENE Ointment

9. LEGAL BASIS FOR SUBMISSION:

Paragraph II Patent Certification

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11. DOSAGE FORM:

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12. STRENGTH/POTENCY:

0.005%

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Topical

14. Rx/OTC DISPENSED: __XX_Rx ___OTC

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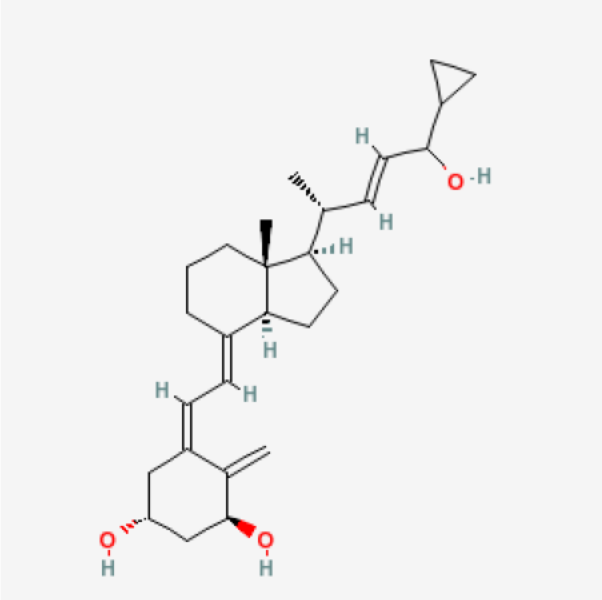
$C_{27}H_{40}O_3$ M.W. 412.6



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	III			4			

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B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

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CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	11/12/08	
Methods Validation	Not required		
Labeling	Acceptable	2/6/09	B. Weitzman
Bioequivalence	Pending		
EA	Not required		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes _xx__ No If no, explain reason(s) below:

The application is Minor

The Chemistry Review for ANDA 90 - 633

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable – Pending Bio.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

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A. Description of the Drug Product(s) and Drug Substance(s)

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C. Basis or Approvability or Not-Approval Recommendation

This application is approvable – Pending Bio.

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30. MICROBIOLOGY:

N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS:

Not required.

32. LABELING:

Labeling is acceptable on 2/6/09 by B. Weitzman.

33. ESTABLISHMENT INSPECTION:

EER is acceptable on 11/12/08

34. BIOEQUIVALENCE:

Bio is pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Satisfactory

GLENMARK claims a categorical exclusion under 21 CFR 25.31(a).
GLENMARK certifies that in their opinion and to the best of its knowledge they are in compliance with all federal, state and local environmental rules and regulations.

cc: ANDA 90-633
ANDA DUP
Division File
Field Copy

Endorsements:

HFD-627/N.Nashed
HFD-620/P.Schwartz
HFD-617/E.Chuh

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90633	ORIG-1	GLENMARK GENERICS INC USA	CALCIPOTRIENE
ANDA-90633	ORIG-1	GLENMARK GENERICS INC USA	CALCIPOTRIENE
ANDA-90633	ORIG-1	GLENMARK GENERICS INC USA	CALCIPOTRIENE
ANDA-90633	ORIG-1	GLENMARK GENERICS INC USA	CALCIPOTRIENE
ANDA-90633	ORIG-1	GLENMARK GENERICS INC USA	CALCIPOTRIENE
ANDA-90633	ORIG-1	GLENMARK GENERICS INC USA	CALCIPOTRIENE

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

/s/

NASHED E NASHED
09/28/2009

PAUL SCHWARTZ
09/30/2009

EUNJUNG E CHUH
10/05/2009

ANDA 90 - 633

CALCIPOTRIENE Ointment, 0.005%

Glenmark Generics Inc., U.S.A.

Nashed E. Nashed, Ph.D.

Chemistry Division 1

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C. Basis for Approvability or Not-Approval Recommendation 8

Chemistry Assessment **8**

Chemistry Review Data Sheet

1. ANDA: 90 - 633

2. REVIEW #: 2 (QbR.QOS)

3. REVIEW DATE: 2/10/09
   Revised: 3/4/2010

4. REVIEWER: Nashed E. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	5/20/08
Acceptable for filing	5/23/08
Citizen Petition	8/6/08
Telephone Amendment (CMC/Commitment for USP <467>)	9/8/08
Labeling Amendment	12/11/08
Minor Amendment (CMC)	1/9/09
Labeling Amendment	1/23/09
Telephone Amendment (CMC)	2/5/09

7. NAME & ADDRESS OF APPLICANT:

Name: Glenmark Generics Inc., USA

Address: 750 Corporate Drive, Mahwah, NJ 07430

Representative: William Mclntyre, Ph.D.

Telephone: 201-684-8017

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): CALCIPOTRIENE Ointment

9. LEGAL BASIS FOR SUBMISSION:

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Reference Listed Drug DOVONEX® (Calcipotriene) ointment, 0.005%, manufactured by Leo Laboratories Limited, holder of NDA 20-273

10. PHARMACOL CATEGORY:

PSORIASIS AGENT

11. DOSAGE FORM:

Ointment

12. STRENGTH/POTENCY:

0.005%

13. ROUTE OF ADMINISTRATION:

Topical

14. Rx/OTC DISPENSED: __XX_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__XX__Not a SPOTS product

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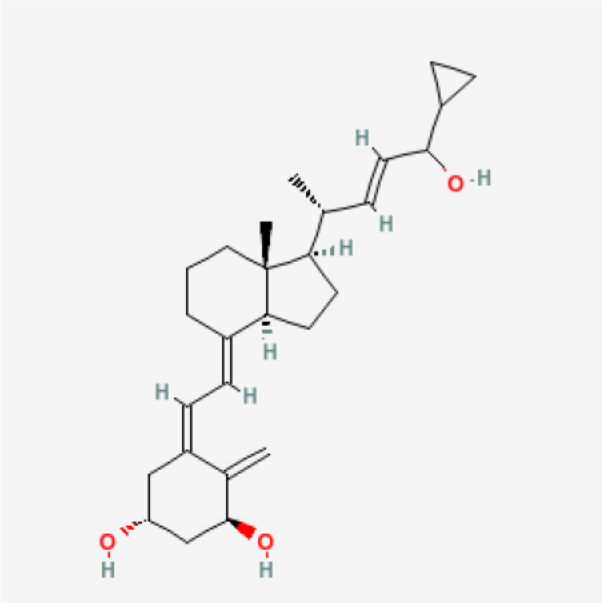
(5Z,7E,22E,24S)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol-

$C_{27}H_{40}O_3$ M.W. 412.6



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	3/4/2010	By N. Nashed
	III			4			

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B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	11/12/08	
Methods Validation	Not required		
Labeling	Acceptable	2/6/09	B. Weitzman
Bioequivalence	Acceptable	2/1/2010	N. Lee
EA	Not required		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes _xx__ No If no, explain reason(s) below:

The application is Minor

The Chemistry Review for ANDA 90 - 633

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable.

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C. Basis or Approvability or Not-Approval Recommendation

This application is approvable.

Following this page,127 pages withheld in full - (b)(4)

30. MICROBIOLOGY:

N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS:

Not required.

32. LABELING: Acceptable

Labeling is acceptable on 2/6/09 by B. Weitzman.

33. ESTABLISHMENT INSPECTION: Acceptable

EER is acceptable on 11/12/08

34. BIOEQUIVALENCE: Acceptable

Bio is acceptable on 2/1/2010 by N. Lee

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Satisfactory

GLENMARK claims a categorical exclusion under 21 CFR 25.31(a).
GLENMARK certifies that in their opinion and to the best of its knowledge they are in compliance with all federal, state and local environmental rules and regulations.

cc: ANDA 90-633
ANDA DUP
Division File
Field Copy

Endorsements:

HFD-627/N.Nashed
HFD-620/P.Schwartz
HFD-617/E.Chuh

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90633	ORIG-1	GLENMARK GENERICS INC USA	CALCIPOTRIENE

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

/s/

NASHED E NASHED
03/04/2010

BING CAI
03/05/2010

EUNJUNG E CHUH
03/05/2010

ANDA 90 - 633

CALCIPOTRIENE Ointment, 0.005%

Glenmark Generics Inc., U.S.A.

Nashed E. Nashed, Ph.D.

Chemistry Division 1

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Chemistry Assessment **8**

Chemistry Review Data Sheet

1. ANDA: 90 - 633

2. REVIEW #: 2 (QbR.QOS)

3. REVIEW DATE: 2/10/09
   Revised: 3/19/2010

4. REVIEWER: Nashed E. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	5/20/08
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Citizen Petition	8/6/08
Telephone Amendment (CMC/Commitment for USP <467>)	9/8/08

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Labeling Amendment	12/11/08
Minor Amendment (CMC)	1/9/09
Labeling Amendment	1/23/09
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Telephone Amendment (CMC)	3/11/2010
Telephone Amendment (CMC)	3/16/2010

7. NAME & ADDRESS OF APPLICANT:

Name: Glenmark Generics Inc., USA

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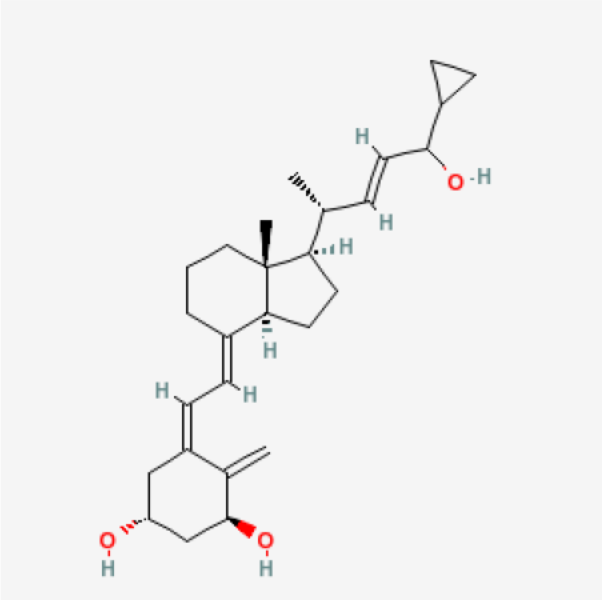
__XX___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(5Z,7E,22E,24S)-24-cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol-

$C_{27}H_{40}O_3$ M.W. 412.6



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	3/4/2010	By N. Nashed
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application

5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	11/12/08	
Methods Validation	Not required		
Labeling	Acceptable	2/6/09	B. Weitzman
Bioequivalence	Acceptable	2/1/2010	N. Lee
EA	Not required		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes _xx__ No If no, explain reason(s) below:

The application is Minor

The Chemistry Review for ANDA 90 - 633

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product Calcipotriene ointment, 0.005% will be marketed in 60 g tubes.

The drug substance is a white or almost white crystalline powder with empirical formula $C_{27}H_{40}O_3$ and molecular weight of 412.6

Calcipotriene ointment contains calcipotriene 50 µg/g in an ointment base of disodium phosphate dehydrate, edentate disodium, mineral oil, petrolatum, propylene glycol, α-tocopherol, stearate-2 and water.

B. Description of How the Drug Product is Intended to be Used

Calcipotriene ointment, 0.005% is indicated for the treatment of plaque psoriasis in adults.

Calcipotriene ointment is applied to the affected skin once or twice daily and rub in gently and completely.

How Supplied:

Calcipotriene ointment, 0.005% supplied in 60 gram aluminum tube

Storage Condition:

Store at controlled room temperature 15ºC – 25ºC (59ºF-77ºF). Do not freeze.

C. Basis or Approvability or Not-Approval Recommendation

This application is approvable.

Following this page,131 pages withheld in full - (b)(4)

30. MICROBIOLOGY:

N/A

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS:

Not required.

32. LABELING: Acceptable

Labeling is acceptable on 2/6/09 by B. Weitzman.

33. ESTABLISHMENT INSPECTION: Acceptable

EER is acceptable on 11/12/08

34. BIOEQUIVALENCE: Acceptable

Bio is acceptable on 2/1/2010 by N. Lee

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Satisfactory

GLENMARK claims a categorical exclusion under 21 CFR 25.31(a).
GLENMARK certifies that in their opinion and to the best of its knowledge they are in compliance with all federal, state and local environmental rules and regulations.

cc: ANDA 90-633
ANDA DUP
Division File
Field Copy

Endorsements:

HFD-627/N.Nashed
HFD-620/B.Cai
HFD-617/E.Chuh

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90633	ORIG-1	GLENMARK GENERICS INC USA	CALCIPOTRIENE

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

/s/

NASHED E NASHED
03/22/2010

BING CAI
03/22/2010

EUNJUNG E CHUH
03/22/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-633

BIOEQUIVALENCE REVIEWS

Review of
A Bioequivalence Study
with
Clinical Endpoints

ANDA # 090633

Calcipotriene Ointment, 0.005%
Glenmark Generics Inc., USA

Nicole Lee, Pharm.D.
Clinical Review Team

Submission dates reviewed: May 20, 2008

Date of Review: January 27, 2010

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Review of a Bioequivalence Study with Clinical Endpoints for ANDA 090633

Executive Summary

Glenmark Generics Inc., USA (Glenmark) conducted a double-blind, randomized, multi-center, parallel-group, placebo-controlled study in the treatment of plaque psoriasis to demonstrate that Glenmark's Calcipotriene Ointment, 0.005%, is safe and bioequivalent to Dovonex® (calcipotriene) Ointment, 0.005%. The sponsor reported "clinical success" rates of 39.74% and 40.26% for the test and reference products, respectively on Day 56. The difference in success rates was -0.52%, with a 90% confidence interval (CI) of (-10.41%, +9.36%) in the per-protocol (PP) population. The "treatment success" rates were reported as 43.05% and 37.01% for the test and reference products, respectively, on Day 56. The difference in success rates was 6.03%, with a 90% confidence interval (CI) of (-3.84%, +15.90) in the per-protocol (PP) population. Both test and reference products showed superiority over the vehicle in the intent-to-treat (ITT) population, with p-values $\leq$ 0.001. The FDA statistical analysis showed clinical success rates of 40% and 41% for the test and reference products, respectively on Day 56. The difference in success rates was -1.0 % and a 90% CI of (-10.5%, 9.5%), which is within the bioequivalence limits of (-20%, +20%). Treatment success rate was 43% and 36% for the test and reference products, respectively. The difference in success rates was 7% and a 90% CI of (-3.1%, 16.8%), which is within the bioequivalence limits of (-20%, +20%). Both test and reference products showed superiority over the vehicle in the intent-to-treat (ITT) population, with p-values < 0.001 for test vs. placebo and reference vs. placebo for treatment success and reference vs. placebo for clinical success, and p-value=0.0017 for test vs. placebo for clinical success. A total of 507 patients were enrolled and randomized. 498 patients were included in the Intent-to-Treat (ITT) population and 383 were included in the Per Protocol (PP) population.

I. Recommendation on Approval

The data submitted to ANDA 090633, using the two primary endpoints of clinical success and treatment success at Day 56, are adequate to demonstrate bioequivalence of Glenmark's Calcipotriene Ointment, 0.005%, with the reference listed drug, Leo Laboratories, Ltd.'s Dovonex® Ointment, 0.005%. Therefore, the test product is recommended for approval.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The study #GLK602 was a randomized, double blind, parallel design, comparative study of Glenmark's Calcipotriene Ointment, 0.005%, versus the reference listed drug, Dovonex® Ointment, 0.005%, in the treatment of plaque psoriasis. Five hundred seven (507) patients were randomized in a 2:2:1 ratio to receive the test, reference or vehicle ointments once a day for 56 days.

B. Comparative Efficacy

The two co-primary endpoints of this study defined by the sponsor are 1) a clinical success at Day 56 and 2) treatment success at Day 56. Clinical success was defined by the sponsor as a Physicians Global Assessment (PGA) score of 0 or 1. Treatment success was defined by the sponsor as a score of 0 or 1 for each of the individual signs and symptoms which include scaling, erythema and plaque elevation. According to the FDA's statistical analysis, the clinical success rates were 40% and 41% for the test and reference products, respectively on Day 56. The difference in success rates was -1.0 % and a 90% CI of -10.5%, 9.5%), which is within the bioequivalence limits of (-20%, +20%). Treatment success rate was 43% and 36% for the test and reference products, respectively. The difference in success rates was 7% and a 90% CI of (-3.1%, 16.8%), which is within the bioequivalence limits of (-20%, +20%). Both test and reference products showed superiority over the vehicle in the intent-to-treat (ITT) population, with p-values < 0.001 for test vs. placebo and reference vs. placebo for treatment success and reference vs. placebo for clinical success, and p-value=0.0017 for test vs. placebo for clinical success.

C. Comparative Safety

Of the 507 patients in the study, 163 experienced one or more treatment-emergent AEs during the study, 53 (26.77%) in the test group, 81 (39.32%) in the reference group and 29 (28.16%) in the placebo group. The most frequently reported adverse event was “headache” that was reported by 5.05%, 6.80% and 3.88% of the patients in the test, reference and placebo groups respectively. The other events reported by more than 2% of patients in any one treatment group were: cough, diarrhea, headache, nasopharyngitis, pain and pruritis. One death was reported in the study. Patient 1545 died while enrolled in the study. He was randomized to placebo. The subject had a complicated hospital course with a number of medical problems, which ultimately contributed to his death. The Serious Adverse Event (SAE) was deemed unrelated to the study medication by the Principal Investigator. There were two other SAEs reported. Patient 1547, randomized to placebo, was admitted to the hospital and underwent cardiac catheterization and subsequently underwent 4 vessel coronary artery bypass grafting. The SAE was deemed unrelated to the study medication by the Investigator. Patient 1508, randomized to the reference group, underwent a scheduled elective in-patient hemorrhoidectomy. The SAE was deemed unrelated to the medication by the Investigator.

Clinical Review

I. Introduction and Background

Psoriasis

Psoriasis is a common benign, acute or chronic skin disease with a prevalence of approximately 2% worldwide. Psoriasis has several variants, with the most common being the plaque type. The disease is clinically characterized by erythematous, dry scaling patches with recurring remissions and exacerbations. Flares may be related to systemic and environmental factors.

Signs and symptoms may include arthritis, pruritis and silvery scales on red plaques most commonly on the knees, elbows and scalp. The cause of this disease is unknown, but possibly may be a genetic error in mitotic control.

A. Drug Established Name, Drug Class

Drug Established Name: Calcipotriene Ointment, 0.005%
Drug Class: Synthetic vitamin D3 derivative

B. Trade Name of Reference Drug, NDA number, Date of approval, Approved Indication(s), Dose, Regimens

Reference Drug (NDA number): Dovonex® Ointment, 0.005%, Leo Laboratories, Ltd. (NDA #20-273, discontinued on May 1, 2007 for limited usefulness and commercial viability in lieu of alternative products available for the topical treatment of plaque psoriasis [according to the Psoriasis Association website]) Lachman Consultant Services, Inc. submitted a Citizen Petition on August 6, 2008 to determine whether the listed drug has been voluntarily withdrawn for safety or efficacy.

Date of approval: 12/29/1993
Approved indication(s): This drug is indicated for the treatment of plaque psoriasis in adults.
Recommended dosing regimens: Apply a thin layer of Dovonex Ointment once or twice daily and rub in gently and completely.

C. Regulatory Background

(b) (4), on behalf of the firm, sent a protocol P05-022 dated May 19, 2005. The Clinical Team reviewed the protocol and provided comments to (b) (4) on June 6, 2006.

D. Other Relevant Information

None

II. Description of Clinical Data and Sources

Study Centers/Investigators:

Site #	#of patients enrolled (total=507)	Principal Investigator	Location
1	110	Hector Wiltz, MD, CCTI	Miami, FL
2	14	Jennifer Claire Waguespack-LaBiche, MD	Lafayette, LA
3	18	Terry M. Jones, MD	College Station, TX
4	24	Steven Kempers, MD	Fridley, MN
5	14	Patricia P. Westmoreland, MD	Simpsonville, SC
6	14	Michael Joseph Donahue, MD	Wilmington, NC
7	1	Paul Getz, MD	West Dundee, IL
8	5	John Arthur Hoekstra, MD	Richmond, VA
9	0	Gordon D. Raphael, MD	Bethesda, MD
10	13	Toivo Rist, MD	Knoxville, TN
11	12	Dowling B. Stough, IV, MD	Hot Springs, AR
12	5	Jonathan S. Weiss, MD	Snellville, GA
13	6	Michael Schneider, MD	Germantown, TN
14	10	Robert B. Rhoades, MD	Martinez, GA
15	2	Juliann S. Wallner	Littleton, CO
16	19	James Alan Solomon, MD, PhD	Ormond Beach, FL
17	20	Thomas M. Krop, MD	Virginia Beach, VA
18	20	Daniel M. Stewart, DO	Clinton Township, MI
19	2	Louis Bonavita, Jr., MD	East Syracuse, NY
20	6	David Ira Wolf, MD	Vista, CA
21	17	George Louis Raad, MD	Charlotte, NC
22	18	Debra Chih-Fen Liu, MD	Winston-Salem, NC
23	14	Lawrence G. Ratcliff, MD	Dayton, OH
24	10	Robert Seth Haber, MD	South Euclid, OH
25	17	Patricia C. Lee, MD	Houston, TX
26	5	Harry Collins, MD	Edison, NJ
27	20	Robert W. Loss, Jr., MD	Rochester, NY
28	25	Stephen K. Tyring, MD, PhD, MBA	Houston, TX
29	6	Howard Lee Sofen, MD	Los Angeles, CA
30	8	Adnan Nasir, MD, PhD	Raleigh, NC
31	36	Alicia Renee Barba, MD	Miami, FL
32	8	Michael H. Gold, MD	Nashville, TN
33	8	Robert Glen Brown, MD	Jacksonville, FL

Study Period: The time from the first patient enrolled to the last patient completed was approximately 9 months from 4/24/2007 to 1/31/2008.

Enrollment: A total of five hundred seven (507) patients were randomized into the study in a 2:2:1 ratio (Test:Reference:Placebo) to one of the three following treatment regimens:

Test: Calcipotriene 0.005% topical ointment (Glenmark Generics Inc., USA)), Batch # Q15317003, expiration date: 12/2008

Reference: Dovonex® (calcipotriene ointment), 0.005%, Bristol Myers Squibb, Batch # EA5258, expiration date: 06/2008

Placebo: Topical ointment base only, Glenmark Generics Inc., USA), Batch # QP15317001, expiration date: n/a

III. Clinical Review Methods

A. Overview of Materials Consulted in Review

Original Submission:
ANDA 090633, vol. 1.3 and **\\FDSWA150\NONECTD\N90633\N_000\2008-05-20**

B. Overview of Methods Used to Evaluate Data Quality and Integrity

Division of Scientific Investigations (DSI) :
A DSI inspection was not requested due to a history of previous acceptable inspections of three of the largest clinical sites for clinical endpoint bioequivalence studies of other topical products.

C. Were Trials Conducted in Accordance with Accepted Ethical Standards?

According to the sponsor, this study was conducted in compliance with U.S. Food and Drug Administration (FDA) regulations (21 CFR Parts 50, 54, 56, and 312), the ethical principles of the Declaration of Helsinki, all applicable International Conference on Harmonisation (ICH) guidelines, and all local laws and regulations concerning clinical studies. Prior to initiation of the study, each Principal Investigator signed Form FDA 1572, agreeing to conduct the trial in compliance with the protocol and according to Good Clinical Practice (GCP). The protocol, informed consent form, and any advertisements employed to recruit subjects were approved by an Investigational Review Board (IRB) whose operations were in compliance with Section 56 of Title 21 of the Code of Federal Regulations (CFR), prior to enrollment of any study subjects.

D. Evaluation of Financial Disclosure:

All Principal Investigators and Sub-Investigators signed a financial disclosure statement with respect to this clinical study. These statements were made in compliance with 21 Code of Federal Regulations (CFR) Part 54 and confirm that no financial arrangements with the Principal Investigators or Sub-Investigators have been made whereby the study outcome could affect compensation, that the Principal Investigators and Sub-Investigators have no proprietary interest in the tested product, that the Principal Investigators and Sub-

Investigators do not have a significant equity interest in the sponsor of the covered study, and that the Principal Investigators and Sub-Investigators have not received significant payment of other sorts.

IV. Review of Bioequivalence Study with Clinical Endpoints

A. Brief Statement of Conclusions

The sponsor's study confirms the bioequivalence of the test product with the reference product. The FDA's calculated 90% CI of the difference in clinical success rate between the test and reference products is (-10.5%, 9.5%) and 90% CI of the difference in treatment success rate between the test and reference products is (-3.1%, 16.8%), which are within the bioequivalence limits of (-20%, +20%).

B. General Approach to Review of the Comparative Efficacy of the Drug

The sponsor's study (protocol #GLK602) was reviewed to determine bioequivalence of the test product and the reference product. The primary endpoints of this study are a 1) clinical success at Day 56 and 2) treatment success at Day 56. Clinical success was defined by the sponsor as a Physicians Global Assessment (PGA) score of 0 or 1. Treatment success was defined by the sponsor as a score of 0 or 1 for each of the individual signs and symptoms which include scaling, erythema and plaque elevation.

C. Detailed Review of Bioequivalence Studies with Clinical Endpoints

Protocol Review:

Sponsor's protocol#: GLK-602

Title: A Randomized, Double-Blind, Placebo Controlled, Parallel Design, Multi-site Clinical Study to Evaluate the Bioequivalence of Calcipotriene Ointment 0.005% (Glenmark Generics Inc., USA)) to Dovonex® (calcipotriene ointment) 0.005% (Bristol Myers Squibb) in Patients with Moderate to Severe Plaque Psoriasis.

Objective: The primary objective of this study was to evaluate the efficacy and safety of the test formulation of calcipotriene 0.005% topical ointment compared to the already marketed formulation Dovonex® (calcipotriene ointment) 0.005% in patients with moderate to severe plaque psoriasis. In addition, the efficacy of both the test and reference ointments was compared to a placebo ointment.

Study Design: This was a randomized, double-blind, parallel-group study design comparing the following three products:

1. Test: Calcipotriene Ointment, 0.005%, Glenmark Generics Inc., USA), lot # Q15317003
2. Reference: Dovonex® Ointment (calcipotriene ointment, 0.005%), Bristol Myers Squibb, lot #EA5258

3. Placebo (Topical ointment base only): Glenmark Generics Inc., USA), lot #QP15317001

Blinding/Randomization/Retention Sample:
All test products were blinded and packaged in sealed boxes. The study staff dispensed the medication only to those patients identified by the Investigator. Each site had a staff member who is identified as the "Independent Dispenser." This person was responsible for the dispensing of the blinded medication and the receipt of used/partial/unused tubes of medication during the visit.

Subjects were assigned treatments in sequential order. The randomization was generated by (b) (4) and held by (b) (4) until after the database had been locked.

Prior to starting the study and at any time new drug supplies were shipped, one block of study drug (blinded study drug supply for 5 patients, including 2 test patients, 2 reference patients and 1 placebo patient) was removed at random by the investigative site to be held as retention samples.

Study Population: Patients who met the following criteria were eligible for the study:

Inclusion Criteria
1. Male or non-pregnant, non-lactating female, 18 years of age or older.
2. Signed informed consent form, which meets all criteria of current FDA regulations.
3. If female and of child bearing potential, abstained from sexual intercourse or used a reliable method of contraception during the study.
4. Had a definite clinical diagnosis of stable plaque psoriasis involving >5% of the body surface area (BSA).
5. Had a combined total lesion severity score (TLSS of $\geq$7) for the target lesion.
6. Had a plaque elevation score $\geq$3 (moderate) for the target lesion.
7. The target lesion must have had an area of at least 5 cm^2.
8. Had a Physicians Global Assessment (PGA) score of 3 (moderate), 4 (moderately severe) or 5 (severe) at baseline for the overall disease severity.

Exclusion Criteria
1. Patient was under the age of 18 years old.
2. Female who was pregnant, nursing, planned to become pregnant during the duration of the study, or if of child bearing potential and sexually active was not prepared to use appropriate contraceptive methods to avoid pregnancy.
3. Had a BSA involvement less than 5%.
4. Total lesion severity score of <7 for the target lesion.
5. A score of <3 (moderate) for the individual sign of plaque elevation for the target lesion.
6. Target lesion area less than 5 cm^2.
7. Physicians Global Assessment Score <3 (moderate) or > 5 (severe) at baseline for the overall disease severity.
8. Patient had current diagnosis of types of psoriasis other than chronic plaque psoriasis (i.e. acute, guttate, erythrodermic, exfoliative or pustular psoriasis) or had psoriasis of any kind on the

face or scalp that will require active treatment during the study. Nonprescription anti-psoriatic shampoos were allowed during the study when applied solely to the scalp.
9. Patient had a history of psoriasis that had been unresponsive to topical calcipotriene or vitamin D derivative treatment.
10. In the Investigator's opinion, the patient had other dermatological conditions, such as atopic or contact dermatitis, that may interfere with the clinical assessments of the signs and symptoms of psoriasis.
11. Patient had a history of allergy or sensitivity to calcipotriene or vitamin D analogues, or history of any drug hypersensitivity or intolerance which, in the opinion of the Investigator, could have compromised the safety of the patient or the results of the study.
12. Patient had a significant history or current evidence of chronic infectious disease, system disorder, organ disorder or other medical condition that in the Investigator's opinion would place the study patient at undue risk by participation in the study.
13. Patient had baseline albumin corrected serum calcium values that exceed the upper limit of normal range for the gender and age of the patient according to the normal ranges provided by the central clinical laboratory.
14. Patient had signs or symptoms of possible vitamin D toxicity.
15. Patient is currently being treated with anti-malarial products or is taking lithium.
16. Patient started beta-blocker therapy within 3 months of the study. Patients who have been on a stable dose of beta-blockers for at least 3 months prior to the first dose of study drug and will remain on the same dose throughout the study may be eligible.
17. Patient is currently receiving or had received any radiation therapy, anti-neoplastic agents or immunosuppressant medication within 4 weeks prior to the first dose of study drug.
18. Patient received any systemic or photo antipsoriatic therapy, within 8 weeks of the first dose of study drug.
19. Patient was treated within 12 weeks (or five half lives whichever is less) of the first dose of study drug with any biological therapies for psoriasis.
20. Patient received any oral or systemic steroids within 4 weeks of the first dose of the study drug. The use of inhaled or intranasal corticosteroids was acceptable as long as usage had been stable for at least 2 weeks prior to the first dose of study drug and was continued during the study.
21. Female using hormonal contraceptives for less than one complete cycle prior to entering the study.
22. Patient who used any topical antipsoriatic agents of any kind or any topical corticosteroids for any reason within 2 weeks prior to first use of study drug. Nonprescription antipsoriatic shampoos used only on the scalp were allowed during the study.
23. Receipt of any drug as part of a research study within 30 days prior to first dosing.
24. In the opinion of the Investigator, the patient will not be compliant with the requirements of the study procedures.
25. Previous participation in this study.

Compliance

Patients were requested to bring the dosing diary with them at each visit and it was reviewed for compliance with the study requirements. Patients who had not applied the study drug on at least 75% of the required times or more than 125% of the required time since being dispensed medication were discontinued from the study.

Patients were discontinued from the study for any of the following reasons:

1. Patient withdrew consent.
2. Significant adverse event that led Investigator or patient to withdraw for safety reason.
3. Non-compliance with protocol requirements, including use of restricted medications.
4. Pregnancy.
5. Significant worsening of psoriasis such that Investigator and/or patient believed it was in the best interest of the patient to withdraw from the study.
6. During the course of the study the patient's albumin corrected serum calcium levels rose above the upper limit of normal range.

Prohibited Concomitant Therapy

- Any prescription or over the counter (OTC) topical, systemic, phototherapy or biological medications or treatments for the psoriasis. Nonprescription antipsoriatic shampoos were allowed if used only on the scalp.
- Any oral, topical or injectable steroid drug use. Use of inhaled or nasal steroids was allowable, on condition that the patient had been on a stable dosing regimen for the two weeks prior to the first dose of study drug and would remain on the same course of treatment throughout the study. Females using hormonal contraceptives were to be using the same method/type for at least one complete cycle prior to first dose of study drug and were required to continue to use the same method/type throughout the study.
- Prescription or OTC, high doses of vitamin D or vitamin D analogues (greater than 400IU/day) or calcium supplement therapy. Over the counter multi-vitamins that included Vitamin D or calcium were allowed on condition the patient had been on a stable dose for at least 2 weeks prior to first dose of the study drug and remained on the same dose throughout the study and the product was not specifically labeled as containing high vitamin D (greater than 400 IU/day) or calcium content.
- Use of any other topical products, medications, sunscreens, cosmetics that the Investigator considered may affect the patient's psoriasis or would prevent the Investigator from making an accurate assessment of the patient's signs and symptoms.
- Use of any anti-malarial products, lithium or beta-blockers. Patients who were on a stable dose regimen of beta-blockers for at least 3 months prior to first dose of study drug and stayed on the same dosing regimen throughout the study were allowed.

Procedures

	Visit 1 Baseline	Day 0	Visit 2 Interim Day 7±2	Visit 3 Interim Day 14±2	Visit 4 Interim Day 28±3	Visit 5 Interim Day 42±3	Visit 6 Final Day 56±4
Informed Consent	X						
Demographics	X						
Medical History	X						
Vital Signs	X						X
Height/Weight	X						
Pregnancy Test	X						X
BSA	X						
% BSA	X		X	X	X	X	X
TLSS	X		X	X	X	X	X
PGA	X		X	X	X	X	X
Clinical Lab Test	X						X
Clinical Chemistry	X		X	X	X	X	X
Dispense Medication		X			X		
Patient Diaries		X	X	X	X	X	X
Adverse Events			X	X	X	X	X
Con Medications	X	X	X	X	X	X	X
Study Discharge							X

Patients were told to apply the study drug as a thin layer to all affected areas, avoiding the face, once a day for 56 days. The "target lesion" had to have an area of at least 5cm^2.

Efficacy Measurements:

Physicians Global Assessment (PGA)

0	Clear. No Evidence of psoriasis other than slight residual coloration or hyper/hypopigmentation. No noticeable plaque elevation.
1	Almost Clear. Minimal scaling and none or minimal residual erythema, overall plaque elevation is minimal and just above normal skin level.
2	Mild. Some scaling present although not extensive, plaque elevation, discernable but not pronounced, erythema generally light red in color.
3	Moderate. Scaling easily observed with red erythema. Plaque elevation generally distinct and elevated with rounded, sloping edges. At least 5% of BSA affected.
4	Moderately Severe. Extensive rough scaling with erythema moderate to dark red. Very noticeable plaque elevation with hard edges. At least 5% of BSA affected.
5	Severe. Scaling is course and thick and cracking may be evident. Erythema is generally dark red. Plaque elevation is pronounced with hard and sharp edges. More than 10% but less than 20% BSA involvement.

6	Very severe. Scaling is very coarse with pronounced cracking and fissures. Erythema is dark red with possible induration. Plaques are markedly elevated with sharp and hard edges 20% or more BSA involvement.

Total Lesion Severity Scale (TLSS):

Scaling

0	Clear. No evidence of scaling.
1	Almost Clear. Occasional fine scales hardly noticeable.
2	Mild. Slight but definite roughness, fine scale present, no cracking.
3	Moderate. Moderate roughness, somewhat coarse scaling.
4	Severe. Marked roughness, coarse/thick scaling, cracking may be evident.
5	Very severe. Very thick scales covering extensive area severe cracking/fissures may be evident.

Erythema

0	Clear. No evidence of erythema.
1	Almost Clear. Pink discoloration, minimal erythema.
2	Mild. Light red coloration.
3	Moderate. Moderate redness, but not dark.
4	Severe. Dark red coloration.
5	Very Severe. Very dark red coloration with induration present.

Plaque Elevation

0	Clear. No evidence of plaques above normal skin level.
1	Almost Clear. Slight, just discernable elevation above normal skin level.
2	Mild. Discernable elevation above normal skin level upon examination, but not pronounced.
3	Moderate. Definite plaque formation with rounded/sloped edges to plaque.
4	Severe. Marked elevation with hard, distinct edges to plaque.
5	Very Severe. Very marked elevation, very hard and sharp edges to plaque.

Study Endpoints:
The two co-primary efficacy endpoints are the proportion of patients in each treatment group having a "clinical success" and the proportion of patients in each treatment group having a "treatment success" at Day 56/Visit 6.

Definitions:

Clinical Success: Physicians Global Assessment (PGA) score of 0 or 1.

Treatment Success: A score of 0 or 1 for each of the individual signs and symptoms which include scaling, erythema and plaque elevation.

Statistical analysis plan

Primary Efficacy: If the 90% confidence interval of the difference between the proportion of patients in the test and reference groups for the primary endpoints of "clinical success" as defined by the PGA and "treatment success" as defined by the TLSS in the Per Protocol Population (PPP) were within -0.20 to +0.20 then bioequivalence of the test product to the reference product was to be concluded.

The primary measure of efficacy in determining superiority of the test and the reference product to the placebo was evaluated using the Intent to Treat (ITT) population. Superiority of both the test and reference groups to the placebo group was confirmed if the proportion of patients in the test and reference groups for the primary endpoints of "clinical success" as defined by the PGA and "treatment success" as defined by the TLSS in the ITT were statistically greater ($p<0.05$) than that seen in the placebo group.

Study Conduct

Discussion of ITT and PP populations:

Two patient populations were defined as follows:

Intent-to-treat (ITT) subjects
• All patients who used the study drug on at least one occasion and had at least one post baseline visit/assessment

Per-protocol (PP) subjects
• Those who met all of the inclusion/exclusion criteria at time of study entry and one of the following criteria:

- All patients who completed the study according to the protocol and whose final visit was within 52 to 60 days inclusive of the day they were first dispensed study drug.
- Patients who were enrolled in the study for at least 14 days and met the minimum dosing requirements prior to being discontinued for lack of efficacy or using a restricted medication to treat their psoriasis.
- Patients who requested to be dropped from the study because of lack of efficacy or were discontinued from the study by the Investigator because of lack of efficacy, were considered a "clinical failure" and "treatment failure" irrelevant of their PGA or their TLSS lesion severity scores at the time of termination.
- Any patient who while actively enrolled in the study used any prohibited medications or had any alternative therapy for the treatment of their psoriasis were included in the PPP and were considered a "clinical failure" and "treatment failure" irrelevant of their PGA or lesion severity scores at the time of termination.

Demographics

In the ITT sample, there were 200 females and 307 males. The population consisted of 337 non-

Hispanic/Latino and 170 patients of Hispanic/Latino origin. In a breakdown of differing races, there were 3 American Indians or Alaska natives, 6 Asians, 30 Blacks/African Americans, 5 Other and 463 Whites. Subjects ranged in age from 18 to 86 years with the mean age being 48.4, 49.8 and 47.8 years in the test, reference and placebo groups respectively. There were no statistically significant differences between the treatment groups for any of the baseline evaluations.

Baseline disease severity

		Test N=198	**Reference N=206**	**Placebo N=103**
% Body Surface Area Affected	Mean + SD	9.8 ± 8.4	9.1 ± 6.1	10.0 ± 6.1
	Range	5.0 – 80.0	5.0 – 42.0	5.0 – 37.8
PGA	3:Moderate	155 (78.28%)	153 (74.27%)	72 (69.90%)
	4:Moderately Severe	29 (14.65%)	43 (20.87%)	28 (27.18%)
	5:Severe	14 (7.07%)	10 (4.85%)	3 (2.91%)
TLSS	Mean ± SD	9.2 ± 1.0	9.3 ± 1.0	9.3 ± 1.0
	Range	7.0 – 15.0	7.0 – 15.0	7.0 – 12.0

Subject Enrollment-per Sponsor

A total of 507 subjects were enrolled into the study. Of these, 498 subjects applied at least one dose of study medication and were included in the ITT analysis.

	Number of Subjects			
	Calcipotriene Ointment 0.005%	Dovonex Ointment	Vehicle	Overall
Subjects Enrolled	198	206	103	507
Subjects Excluded from the ITT Analysis	1	5	3	9
Subjects Included in the ITT Analysis	197	201	100	498
Subjects Excluded from the PP analysis	46	47	22	115
Subjects Included in the PP analysis	151	154	78	383

Primary Efficacy Results

Equivalence (PPP)

Clinical Success					
	N	% Success	T-R	Lower 90% CI	Upper 90% CI
Test	151	39.74%			
Reference	154	40.26%	-0.52	-10.41	9.36
Treatment Success					
	N	% Success	T-R	Lower 90% CI	Upper 90% CI
Test	151	43.05%			
Reference	154	37.01%	6.03	-3.84	15.9

Superiority over Placebo (ITT)

Clinical Success				
	N	% Success	T v P p value	R v P p value
Test	197	34.52%	<0.001	
Reference	201	37.81%		<0.0001
Placebo	100	17.00%		
Treatment Success				
	N	% Success	T v P p value	R v P p value
Test	197	37.06%	<0.0001	
Reference	201	37.31%		<0.0001
Placebo	100	15.00%		

Reviewer's Comments:

- *The following patients should be excluded from the PP population for using prohibited medications during the study: 21/1475 (cortisone and calcipotriene);, 25/1269 (hydrocortisone); 25/1267 (hydroxizine); 21/1464 (diphenhydramine); 14/1510, 1506 (eucerin lotion); 04/1455 (petroleum jelly); 04/1453 (cetaphil lotion); 04/1448 (petroleum jelly). The eucerin, petroleum jelly and cetaphil lotion were used on a continuous basis throughout the study, with no stop date. This means there is a chance that these lotions were used about 24 hours prior to the study endpoint visits, which means it could interfere with evaluations for scaling.*

- *Patient 22/1572 should be excluded from the PP population because they were out of window for Visit 6.*

D. Bioequivalence Conclusion

The FDA statistical analyses shows the clinical success rates were 40% and 41% for the test and reference products, respectively, on Day 56. The difference in success rates was -1.0%, with a 90% CI of (-10.5%, +9.5%), which is within the bioequivalence limits of (-20%, +20%).

Treatment success rate was 43% and 36% for the test and reference products, respectively. The difference in success rates was 7%, with a 90% CI of (-3.1%, +16.8%), which is within the bioequivalence limits of (-20%, +20%).

V. Comparative Review of Safety

A. Brief Statement of Conclusions

This study showed no significant difference between the generic and reference products with regard to the adverse events reported.

B. Description of Adverse Events

Of the 507 subjects, 163 experienced one or more treatment-emergent AEs during the study, 53 (26.77%) in the test group, 81 (39.32%) in the reference group, and 29 (28.16%) in the placebo group. The most frequently reported adverse event was "headache" that was reported by 5.05%, 6.80% and 3.88% of the patients in the test, reference and placebo groups respectively. The other events reported by more than 2% of patients in any one treatment group were: cough, diarrhea, headache, nasopharyngitis, pain and pruritis. One death was reported in the study. Patient 1545 died while enrolled in the study. He was randomized to placebo. The subject had a complicated hospital course with a number of medical problems, which ultimately contributed to his death. The Serious Adverse Event (SAE) was deemed unrelated to the study medication by the Principal Investigator. There were two other SAEs reported. Patient 1547, randomized to placebo, was admitted to the hospital and underwent cardiac catheterization and subsequently underwent 4 vessel coronary artery bypass grafting. The SAE was deemed unrelated to the study medication by the Investigator. Patient 1508, randomized to the reference group, underwent a scheduled elective in-patient hemorrhoidectomy. The SAE was deemed unrelated to the medication by the Investigator.

Summary of Adverse Events for Skin and Subcutaneous Tissue Disorders and Calcium level

	Test	Reference	Placebo
Adverse Event			
Calcium Decreased	1 (0.51%)	0	0
Calcium Increased	0	1 (0.49%)	0
Skin and Subcutaneous Tissue Disorder			
Dermatitis Contact	1 (0.51%)	0	0
Exacerbation of Psoriasis	2 (1.01%)	1 (0.49%)	1 (0.97%)
Granuloma	0	0	1 (0.97%)
Hyperhidrosis	0	0	1 (0.97%)
Pruritis	4 (2.02%)	6 (2.91%)	1 (0.97%)
Psoriasis	2 (1.01%)	2 (0.97%)	1 (0.97%)
Rash	1 (0.51%)	3 (1.46%)	0
Rash Trunk	0	1 (0.49%)	0

Seborrhoeic Dermatitis	0	1 (0.49%)	0
Skin discomfort	0	1 (0.49%)	0
Skin Exfoliation	0	1 (0.49%)	0
Skin Irritation	0	1 (0.49%)	0
Skin roughness	0	1 (0.49%)	0
Swelling Face	1 (0.51%)	0	0

Serum calcium levels were measured at every visit under the clinical chemistry procedure. The firm does not state what the lab considered to be normal serum calcium levels, but according to the firm, patient 1078 had a decrease in serum calcium and patient 1463 had an increase in serum calcium.

Patient 1078 had levels of 6.9, 7.1, 7.1, 7.1, 6.7 and 7.2 at visits 1 through 6. Patient 1463 had levels of 10.4, 10.4, 10.9 and 10.2 at visit 1, visit 3, visit 4 and visit 6, respectively.

VI. Relevant Findings from Division of Scientific Investigations, Statistics and/or Other Consultant Reviews

A. Review of the Division of Scientific Investigation (DSI) Report:

A DSI inspection was not requested due to a previous history of inspections for the following sites:

Hector Wiltz, ANDA 65-443, clindamycin and benzoyl peroxide gel, VAI 1/7/08
Steven Kempers, ANDA 78-837, Imiquimod cream, NAI 2/21/08
Alicia Renee Barba, NDA 21-623, S-Caine patch, VAI 5/23/05

B. Review of the FDA Statistical Report

The following comments were forwarded to the FDA statistician:

- *A statistical analysis is requested to verify the sponsor's equivalence analysis of the two co-primary efficacy endpoints in the PP population. They are the proportion of patients in each treatment group having a "clinical success" on the Physicians Global Assessment (PGA) and the proportion of patients in each treatment group having a "treatment success" on individual signs and symptoms scores at Day 56/Visit 6. Clinical Success is defined as a (PGA) score of 0 or 1, and a treatment Success is defined as a score of 0 or 1 for each of the individual signs and symptoms which include scaling, erythema and plaque elevation.*

- *A statistical analysis is also requested to verify the test and reference products demonstrate superiority over placebo at Visit 6 in the ITT population, demonstrating that the study is sensitive enough to discriminate product differences.*

- *The following patients should be excluded from the PP population for using prohibited medications during the study: 21/1475 (cortisone and calcipotriene);, 25/1269*

(hydrocortisone); 25/1267 (hydroxizine); 21/1464 (diphenhydramine); 14/1510, 1506 (eucerin lotion); 04/1455 (petroleum jelly); 04/1453 (cetaphil lotion); 04/1448 (petroleum jelly). The eucerin, petroleum jelly and cetaphil lotion were used on a continuous basis throughout the study, with no stop date. This means there is a chance that these lotions were used about 24 hours prior to the study endpoint visits, which means it could interfere with evaluations for scaling.

- *Patient 22/1572 was out of window for Visit 6 and should be excluded from the PP population.*

Per FDA statistical review:

Bioequivalence:

Parameter	Test	Reference	90% CI	Pass/fail
Overall success	0.32 (48/150)	0.30 (44/148)	(-0.072, 0.117)	Pass
Clinical Success rate	0.40 (60/50)	0.41 (60/148)	(-0.105, 0.095)	Pass
Treatment success rate	0.43 (65/150)	0.36 (54/148)	(-0.31, 0.168)	Pass

Efficacy:

	Test vs. Placebo			Reference vs. Placebo		
Parameter	Test	Placebo	p-value	Reference	Placebo	p-value
Overall success	0.2821 (55/195)	0.1414 (14/99)	0.0085	0.30 (60/200)	0.1414 (14/99)	0.0027
Clinical success	0.3487 (68/195)	0.1717 (17/99)	0.0017	0.39 (78/200)	0.1717 (17/99)	<0.0001
Treatment success	0.3744 (73/195)	0.1515 (15/99)	<0.0001	0.38 (76/200)	0.1515 (15/99)	<0.0001

Although the statistician evaluated overall success for the two combined co-primary endpoints, the determination of bioequivalence depends on the success rates for each individual endpoint meeting BE limits.

VII. Formulation

	Dovonex® Ointment, 0.005% manufactured by Leo Laboratories Ltd * (%w/w)	Calcipotriene Ointment, 0.005% Glenmark Generics Ltd. (%w/w)	Proportional % Difference
Calcipotriene anhydrous	0.005	0.005	0
Dibasic sodium phosphate USP	(b) (4)	(b) (4)	0
Edetate disodium USP			0
Mineral Oil USP (b) (4)			0
Propylene glycol USP			0
(b) (4) α-tocopherol USP-NF			0
(b) (4) (Steareth 2)			0
(b) (4) petrolatum USP (b) (4)			n/a
Purified water USP			0

*Formulation from FDA Legacy system for NDA 20-273

Reviewer's Comment: *The test formulation and the reference formulation are qualitatively and quantitatively identical.*

VIII. Conclusion and Recommendation

A. Conclusion

The data presented in this ANDA 090633 demonstrate that Glenmark's Calcipotriene Ointment, 0.005% is bioequivalent to the reference listed drug, Dovonex® Ointment, 0.005% The FDA statistical review confirms that the 90% CI of the difference in clinical and treatment success rates between the test and reference products at Day 56, Visit 6 is within (-20%, +20%). The test and reference products also demonstrate superiority over placebo at Visit 6, demonstrating that the study is sensitive enough to detect differences in product performance.

B. Recommendation

This application is recommended for approval from a bioequivalence standpoint.

_____ _____
Nicole Lee, Pharm.D. **Date**
Clinical Reviewer
Office of Generic Drugs

_____ _____
Dena Hixon, M.D. **Date**
Associate Director for Medical Affairs
Office of Generic Drugs

_____ _____
Dale P. Conner, Pharm.D. **Date**
Director
Division of Bioequivalence I
Office of Generic Drugs

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:090633 APPLICANT: Glenmark Generics Inc., USA

DRUG PRODUCT: Calcipotriene Ointment, 0.005%

The Division of Bioequivalence has completed its review and has no further questions at this time.

The data submitted to ANDA 090633, using the primary endpoints of clinical success rate and treatment success rate at Visit 6, are adequate to demonstrate bioequivalence of Glenmark's Calcipotriene Ointment, 0.005%, with the reference listed drug, Dovonex® Ointment, 0.005%.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90633	ORIG-1	GLENMARK GENERICS INC USA	CALCIPOTRIENE

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

/s/

NICOLE LEE
02/01/2010

DENA R HIXON
02/01/2010
I concur.

DALE P CONNER
02/01/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-633

STATISTICAL REVIEWS

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ANDA/Serial Number:	90-633
Drug Name:	Generic version of Calcipotriene Ointment, 0.005%
Indication(s):	Treatment of plaque psoriasis in adults
Reference Listed Drug:	Dovonex® (calcipotriene) Ointment, 0.005%
Applicant:	Glenmark Pharmaceuticals Ltd.
Date(s):	Submitted May 20, 2008
Biometrics Division:	DB6
Statistical Reviewer:.	Misook Park, Ph.D.
Concurring Reviewers:	Stella Grosser, Ph.D., Team Leader
Medical Division:	Clinical team in OGD
Clinical Team:	Nicole Lee, Pham. D.

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The data from study ANDA 90-633 support the conclusion that Glenmark's Calcipotriene Ointment, 0.005% (test product), is bioequivalent to Dovonex® (calcipotriene) Ointment, 0.005% (reference product) in the treatment of plaque psoriasis. The study results also show the efficacy of both the test and reference products in the treatment of plaque psoriasis.

Our equivalence test for the test and reference products was passed for the overall primary endpoint ("overall success" rate) defined as the proportion of patients having both "clinical success" and "treatment success" at the final visit (Day 56/visit 6) in the FDA Per Protocol (FPP) population. The proportions of patients in the test and reference groups who were considered an "overall success" on Day 56/Visit 6 were 0.32 and 0.30, respectively. The difference in success rate between two groups was 0.023 and the 90% CI of this difference was –0.072 to + 0.117. This is within the range -0.20 to +0.20, supporting clinical equivalence. The equivalence test was also passed for the two co-primary endpoints ("clinical success" rate and "treatment success" rate). For the efficacy test, our analysis showed that, using the FDA Intent-to-Treat (FITT) population, both the test and reference products were superior to placebo for the overall primary endpoint (both the products were statistically significant at the 0.05 level of significance). The efficacy test was also passed for the two co-primary endpoints at Day 56/visit 6.

1.2 Brief Overview of Clinical Studies

This study was a randomized, double blind, parallel design, comparative study of Glenmark's Calcipotriene Ointment, 0.005%, versus the reference listed drug, Dovonex® Ointment, 0.005%, in the treatment of plaque psoriasis. The study included male or female subjects who were ≥18 years of age with a definite clinical diagnosis of stable plaque psoriasis involving ≥5% of the body surface area. Patients who used prohibited medications during the study were excluded from the bioequivalence analysis. Five hundred seven (507) patients were enrolled and randomized in a 2:2:1 ratio to receive the test, reference or vehicle ointments once a day for 56 days. Evaluation of the bioequivalence and the efficacy of each active product (test and reference) were based on the data from the final visit (Day 56/visit 6).

The two co-primary endpoints of this study defined by the sponsor are 1) a clinical success at Day 56 and 2) a treatment success at Day 56. Clinical success was defined by the sponsor as a Physicians Global Assessment (PGA) score of 0 or 1. Treatment success was defined by the sponsor as a score of 0 or 1 for each of the individual signs and symptoms which include scaling, erythema and plaque elevation. The overall primary endpoint of this study defined by the FDA clinical reviewer is the "overall success" rate. Overall success rate was defined by the clinical reviewer as the proportion of patients in each treatment who had both "clinical success" and "treatment success" at Day 56. For the FDA analysis, the overall primary endpoint was used to determine the equivalence and the efficacy of each active product (test and reference) instead of the sponsor's two co-primary endpoints.

1.3 Statistical Issues and Findings

Choice of the primary endpoints

The sponsor used two co-primary endpoints ("clinical success" rate and "treatment success" rate) for the primary determination of bioequivalence and also for the primary determination of superiority of active treatment versus vehicle. However, per the FDA clinical reviewer's request, we used "overall success" rate to determine the equivalence and the efficacy of each active product (test and reference) instead of the sponsor's two co-primary endpoints. Our analysis results for the co-primary endpoints were also presented in this review as supportive evidence. The sponsor reported similar results and reached the same conclusion as our review for the two co-primary endpoints. It was expected that using "overall success" rate as the primary endpoint for the efficacy analysis would be more conservative than using two co-primary endpoints and this was confirmed by our findings.

2 INTRODUCTION

2.1 Overview

Study GLK602 was a randomized, double blind, parallel design, comparative study of Glenmark's Calcipotriene Ointment, 0.005%, versus the reference listed drug, Dovonex® Ointment, 0.005%, for the treatment of plaque psoriasis. Five hundred seven (507) patients were randomized in a 2:2:1 ratio to receive the test, reference or vehicle ointments once a day for 56 days.

Reference drug

The reference drug is Dovonex® Ointment, 0.005%, Leo Laboratories, Ltd. (NDA #20-273) indicated for the treatment of plaque psoriasis in adults. The original date of approval was 12/29/1993. Dovonex® ointment was discontinued by the manufacturers on April 16, 2007 for limited usefulness and commercial viability in lieu of alternative products available for the topical treatment of plaque psoriasis [according to the Psoriasis Association website].

Psoriasis

Psoriasis is a common benign, acute or chronic skin disease with a prevalence of approximately 2% worldwide. Psoriasis has several variants, with the most common being the plaque type. The disease is clinically characterized by erythematous, dry scaling patches with recurring remissions and exacerbations. Flares may be related to systemic and environmental factors. Signs and symptoms may include arthritis, pruritis and silvery scales on red plaques most commonly on the knees, elbows and scalp. The cause of this disease is unknown, but possibly may be a genetic error in mitotic control.

2.2 Data Sources

This review is based on the paper vol. 1.3 of the study report for ANDA 90-633. The data were electronically submitted.

The data files are located in the following directory:

\\FDSWA150\NONECTD\N90633\N_000\2008-05-20

3 STATISTICAL EVALUATION

3.1 Evaluation of efficacy and bioequivalence

3.1.1 Study design and endpoints

Objective

The primary objective of this study was to establish bioequivalence of the test formulation of calcipotriene 0.005% topical ointment (Glenmark Pharmaceuticals) and the already marketed formulation Dovonex® (calcipotriene ointment) 0.005% (Bristol Myers Squibb) in patients with moderate to severe plaque psoriasis. In addition, the efficacy of both the test and reference ointments was compared to a placebo ointment.

Study Design

This was a randomized, double-blind, placebo controlled, parallel-group study design, multi-site clinical study comparing the following three products:

1. Test: Calcipotriene Ointment, 0.005%, Glenmark Pharmaceuticals, Inc., lot # Q15317003
2. Reference: Dovonex® Ointment (calcipotriene ointment, 0.005%), Bristol Myers Squibb, lot #EA5258
3. Placebo (Topical ointment base only): Glenmark Pharmaceuticals, Inc., lot #QP15317001

The study lasted for 8 weeks, with visits as shown below:

Procedure (visit schedule)

	Visit 1 Baseline	Day 0	Visit 2 Interim Day 7±2	Visit 3 Interim Day 14±2	Visit 4 Interim Day 28±3	Visit 5 Interim Day 42±3	Visit 6 Final Day 56±4
Informed Consent	X						
Demographics	X						
Medical History	X						
Vital Signs	X						X
Height/Weight	X						
Pregnancy Test	X						X
BSA	X						
% BSA	X		X	X	X	X	X
TLSS	X		X	X	X	X	X
PGA	X		X	X	X	X	X
Clinical Lab Test	X						X
Clinical Chemistry	X		X	X	X	X	X
Dispense Medication		X			X		
Patient Diaries		X	X	X	X	X	X
Adverse Events			X	X	X	X	X
Con Medications	X	X	X	X	X	X	X
Study Discharge							X

Blinding/Randomization/Retention Sample

All test products were blinded and packaged in sealed boxes. The study staff dispensed the medication only to those patients identified by the Investigator. Each site had a staff member who was identified as the "Independent Dispenser." This person was responsible for the dispensing of the blinded medication and the receipt of used/partial/unused tubes of medication during the visit.

Subjects were assigned treatments in sequential order. The randomization was generated by (b) (4).

Prior to starting the study and at any time new drug supplies were shipped, one block of study drug (blinded study drug supply for 5 patients, including 2 test patients, 2 reference patients and 1 placebo patient) was removed at random by the investigative site, to be held as retention samples.

Study Endpoints

The two co-primary efficacy endpoints defined by the sponsor are the proportion of patients in each treatment group having a "clinical success" (clinical success rate) and the proportion of patients in each treatment group having a "treatment success" (treatment success rate) at Day 56/Visit 6 for the sponsor's Intent-to-Treat population (ITT) and the sponsor's Per-Protocol population (PPP).

Per the FDA clinical reviewer's request, the overall primary endpoint (overall success rate) is defined as the proportion of patients in each treatment group having both clinical and treatment success. For the FDA analysis the overall primary endpoint was used to determine the bioequivalence and superiority of each active product for the FDA's Per-Protocol (FPP) population and the FDA's Intent-to-Treat population (FITT) respectively. The sponsor's two co-primary endpoints also were used for our additional analysis.

Definitions:

Clinical Success: Physicians Global Assessment (PGA) score of 0 or 1.

Treatment Success: A score of 0 or 1 for each of the individual signs and symptoms which include scaling, erythema and plaque elevation.

Overall Success: If the patient had both clinical success and treatment success, then the patient was considered to be an overall success.

Efficacy measurements & Severity Scales

The following efficacy measurements were evaluated in this study: the Physicians Global Assessment (PGA) score and the individual signs and symptoms (scaling, erythema and plaque elevation) in the total lesion severity score. These scales are defined as follows:

Physicians Global Assessment (PGA)

0	Clear. No Evidence of psoriasis other than slight residual coloration or hyper/hypopigmentation. No noticeable plaque elevation.
1	Almost Clear. Minimal scaling and none or minimal residual erythema, overall plaque elevation is minimal and just above normal skin level.
2	Mild. Some scaling present although not extensive, plaque elevation, discernable but not pronounced, erythema generally light red in color.
3	Moderate. Scaling easily observed with red erythema. Plaque elevation generally distinct and elevated with rounded, sloping edges. At least 5% of BSA affected.
4	Moderately Severe. Extensive rough scaling with erythema moderate to dark red. Very noticeable plaque elevation with hard edges. At least 5% of BSA affected.
5	Severe. Scaling is course and thick and cracking may be evident. Erythema is generally dark red. Plaque elevation is pronounced with hard and sharp edges. More than 10% but less than 20% BSA involvement.
6	Very severe. Scaling is very coarse with pronounced cracking and fissures. Erythema is dark red with possible induration. Plaques are markedly elevated with sharp and hard edges 20% or more BSA involvement.

Individual signs and symptoms in the TLSS (Total Lesion Severity Score)

Scaling

0	Clear. No evidence of scaling.
1	Almost Clear. Occasional fine scales hardly noticeable.
2	Mild. Slight but definite roughness, fine scale present, no cracking.
3	Moderate. Moderate roughness, somewhat coarse scaling.
4	Severe. Marked roughness, coarse/thick scaling, cracking may be evident.
5	Very severe. Very thick scales covering extensive area severe cracking/fissures may be evident.

Erythema

0	Clear. No evidence of erythema.
1	Almost Clear. Pink discoloration, minimal erythema.
2	Mild. Light red coloration.
3	Moderate. Moderate redness, but not dark.
4	Severe. Dark red coloration.
5	Very Severe. Very dark red coloration with induration present.

Plaque Elevation

0	Clear. No evidence of plaques above normal skin level.
1	Almost Clear. Slight, just discernable elevation above normal skin level.
2	Mild. Discernable elevation above normal skin level upon examination, but not pronounced.
3	Moderate. Definite plaque formation with rounded/sloped edges to plaque.
4	Severe. Marked elevation with hard, distinct edges to plaque.
5	Very Severe. Very marked elevation, very hard and sharp edges to plaque.

3.1.2 Patient disposition

Study Population

Seven hundred twenty two (722) patients were screened for study participation and 507 patients were enrolled into the study and provided study medication. All 33 of the sites enrolled at least 1 patient except site 9 (no patient enrolled). Of the 507 patients who were randomized, 198 were randomized to the test product, 206 were randomized to the reference product and 103 were randomized to the placebo treatment group.

Baseline analysis was performed on all patients who were randomized and given study drug. Three hundred seventy four (374) patients were eligible for inclusion in the FDA's Per Protocol population (FPP). One hundred and fifty (150) patients in the FPP were in the test group, 148 were in the reference group, and 76 were in the placebo group. Four hundred ninety four (494) patients were included in the FDA's Intent to Treat Population (FITT), 195 in the test product

group, 200 in the reference product group and 99 in the placebo group. Table 1 presents the number of patients in each population per treatment group for the FDA analysis.

Table 1: patient disposition (number of patients in each population per treatment group)

	Test	Reference	Placebo	Total
Enrollment	**198**	**206**	**103**	**507**
Lost to follow up	0	2	3	5
Outside visit window	1	0	0	1
Withdrew consent	0	1	0	1
Other	0	2	0	2
Total exclusion from Sponsor's ITT population	1	5	3	9
Total Sponsor's ITT population (ITT)	**197**	**201**	**100**	**498**
Missed visit	5	1	3	9
Failed inclusion/exclusion criteria	4	4	1	9
Adverse event	1	1	0	2
Lost to follow up	8	13	5	26
Withdrew consent	3	5	3	11
Non compliant with dosing	5	3	1	9
Outside visit window	14	14	7	35
Took restricted medicine	5	4	2	11
Other	2	7	3	12
Total exclusion from sponsor's PP population	47	52	25	124
Total Sponsor's PP population (PP)	**151**	**154**	**78**	**383**
Failed inclusion criteria*	2	1	1	4
Total exclusion from FDA's ITT population	3	6	4	13
Total FDA's ITT population (FITT)	**195**	**200**	**99**	**494**
Prohibited medicine used**	1	5	2	8
Outside visit window at visit6***	0	1	0	1
Total exclusion from FDA's PP population	48	58	27	133
Total FDA's PP population (FPP)	**150**	**148**	**76**	**374**

* Four subjects: #1111 #1748(test) #1112(placebo) #1543 (reference)
** Eight subjects: #1455 (test) #1267, #1269, #1448, #1475, #1506 (reference) #1510, #1453(placebo)
*** One subject: #1572 (reference)

Demographics and baseline characteristics

Table 2 shows the distribution of age, gender, and race for the FITT population. There were no statistically significant differences across treatment groups in these characteristics.

Table 2: Demographic characteristics of the FITT population

	Total (N=494)	Test (N=195)	Reference (N=200)	Placebo (N=99)	P-value
Age (years)					
Mean (STD) Median(Range)	48.9 (14.2) 49.5 (18-86)	48.3 (14.0) 49.0 (19-84)	50.2 (14.8) 51.0 (18-86)	47.7 (13.5) 48.0 (19-77)	0.28*
Gender (n, %)					
Male Female	298 (60%) 196 (40%)	124(64%) 71 (36%)	117 (59%) 83 (41%)	57 (58%) 42 (42%)	0.48**
Race					
White Black/African American American Indian/Alaskan Asian Other	452 28 3 6 5	182 10 1 2 0	182 12 1 3 2	88 6 1 1 3	0.52**

* P-value is derived from ANOVA using Age as a factor.
** P-values are derived from the Pearson chi-square test. Since there were few subjects who are American Indian or Asian, they are added to the "Other" category for statistical analysis.

Baseline comparability

To examine the homogeneity of signs and symptoms across the treatment groups at the baseline visit, the Physicians Global Assessment (PGA) and individual signs and symptoms (scaling, erythema, and plaque elevation) were compared for the FITT population. There were no statistically significant differences between treatment groups with regard to severity for these signs and symptoms at the baseline visit in the FITT population.
Table 3 shows the results for the FITT population.

Table 3: Summary of Signs and Symptoms Scores at Baseline for the FITT population

	Total (N=494)	Test (N=195)	Reference (N=139)	Placebo (N=48)	p-value*
PGA					
Mean (Std)	3.30(0.56)	3.28(0.58)	3.31(0.56)	3.33(0.53)	0.74
Median	3	3	3	3	
Range	3-5	3-5	3-5	3-5	
Scaling					
Mean (Std)	3.17(0.55)	3.16(0.58)	3.18(0.53)	3.17(0.52)	0.98
Median	3	3	3	3	
Range	1-5	1-5	2-5	2-5	
Plaque elevation					
Mean (Std)	3.11 (0.34)	3.09(0.32)	3.12(0.36)	3.13(0.34)	0.13
Median	3	3	3	3	
Range	3-5	3-5	3-5	3-4	
Erythema					
Mean (Std)	2.98(0.50)	2.93(0.47)	3.03(0.52)	3.01(0.52)	0.48
Median	3	3	3	3	
Range	1-5	1-5	1-5	1-4	

*p-values were derived from the general linear model with treatment as a factor

3.1.3 Statistical methodologies

Statistical Analysis Methods

Efficacy Analysis

Tests for superiority of each active treatment (test or reference) over the placebo were conducted separately by using the two-sided Fisher's exact test at the 5 % level of significance. The two co-primary efficacy endpoints are the clinical success rate (the proportion of patients in each treatment group having a "clinical success") and treatment success rate (the proportion of patients in each treatment group having a "treatment success") at Day 56/Visit 6 for the FITT population.

The overall success rate at visit 6 in the FITT population was the primary outcome for determining the superiority of each active treatment over the placebo. Additional analyses based on co-primary endpoints (clinical success rate and treatment success rate) were conducted to provide supportive evidence. The proportion of subjects that have missing data at the final visit in the FITT population is 0.154 (76/494). The Last Observation Carried Forward (LOCF) approach was used to impute the endpoints for these 76 subjects.

Number of subjects whose final visit data are missing in each treatment group

test	reference	placebo	Total
31	32	13	76

Equivalence Analysis

Based on the usual method used in the Office of Generic Drugs (OGD) for binary outcomes, the 90% confidence interval for the difference in proportions between the test and reference treatments should be contained within -0.20 to 0.20 in order to establish equivalence. The overall success rates at visit 6 in the FPP population were used as the primary outcomes for the clinical equivalence analysis.

The compound hypothesis to be tested is:

H_0: $p_T - p_R < -0.20$

or $p_T - p_R > 0.20$

versus

H_A : $-0.20 \leq p_T - p_R \leq 0.20$

where p_T = success rate of test treatment and p_R = success rate of reference treatment.

Let n_T = sample size of test treatment, n_R = sample size of reference treatment,

and $se = (\hat{p}_T(1-\hat{p}_T)/n_T + \hat{p}_R(1-\hat{p}_R)/n_R)^{1/2}$

where $\hat{p}_T$ and $\hat{p}_R$ are the observed success rates for the test and reference treatments respectively. The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

$$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)/2$$
$$U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2$$

We reject H_0 if $L \geq -0.20$ and $U \leq 0.20$

Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

3.1.4 Results and conclusions

3.1.4.1 Sponsor's analysis results

The sponsor used the two dichotomous primary variables ("clinical success" rate and "treatment success" rate) as primary endpoints to determine the equivalence of the test and reference products using the Per Protocol Population (PPP).

To test the equivalence between the two treatments, the sponsor used the 90% confidence interval (CI) approach (with Yates correction factor) for both of the dichotomous primary efficacy variables using the PPP. The sponsor reported that clinical success rates on Day 56 for the test and reference treatment groups were 0.397 and 0.403, respectively. The difference in success rate between two groups was -0.005. The 90% CI of the difference between success rates in the two groups for this dichotomous variable was -0.104 to + 0.094. The sponsor concluded that the equivalence test was passed for the clinical success rate at visit 6 for the PP population. The proportion of patients who were considered a treatment success on Day 56 for the test and reference treatment groups were 0.43 and 0.37, respectively. The difference in success rates between the two groups was 0.06. The 90% CI of the difference between success rates for this dichotomous variable was -0.038 to + 0.159. This result also supported clinical equivalence (Table 4a).

The sponsor determined superiority using the ITT population with last observation carried forward (LOCF). The proportion of patients who were considered a clinical success on Day 56 for the test, reference, and placebo treatment groups were 0.345, 0.378, and 0.170 respectively. The proportion of patients who were considered a "treatment success" on Day 56/visit 6 for the test, reference, and placebo treatment groups were 0.371, 0.373, and 0.15 respectively.

The sponsor reported that the efficacy tests for both active products based on clinical success rate were statistically significant (p=0.001 for test vs. placebo and p=0.0001 for reference vs. placebo). The efficacy test for each active product based on treatment success rate also was statistically significant (p=0.0001 in all cases). (See Table 4b).

The sponsor's results are similar to those of this review with regard to superiority of each active treatment (test or reference) over the placebo for clinical success rate and treatment success rate.

Table 4: Primary Efficacy Results (Sponsor's analyses)

4a: Equivalence (PPP)

Clinical Success					
	N	Success Rate	T-R	Lower 90% CI*	Upper 90% CI*
Test	151	0.3974			
Reference	154	0.4026	-0.0052	-0.1041	0.0936
Treatment Success					
	N	Success Rate	T-R	Lower 90% CI*	Upper 90% CI*
Test	151	0.4305			
Reference	154	0.3701	0.0603	-0.0384	0.159

*Yates' continuity correction was applied by the sponsor. Source: Clinical Study Report, Vol 1.3, p000052, Table 2.

4b: Superiority (ITT)

Clinical Success				
	N	Success Rate	T v P p value**	R v P p value**
Test	197	0.3452	<0.001	
Reference	201	0.3781		<0.0001
Placebo	100	0.17		
Treatment Success				
	N	Success Rate	T v P p value**	R v P p value**
Test	197	0.3706	<0.0001	
Reference	201	0.3731		<0.0001
Placebo	100	0.15		

** Based on the sponsor's output files, it seems that Pearson chi-square test was used to obtain their p-values. Source: Clinical Study Report, Vol 1.3, p000052, Table 2.

3.1.4.2 Reviewer's results

Efficacy Analysis results:

Table 5 summarizes the efficacy analyses results for the FITT population.

Overall Primary endpoint: Overall success rate at visit 6.

The primary efficacy analyses based on the "overall success" rate show that, using the FITT population, the proportions of patients who were considered an "overall success" on Day 56/visit 6 for the test, reference, and placebo treatment groups were 0.282, 0.300 and 0.141, respectively.

Both the test and reference products were statistically significantly superior to placebo (p=0.009 for test vs. placebo and p=0.003 for reference vs. placebo).

Co-primary endpoints: Clinical Success rate and Treatment Success rate at visit 6.

In addition, comparisons based on co-primary endpoints were conducted. The analysis based on the clinical success rate at visit 6 demonstrated that both the test and reference products were found to be statistically significantly superior to placebo (p=0.002 for test vs. placebo and p<0.0001 for reference vs. placebo). Based on the treatment success rate, both the test and reference products were also shown to be statistically superior to placebo (p<0.0001 for test v. placebo and p=0.0001 for reference vs. placebo).

Table 5: Efficacy analyses based on the FITT population at visit 6

	Test vs. Placebo			Reference vs. Placebo		
parameter	Test Rate (n/N)	Placebo Rate (n/N)	p-value[&]	Reference Rate (n/N)	Placebo Rate (n/N)	p-value[&]
Overall Success	**0.2821 (55/195)**	**0.1414 (14/99)**	**0.0085**	**0.30 (60/200)**	**0.1414 (14/99)**	**0.0027**
Clinical Success	0.3487 (68/195)	0.1717 (17/99)	0.0017	0.39 (78/200)	0.1717 (17/99)	<0.0001
Treatment Success	0.3744 (73/195)	0.1515 (15/99)	<0.0001	0.38 (76/200)	0.1515 (15/99)	<0.0001

[&] The p-values were derived from Fisher's exact test (two-sided at the 5 % level of significance).

Equivalence Analysis results:

The equivalence tests for the test and reference products were passed for the overall success rate at visit 6 in the FPP population. The proportion of patients in the test and reference groups who were considered an "overall success" on Day 56/Visit 6 were 0.32 and 0.2973 respectively. The difference in success rate between the two groups was 0.023. The 90% CI of the difference between success rates in the two groups was –0.072 to + 0.117. This is within the range -0.20 to +0.20, demonstrating equivalence.

In addition, the equivalence test based on co-primary endpoints provided supportive evidence of the equivalence of the test and reference products. Table 6 summarizes the bioequivalence analyses results.

Table 6: Bioequivalence Analyses based on the FPP population at visit 6

parameter	Test rate (n/N)	Reference rate (n/N)	90% Confidence Interval*	Pass/Fail
Overall Success	**0.32 (48/150)**	**0.30 (44/148)**	**(-0.072 , 0.117)**	**Pass**
Clinical Success rate	0.40 (60/150)	0.41 (60/148)	(-0.105 , 0.095)	Pass
Treatment Success rate	0.43 (65/150)	0.36 (54/148)	(-0.031 , 0.168)	Pass

* Yates' continuity correction has been applied.

The proportions of patients in the placebo group who were considered "overall success", "clinical success", and "treatment success" on Day 56/Visit 6 were 0.13, 0.14, and 0.14 respectively.

4 SUMMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

Main difference between Sponsor's Results and Our Results:

The sponsor used two co-primary endpoints ("clinical success" rate and "treatment success" rate) for the primary determination of bioequivalence and also for the primary determination of superiority to placebo. The sponsor reported similar results and reached the same conclusion as our review for the two co-primary endpoints. In this study, per the clinical reviewer's request, we used "overall success" rate to determine the equivalence and the efficacy of two active products (test and reference) instead of the sponsor's co-primary endpoints. Analysis results for the co-primary endpoints were also presented as supportive evidence. It was expected that using "overall success" rate as the primary endpoint for the efficacy analysis would make it harder to pass than using the two co-primary endpoints and this was confirmed by our findings (see Table 5).

4.2 Conclusions and Recommendations

Our analyses show that both the test and reference products were statistically significantly better than placebo for overall success rate (FDA-defined primary endpoint) at the final visit (visit 6) in the FITT population. The efficacy tests based on both co-primary endpoints (clinical success rate and treatment success rate) were also passed. Thus there was enough evidence in the data presented in this ANDA to show that both the test and reference products are statistically significantly superior to placebo at the final visit (visit 6) for the FITT population.

The equivalence test for the FPP population was passed for the overall primary endpoint. The equivalence test was also passed for both co-primary endpoints. Thus there was enough evidence

in the data presented in this ANDA to show that the test product was clinically equivalent to the reference product at the final visit (visit 6) for the FPP population.

_____	_____
Misook Park, Ph.D.	Stella Grosser, Ph.D
Mathematical Statistician, DB6/OB	Statistical Team Leader, DB6/OB

_____
Stella G. Machado, Ph.D.
Director, DB6/OB

cc:
HFD-600 Dena R Hixon, Sarah Seung, Debra M Catterson
HFD-700 Lillian Patrician
HFD-705 Stella G. Machado, Stella Grosser, Misook Park

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90633	ORIG-1	GLENMARK GENERICS INC USA	CALCIPOTRIENE

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

/s/

MISOOK PARK
12/03/2009

STELLA G MACHADO
12/03/2009

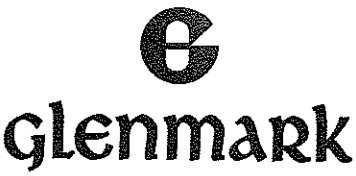
STELLA C GROSSER
12/08/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-633

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS



MAY 2 0 2008

VIA FEDERAL EXPRESS

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855

SUBJECT: Original Abbreviated New Drug Application
Calcipotriene Ointment, 0.005%

Dear Mr. Buehler:

Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, Glenmark Generics Inc., USA, herewith submits an Abbreviated New Drug Application (ANDA) for Calcipotriene Ointment, 0.005%.

This application references Leo Laboratories Limited's Dovonex® (calcipotriene) Ointment, 0.005% as listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book). The dosage form, route of administration, active ingredient and potency are the same for Glenmark's Calcipotriene Ointment, 0.005% and Leo Laboratories Limited's Dovonex® (calcipotriene) Ointment, 0.005%. Differences in labeling between Glenmark's Calcipotriene Ointment, 0.005% and Leo Laboratories Limited's Dovonex® (calcipotriene) Ointment, 0.005% are annotated in Module 1 of the ANDA and are limited to product name and manufacturer.

This application is provided in CTD format and in accordance with Agency and ICH Guidances. In support of this ANDA, the information outlined below is provided:

- Table of Contents
- Signed Application Form FDA 356h
- Basis for Submission
- Patent Certification/Exclusivity Statement
- Debarment, cGMP and Field Copy Certifications. We certify that the Field Copy is a true copy of the technical section contained in the Archival and Review Copies of this ANDA.
- Comparison between the proposed drug and the reference listed drug (Leo Laboratories Limited's Dovonex® (calcipotriene) Ointment, 0.005%).
- Draft labels and electronic content of labeling (one reference copy each in each of the submission copies).

- A Randomized, Double-Blind, Placebo Controlled, Parallel Design, Multiple-Site Clinical Study to Evaluate the Bioequivalence of Calcipotriene Ointment, 0.005% (Glenmark Generics) to Dovonex® (calcipotriene) Ointment, 0.005% (Leo Laboratories Limited) in Patients with Moderate to Severe Plaque Psoriasis.

- Chemistry, manufacturing and controls information.

- Methods validation package (three independently bound method validation packages). Glenmark commits to resolve any issues identified during the methods validation process after approval.

The following CD-ROMs are included with this submission, copies as indicated:

1. Electronic Content of Labeling (archival and review copy)
   - Cover Letter
   - 356h
   - Draft Labeling in MS Word and PDF

2. Quality Overall Summary (archival and review copy)
   - Quality Overall Summary and Clinical Summary in MS Word and PDF

3. Summary Tables of Biostudy Results (archival and Bioequivalence copy)
   - Tables 1-16 as requested by the Division of Bioequivalence
   - SAS transport files the study

We request that all information in this file be treated as confidential within the meaning of 21 CFR 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

Please contact the undersigned at 201-684-8017 if you should have any questions concerning this submission.

Sincerely,
GLENMARK GENERICS INC., USA

Danielle Ahlendorf for

William R. McIntyre, Ph.D.
Executive Vice President, Regulatory Affairs
Tel: (201) 684-8017
Fax: (201) 831-0080

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : July 18, 2008

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 90-633 for Calcipotriene Ointment, 0.005% to determine if the application is substantially complete for filing.

Glenmark Generics Limited has submitted ANDA 90-633 for Calcipotriene Ointment, 0.005%. In order to accept an ANDA the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Glenmark Generics Limited on May 23, 2008 for its Calcipotriene product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

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

/s/

Eda Howard
7/18/2008 10:33:41 AM
APPLICATIONS EXA

glenmark

August 6, 2008

VIA FEDERAL EXPRESS

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855

ORIG AMENDMENT

N-000-MC

SUBJECT: **ANDA #90-633**
Calcipotriene Ointment, 0.005%
Additional Information

Dear Mr. Buehler:

Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, Glenmark Generics Inc., USA herewith submits this additional information for Calcipotriene Ointment, 0.005% in response to the telephone conversation with Ted Palat, Senior Regulatory Reviewer, OGD on July 22, 2008.

During the above referenced conversation, Mr. Palat indicated that the RLD Dovonex® (calcipotriene) Ointment, 0.005% (NDA #20-273) was discontinued; furthermore, he stated in order to reference the innovator product within our application, Glenmark needed to submit a Citizen Petition to the FDA for determining whether the RLD had been withdrawn for reasons regarding safety and efficacy. Lachman Consultant Services Inc. has submitted a Citizen Petition on behalf on Glenmark Generics Inc., USA requesting that the Food and Drug Administration determine whether the Dovonex® (calcipotriene) Ointment, 0.005%, NDA 20-273 held by Leo Pharma, has been voluntarily withdrawn or withheld from sale for safety or efficacy reasons. A copy of this Citizen Petition is provided in **Attachment 1** as reference.

This amendment is being submitted as archival and duplicate copies. If I can provide any additional information or clarify the above, please do not hesitate to contact me directly at the number provided below.

Field Copy: This is to certify that the Field Copy, submitted in accord with 21 CFR 314.96(b), is a true copy of the technical section of this submission.

Sincerely,
GLENMARK GENERICS INC., USA

Danielle Ohlendorf for

Anthony M. Maffia, III
Associate Director, Regulatory Affairs
Tel: (201) 684-8028
Fax: (201) 831-0080

RECEIVED
AUG 07 2008
OGD

CLINICAL REVIEW TEAM CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS

ANDA# 90-633_____**FIRM NAME**___Glenmark Generics Inc., USA_____

DRUG NAME __Calcipotriene Ointment, 0.005%_____

DOSAGE FORM __topical ointment_____

Requested by: _Howard, Eda_____ Date: _6/10/08_____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Clinical Review Team
X	**Study meets statutory requirements**
	Study does NOT meet statutory requirements
	Reason:
	Waiver meets statutory requirements
	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION: **_X__COMPLETE** **___INCOMPLETE**

Reviewed by:

_____ Date: _____
Reviewer
Carol Y. Kim, Pharm.D.
Clinical Reviewer

_____ Date: _____
Dena R. Hixon, M.D.
Associate Director for Medical Affairs

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	X				Protocol #GLK602 Study # 70644001
Summary of Study	X				
Clinical Site (s)	X				
Study Investigator (s)	X				
List of subjects included in PP/ (M)ITT populations per treatments	X				
List of subjects excluded/ from PP/ (M)ITT per treatments	X				
Reasons for discontinuation from the study if discontinued	X				
Adverse Events	X				
Concomitant Medications	X				
Individual subject's scores/data per visit	X				
Pre-screening of Patients	X				
IRB Approval	X				
Consent Forms	X				
Randomization Schedule	X				
Protocol Deviations	X				
Case Report Forms	X				
PD Data Disk (or Elec Subm)	X				
Study Results	X				
Clinical Raw Data/ Medical Records	X				

Composition	X				
BioStudy Lot Numbers	X				
Date of Manufacture	X				
Exp. Date of RLD	X				
Statistical Reports	X				
Defined BE endpoints	X				
Summary results provided by the firm indicate studies pass BE criteria	X				See below for comments
Summary results provided by the firm indicate superiority of the active treatments over the vehicle/placebo	X				
Waiver requests for other strengths / supporting data		X			N/A

Comments to be conveyed to the sponsor

Your application is acceptable for filing.

Comments <u>not to be conveyed</u> to the sponsor:

1. The sponsor conducted a bioequivalence study in patients with moderate to severe plaque psoriasis. Bioequivalence was evaluated with two primary endpoints, clinical success based on PGA and treatment success based on total lesion severity score (TLSS). According to the sponsor's analysis, the 90% CI of the difference in clinical success rate based on PGA score between the test and reference products in the PP population at Day 56 (end of treatment) is (-0.104 to +0.094), which is within established bioequivalence limits of (-0.20 to +0.20). 39.74% of test patients and 40.26% of reference patients were considered as a clinical success in the PP population at Day 56 by the sponsor. Both active drug products show superiority over the vehicle group in the ITT population ($P \leq 0.001$), demonstrating that the study is sufficiently sensitive to detect differences between products.

According to the sponsor, the 90% CI of the difference in treatment success based on total lesion severity score between the test and reference products in the PP population at Day 56 (end of treatment) is (-0.038 to +0.159), which is within established bioequivalence limits of (-0.20 to +0.20). 43.05% of test patients and 37.01% of reference patients were considered treatment success in the PP population at Day 56 by the sponsor. Both active drug products show superiority over the vehicle group in the ITT population ($P<0.0001$), demonstrating that the study is sufficiently sensitive to detect differences between products. Therefore, the sponsor's data support

that their product is bioequivalent to the RLD.

Patients were considered as a clinical success if they had a score of 0 (clear) or 1 (almost clear) based on the PGA and treatment success if they had a score of 0 (clear) or 1 (almost clear) for each of the individual lesion signs and symptoms (scaling, erythema, and plaque elevation) of TLSS.

Patients with a confirmed diagnosis of moderate to severe plaque psoriasis defined as an affected body surface area (BSA) of $\geq$ 5%, PGA score of 3, 4, 5, a "target lesion" with an area of at least 5 cm^2, a TLSS of $\geq$ 7 for target lesion and a plaque elevation score $\geq$ 3 for target lesion were eligible for inclusion in the study.

2. The sponsor's statistical summary of primary and secondary endpoints is shown below.

A Randomized, Double-Blind, Placebo Controlled, Parallel Design, Multi-Site Clinical Study to Evaluate the Bioequivalence of Calcipotriene Ointment 0.005% (Glenmark Generics) to DOVONEX® (calcipotriene ointment) 0.005% (Bristol Myers Squibb) in Patients with Moderate to Severe Plaque Psoriasis

Study No. 70644001

Normal Distribution Analysis 90% Confidence Intervals				
Parameter	**Test**	**Reference**	**Difference**	**90% C.I.**
Clinical Success (PPP)	39.74%	40.26%	-0.52	-10.41 - 9.36
Treatment Success (PPP)	43.05%	37.01%	6.03	-3.84 - 15.90
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
Mean change in PGA score (PPP)	1.42	1.43	99.67	86.99 - 112.35
Mean change in TLSS score (PPP)	4.81	4.90	98.20	88.38 - 108.03
Superiority Testing				
Parameter	**Test vs Placebo**	**Reference vs Placebo**		
Clinical Success (ITT)	p=.0010	p=.0001		
Treatment Success (ITT)	p<.0001	p<.0001		
Mean change in PGA score (ITT)	p<.0001	p<.0001		
Mean change in TLSS score (ITT)	p<.0001	p<.0001		

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/s/

Dena Hixon

7/21/2008 10:03:13 AM

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
*** **A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ ***

ANDA #: 90-633 **FIRM NAME**: GLENMARK GENERICS LIMITED

PIV: NO **Electronic or Paper Submission:** CTD FORMAT PAPER

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: CALCIPOTRIENE

DOSAGE FORM: OINTMENT, 0.005%

Random Queue: 3

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☒ **BCE**	
☐ **BST**	☐ **BDI**	

Chem Team Leader: Fan, Jim Chem PM: Rosalyn Adigun Labeling Reviewer: Beverly Wietzman
Bio PM: Nam J. Chun (Esther)

Letter Date: MAY 20, 2008 **Received Date**: MAY 23, 2008

Comments: EC- 1 YES **On Cards:** YES
Therapeutic Code: 4029050 PSORIASIS AGENTS

Archival copy: CTD FORMAT PAPER **Sections** I
Review copy: YES E-Media Disposition: YES
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Ted Palat Date 08/20/2008	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: _____	**Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:
1. the RLD is listed in the discontinued section of the OB. Please see CFR 314.122.

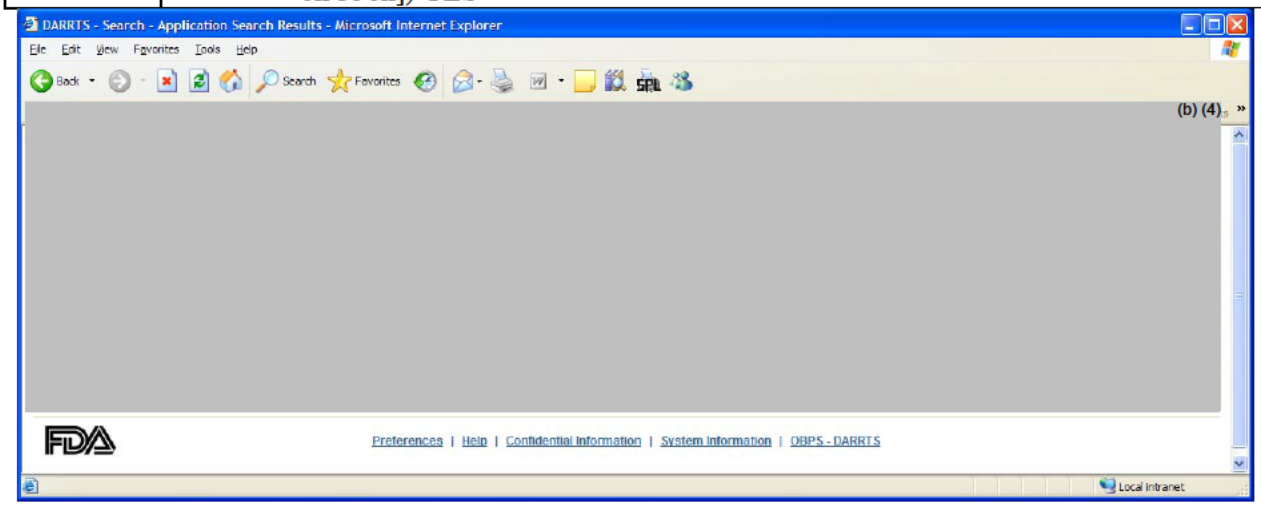
spoke with William McIntyre and Anthony Maffia on 07/22/2008. Requested file CP under 314.122. Sponsor responded with CP on August 6, 2008.

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: MAY 20, 2008	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES, form 3454 or Disclosure Statement (Form FDA 3455) NA	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) **Patent and Exclusivity Search Results from query on Appl No 020273 Product 001 in the OB_Disc list.** **Patent Data** Appl No: 020273 | Prod No: 001 | Patent No: 4866048 | Patent Expiration: Dec 29, 2007 | Drug Substance Claim: | Drug Product Claim: | Patent Use Code: | Delist Requested: **Exclusivity Data** **There is no unexpired exclusivity for this product.** Product is listed in the discontinued section of the Orange Book. *Active Ingredient CALCIPOTRIENE* *Dosage Form;Route OINTMENT; TOPICAL* *Proprietary Name DOVONEX* *Applicant LEO PHARM* *Strength 0.005%* *Application Number 020273* *Product Number 001* *Approval Date Dec 29, 1993* ***RX/OTC/DISCN: DISCN*** Please submit CP to determine if w/d for safety or efficacy. CP filed on August 6, 2008. 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☒ PIII ☐ PIV ☐ (Statement of Notification) ☐ 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES	☒

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient YES, DMF (b) (4) b. Type III DMF authorization letter(s) for container closure YES 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) YES	☒

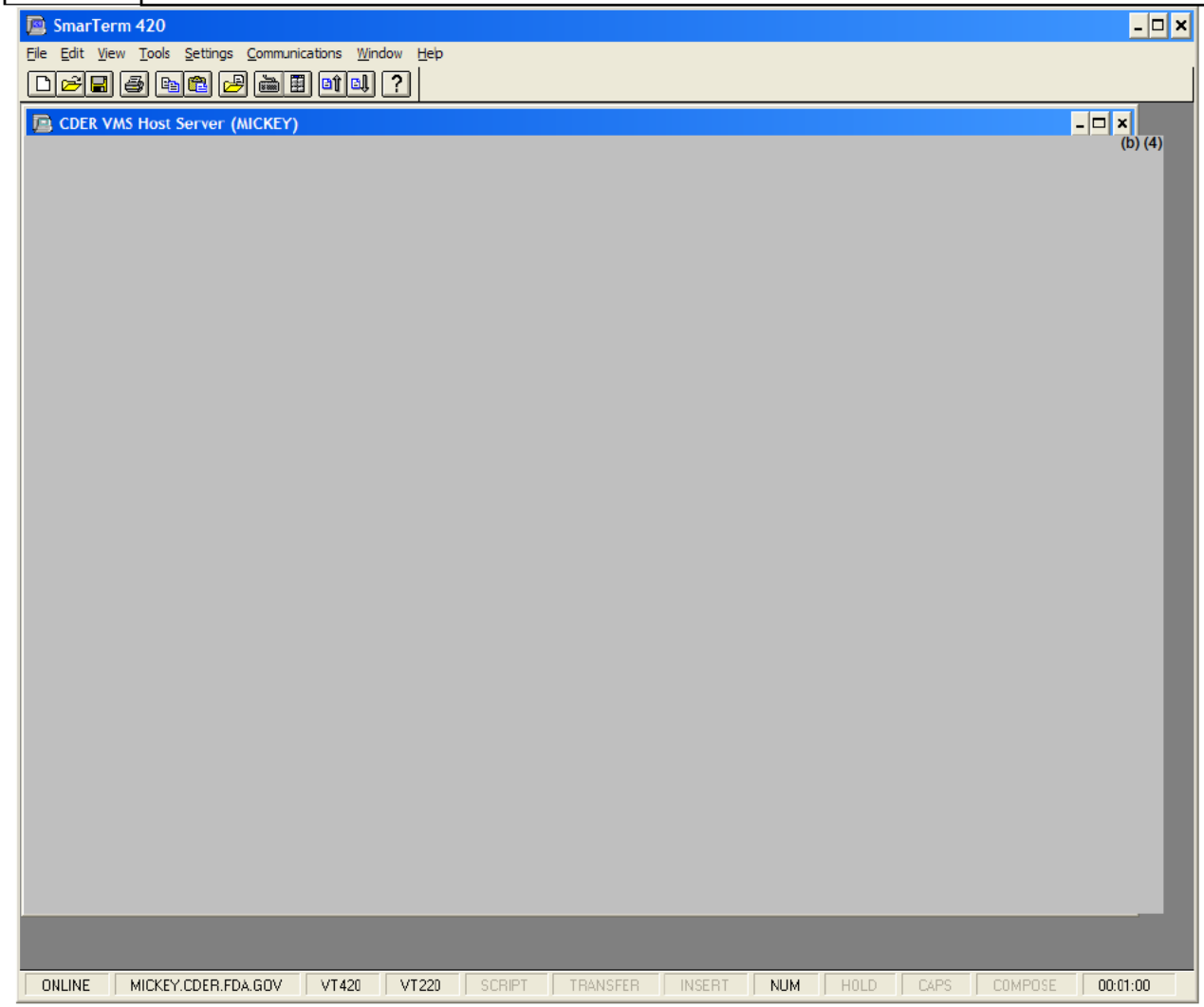


1.12.11	**Basis for Submission** NDA# : 20-273 Ref Listed Drug: DONOVEX Firm: LEO LABORATORIES LTD ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use same 2. Active ingredients same 3. Inactive ingredients same 4. Route of administration same 5. Dosage Form same 6. Strength same	☒



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1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) 1 copy, e-submission **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES **1.14.1.3** 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES **1.14.3.3** 1 RLD label and 1 RLD container label YES	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** NO **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** YES **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** YES **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary YES Table 4. Bioanalytical Method Validation NA Table 6. Formulation Data YES **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution NA **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies YES Table 3. Statistical Summary of the Comparative BA Data YES **2.7.1.4 Appendix** YES **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study YES **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies YES	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature YES** **3.2.S.1.2 Structure YES** **3.2.S.1.3 General Properties YES**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) Active ingredient: Calcipotriene Manufacturer/Supplier: (b) (4) Address Name of contact Designation Phone FAX Email Establishment Registration No. (CFN) Type II DMF No. Date of last inspection US agent for DMF 2. Function or Responsibility YES 3. Type II DMF number for API DMF (b) (4) 4. CFN or FEI numbers YES	☒
3.2.S.3	**Characterization**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) YES **3.2.S.4.2 Analytical Procedures** YES **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance YES b. Same lot number(s) F0420603 and F0420604 **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) YES 2. Applicant certificate of analysis YES **3.2.S.4.5 Justification of Specification**	☒

3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems**	☒
3.2.S.7	**Stability**	☒

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3.2.P.3 **Manufacture** ☒

3.2.P.3.1 Manufacture(s) (Finished Dosage Manufacturer and Outside Contract Testing Laboratories)

1. Name and Full Address(es)of the Facility(ies)

Finished Dosage Manufacturer:

Glenmark Generics Limited

Plot No. S-7, Colvale Industrial Estate,

Colvale, Bardez, Goa 403513, India

Responsible person: Mr. Anil Agrawal, Senior Manager – Production

Registration Number (CFN): 3004672766

For cGMP certification refer section 3.2.P.3.1 and Debarment certification is enclosed in section 1.3.3.

2. CGMP Certification: YES
3. Function or Responsibility YES
4. CFN or FEI numbers YES

3.2.P.3.2 Batch Formula

Formula comparison between pivotal batch and the intended commercial batch of Calcipotriene Ointment, 0.005%

Sr. No.	Ingredients	Quantity	Exhibit batch size	Intended commercial production (b) (4)
		(% w/w)		
1.	* Calcipotriene (b) (4)	0.005		
2.	Dibasic sodium phosphate	(b) (4)		
3.	Edetate disodium			
4.	Mineral Oil (b) (4)			
5.	Propylene glycol			
6.	(b) (4) α-tocopherol			
7.	(b) (4) (D) (4) (Steareth 2)			
8.	(b) (4) petrolatum (b) (4)			
9.	Purified water			

3.2.P.3.3 Description of Manufacturing Process and Process Controls

1. Description of the Manufacturing Process YES
2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES

exhibit batch: (b) (4)

commercial batch: (b) (4)

3. If sterile product: Aseptic fill / Terminal sterilization NA
4. Reprocessing Statement YES

3.2.P.3.4 Controls of Critical Steps and Intermediates

3.2.P.3.5 Process Validation and/or Evaluation

1. Microbiological sterilization validation NA
2. Filter validation (if aseptic fill) NA

3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified YES **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) YES 2. Suppliers' COA (specifications and test results) YES **3.2.P.4.2 Analytical Procedures** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA YES	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** YES **3.2.P.5.2 Analytical Procedures** YES **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form YES 2. Same lot numbers Q15317003 **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form YES **3.2.P.5.5 Characterization of Impurities** **3.2.P.5.6 Justification of Specifications**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) YES 2. Components Specification and Test Data YES 3. Packaging Configuration and Sizes **HOW SUPPLIED** Calcipotriene ointment, 0.005% is available in: 60 gram aluminum tube NDC (68462-310-65) 4. Container/Closure Testing YES 5. Source of supply and suppliers address YES	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted YES 2. Expiration Dating Period 24 months **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments YES **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data YES 2. Batch numbers on stability records the same as the test batch **YES**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available) NO** **3.2.R.2.S Comparability Protocols NO** **3.2.R.3.S Methods Validation Package YES** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation YES **Packaging Reconciliation** (b) (4) [redacted] **3.2.R.1.P.2 Information on Components** NO **3.2.R.2.P Comparability Protocols** NONE **3.2.R.3.P Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒

5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) NA b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) YES **2. Lot Numbers of Products used in BE Study(ies):** ANDA: Q15317003, RLD: EA5258 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) NA 2. Summary Bioequivalence tables: Table 10. Study Information YES Table 12. Dropout Information YES Table 13. Protocol Deviations YES **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information YES Table 16. Composition of Meal Used in Fed Bioequivalence Study NA **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples NA Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses YES Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples YES **5.3.7** **Case Report Forms and Individual Patient Listing** YES	☒
5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) NA 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) NA 2. EDR Email: Data Files Submitted: NA 3. In-Vitro Dissolution: NA	☐

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** YES/STU BIO 1. Properly defined BE endpoints (eval. by Clinical Team) found complete by Dr. Carol Kim. See DFS document dated 07/21/2008. signed by Dena Hixon. 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25).	☒

Table 3 Statistical Summary of the Comparative Bioavailability Data

A Randomized, Double-Blind, Placebo Controlled, Parallel Design, Multi-Site Clinical Study to Evaluate the Bioequivalence of Calcipotriene Ointment 0.005% (Glenmark Generics) to DOVONEX® (calcipotriene ointment) 0.005% (Bristol Myers Squibb) in Patients with Moderate to Severe Plaque Psoriasis

Study No. 70644001

Normal Distribution Analysis 90% Confidence Intervals

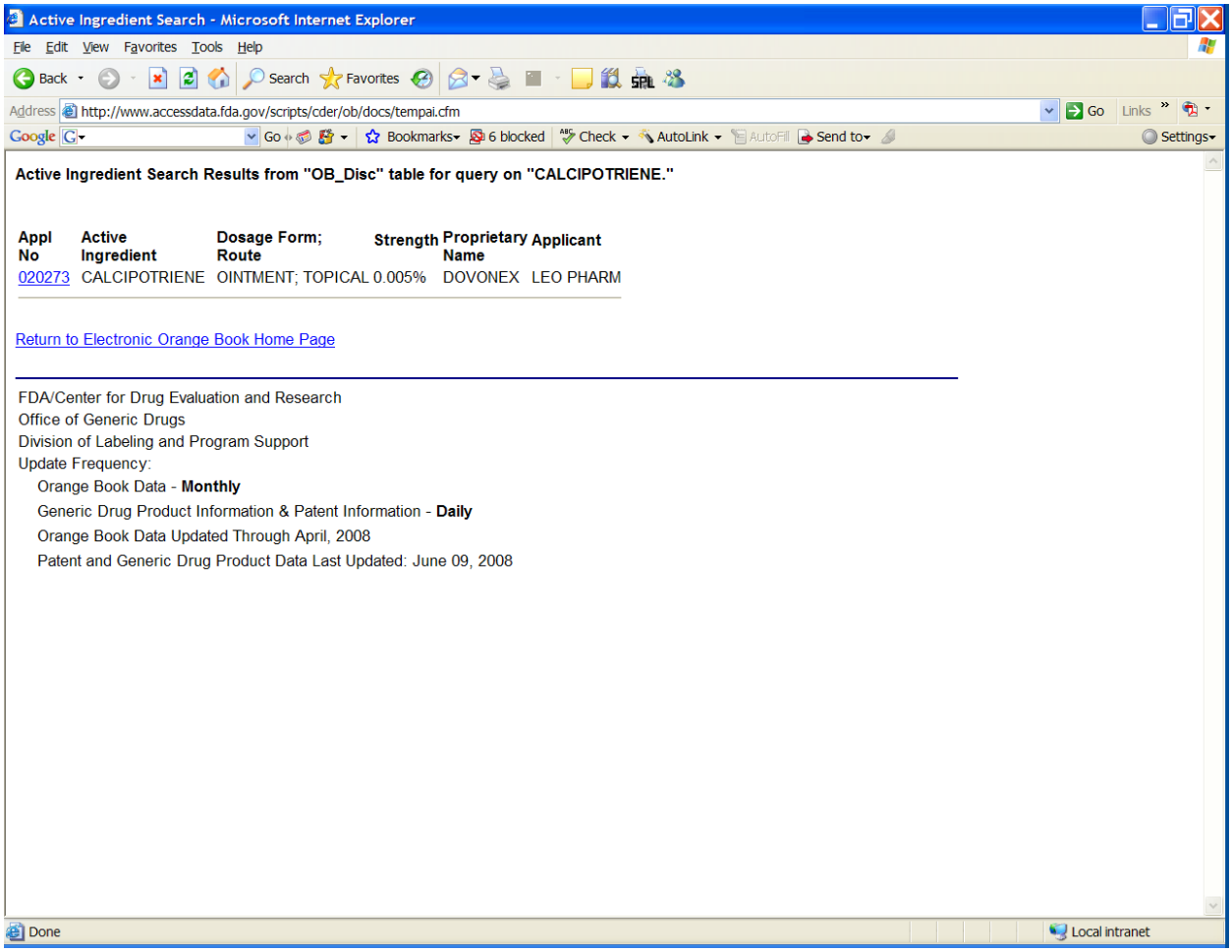
Parameter	Test	Reference	Difference	90% C.I.
Clinical Success (PPP)	39.74%	40.26%	-0.52	-10.41-9.36
Treatment Success (PPP)	43.05%	37.01%	6.03	-3.84-15.90
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
Mean change in PGA score (PPP)	1.42	1.43	99.67	86.99-112.35
Mean change in TLSS score (PPP)	4.81	4.90	98.20	88.38-108.03
Superiority Testing				
Parameter	**Test vs Placebo**	**Reference vs Placebo**		
Clinical Success (ITT)	p=.0010	p=.0001		
Treatment Success (ITT)	p<.0001	p<.0001		
Mean change in PGA score (ITT)	p<.0001	p<.0001		
Mean change in TLSS score (ITT)	p<.0001	p<.0001		

3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) found complete by Dr. Carol Kim. See DFS document dated 07/21/2008. signed by Dena Hixon.
4. EDR Email: Data Files Submitted YES SENT TO EDR

Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐

Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 5/28/08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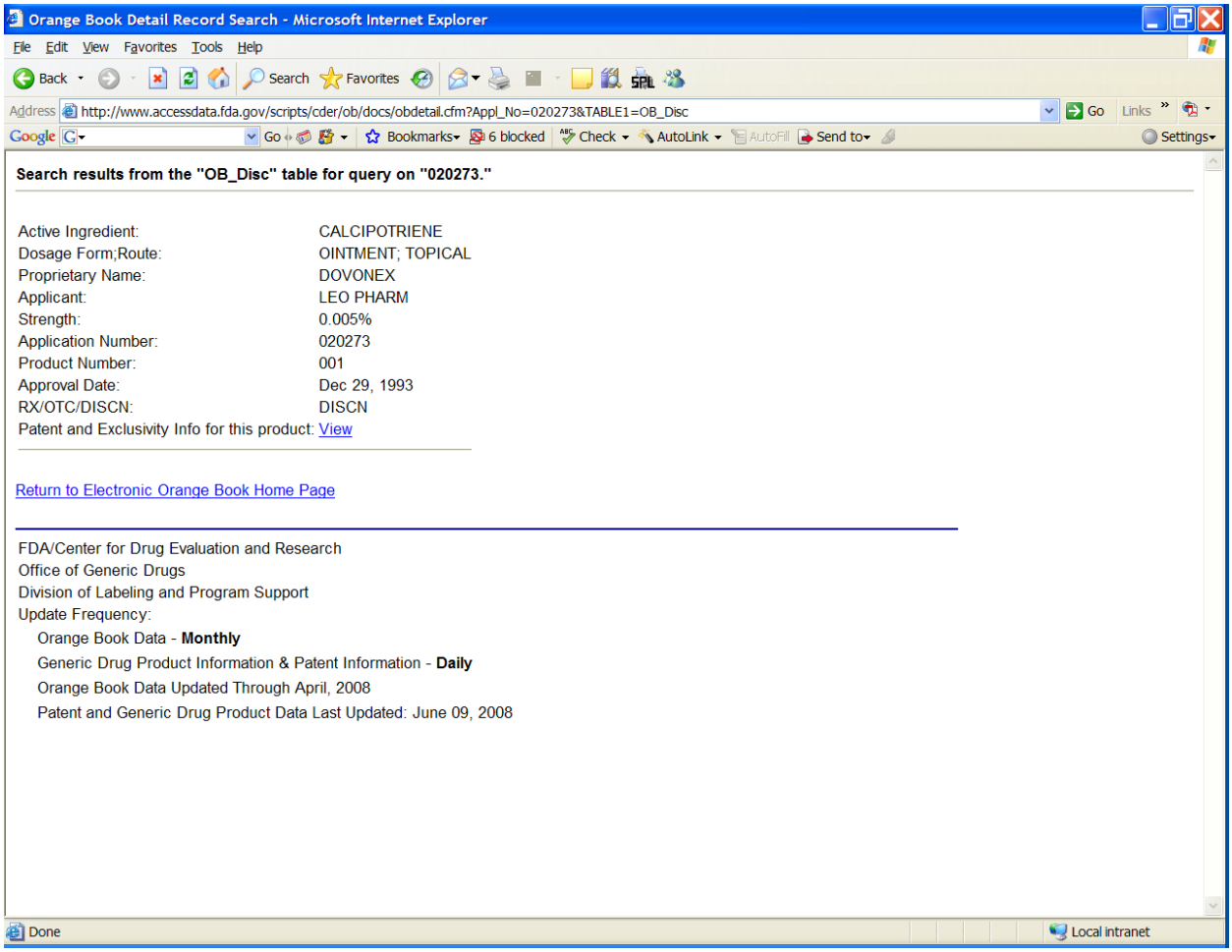
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Google Go Bookmarks 6 blocked Check AutoLink AutoFill Send to Settings
Search results from the "OB_Disc" table for query on "020273."
Active Ingredient: CALCIPOTRIENE
Dosage Form;Route: OINTMENT; TOPICAL
Proprietary Name: DOVONEX
Applicant: LEO PHARM
Strength: 0.005%
Application Number: 020273
Product Number: 001
Approval Date: Dec 29, 1993
RX/OTC/DISCN: DISCN
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
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Orange Book Data Updated Through April, 2008
Patent and Generic Drug Product Data Last Updated: June 09, 2008
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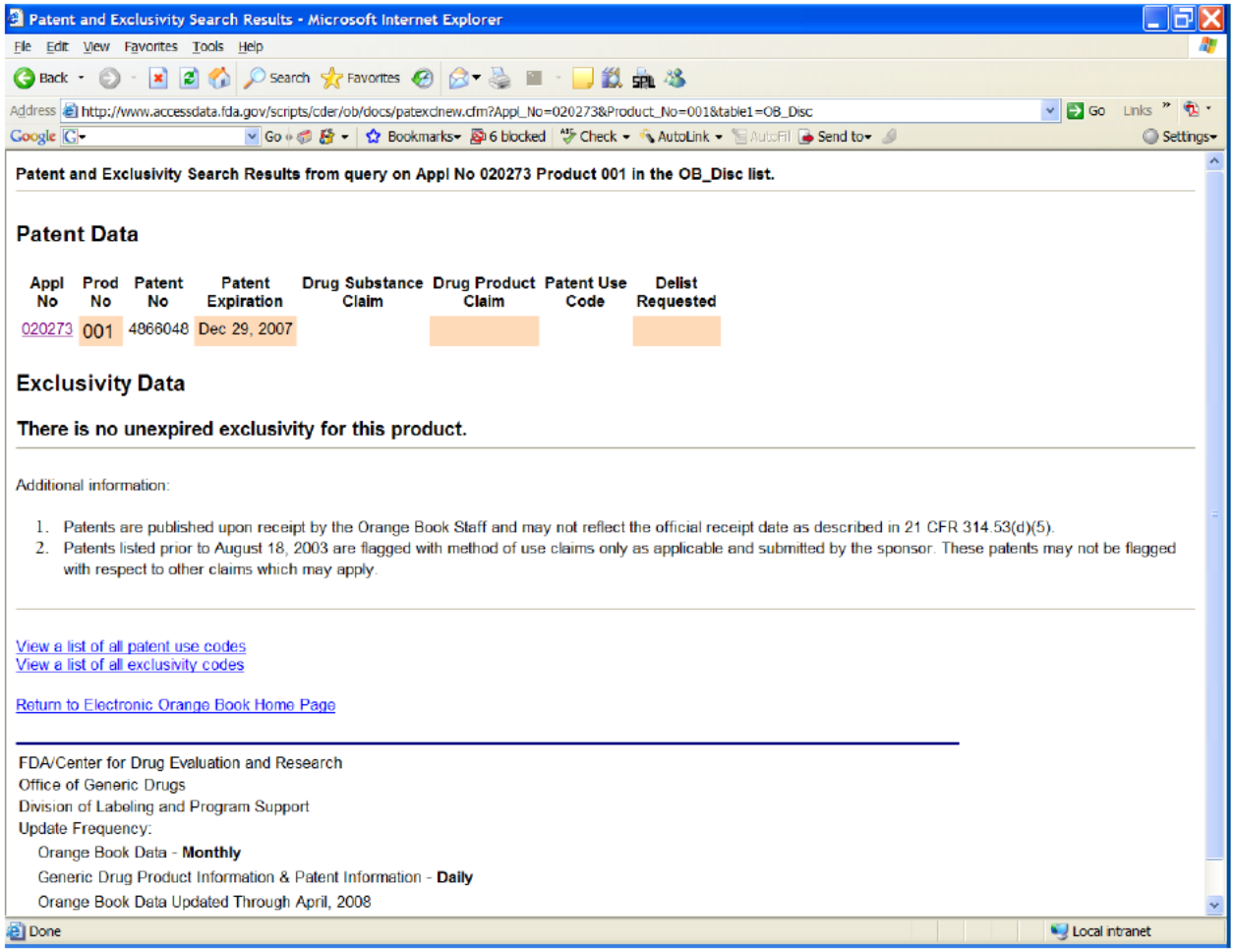
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Patent Data
Appl No
Prod No
Patent No
Patent Expiration
Drug Substance Claim
Drug Product Claim
Patent Use Code
Delist Requested
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4866048
Dec 29, 2007
Exclusivity Data
There is no unexpired exclusivity for this product.
Additional information:
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
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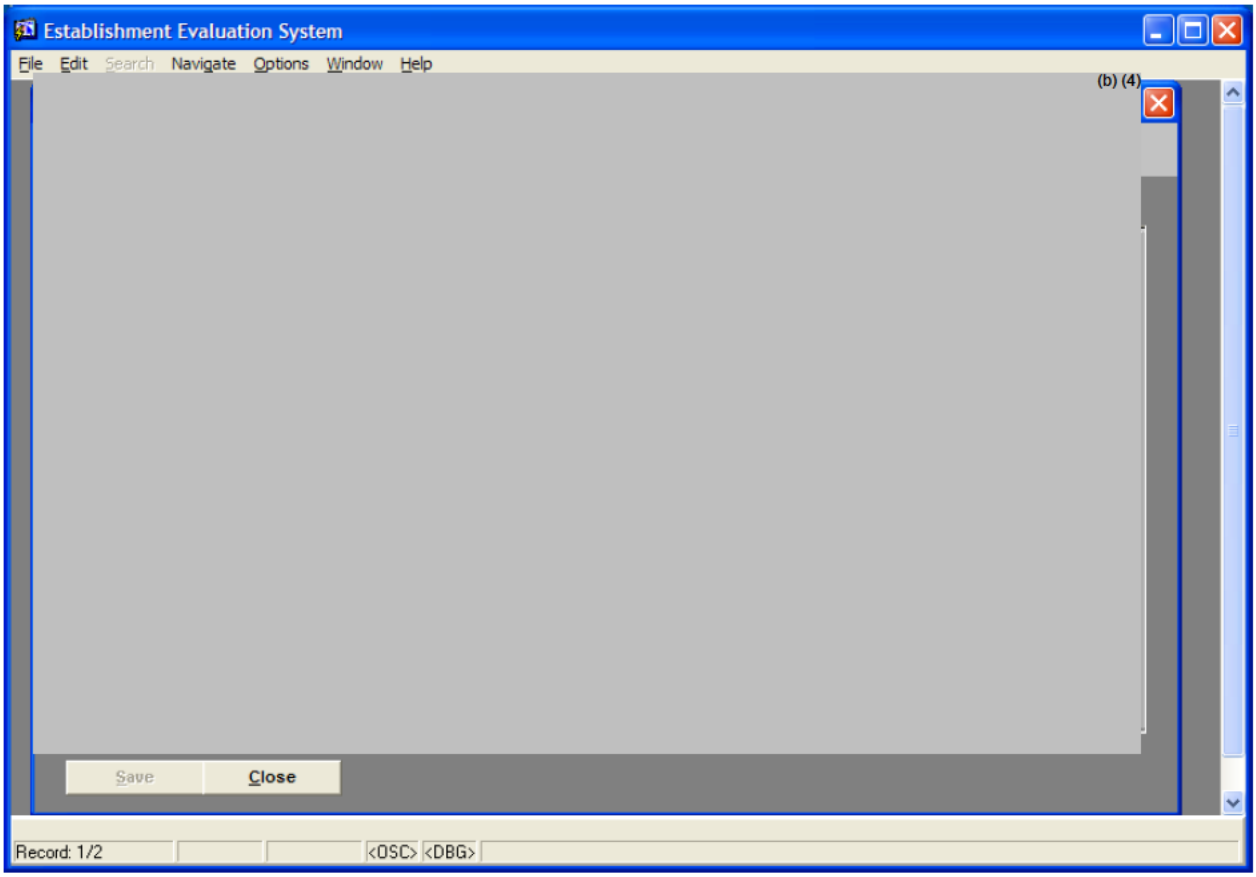
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/s/

Martin Shimer

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 90-633

Glenmark Generics Inc., USA
Attention: Anthony Maffia
750 Corporate Drive
Mahwah, NJ 07430

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated July 22, 2008 and your correspondence dated August 6, 2008.

NAME OF DRUG: Calcipotriene Ointment, 0.005%

DATE OF APPLICATION: May 20, 2008

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 23, 2008

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Rosalyn Adigun
Project Manager
240-276-8518

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Martin Shimer
8/26/2008 02:26:54 PM
Signing for Wm Peter Rickman

Glenmark

September 8, 2008

VIA FEDERAL EXPRESS

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855

ORIG AMENDMENT
N. AE

SUBJECT: ANDA #90-633
Calcipotriene Ointment, 0.005%
Telephone Amendment – USP <467> Commitment

Dear Mr. Buehler:

Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, Glenmark Generics Inc., USA (formerly Glenmark Pharmaceuticals Inc., USA) herewith submits this Telephone Amendment for Calcipotriene Ointment, 0.005% in response to the September 8, 2008 telephone contact with Nashed Nashed, Chemistry Reviewer, OGD.

In accordance with additional information provided by the Office of Generic Drugs regarding the implementation of USP <467>, for which it states applications otherwise acceptable for tentative approval , they may be granted tentative approval status if there is a commitment to administrate compliance with USP <467> prior to Final Approval.

Glenmark Generics Inc., USA commits to administrate compliance with USP <467> prior to Final Approval. The items identified by the Office of Generics Drugs on September 8, 2008 regarding Residual Solvents for excipients will be addressed by Glenmark prior to final approval of the application; therefore, at this time Glenmark respectively requests tentative approval of ANDA #90-633, Calcipotriene Ointment, 0.005%.

This amendment is being submitted as archival and duplicate copies. If I can provide any additional information or clarify the above, please do not hesitate to contact me directly at the number provided below.

Sincerely,
GLENMARK GENERICS INC., USA

Danielle Onlendory for

Anthony M. Maffia III
Associate Director, Regulatory Affairs
Tel: (201) 684-8028
Fax: (201) 831-0080

COMPLETE RESPONSE -- MINOR

ANDA 90-633

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Glenmark Pharmaceuticals Inc., USA TEL: 201-684-8017

ATTN: William McIntyre FAX: 201-831-0080

FROM: Rosalyn Adigun FDA CONTACT PHONE: (240) 276-8518

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated May 20, 2008, and September 8, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Calcipotriene Ointment, 0.005%.

Reference is also made to your amendment dated May 20, 2008, and September 8, 2008.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (**3** pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Following this page, 1 page withheld in full - (b)(4)

10

11. (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The firms referenced in your application should be in compliance with cGMP at the time of approval.

2. Please provide all available drug product room temperature stability data.

3. The Bioequivalence information you have provided is pending review by our Division of Bioequivalence. After the review is completed, any deficiencies found will be communicated to you under a separate cover.

4. The labeling information you have provided is pending review. After the review is completed, any deficiencies found will be communicated to you under a separate cover.

Sincerely yours,

{See appended electronic page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Paul Schwartz
10/17/2008 05:31:16 PM
Signed for R. Patel

Telephone Fax

ANDA 90-633

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8984

TO: Glenmark Pharmaceuticals Inc, USA

TEL: (202)684-8017

ATTN: William McIntyre

FAX: (202)831-0080

FROM: Beverly Weitzman

:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Calcipotriene Ointment, 0.005%.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 90-633

Date of Submission: May 20, 2008

Applicant's Name: Glenmark Pharmaceuticals

Established Name: Calcipotriene Ointment 0.005%

Labeling Deficiencies:

1. **CONTAINER:** (60 gram): Satisfactory in DRAFT

2. **CARTON:** (60 gram): Satisfactory in DRAFT

3. **INSERT:** DESCRIPTION: Inactives: Revise water to read as "purified water"

Revise your labeling, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with that of your last submission with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

John Grace
11/24/2008 10:34:41 AM
for Wm Peter Rickman

December 11, 2008

VIA FEDERAL EXPRESS

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855

SUBJECT: ANDA #90-633
Calcipotriene Ointment, 0.005%
Labeling Amendment.

Dear Mr. Buehler:

Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, Glenmark Generics Inc., USA herewith submits this Labeling Amendment for Calcipotriene Ointment, 0.005% in response to the deficiency letter received from the Agency on December 5 2008.

Pursuant to Code of Federal Regulations Title 21 § 314.94(a)(8)(iv), we are submitting the FPL for the package insert electronically as PDFs .The hard copy of the FPL for the package insert is followed by a side-by-side comparison for reference in **Attachment 1.**

Below we have restated the Agency's comments followed by Glenmark's response.

Labeling Deficiencies:

1. **CONTAINER : (60 gm) : Satisfactory in DRAFT**

2. **CARTON : (60 gm) : Satisfactory in DRAFT**

Glenmark acknowledges the Agency's comments.

3. **INSERT : DESCRIPTION: Inactives : Revise water to read as " purified water"**

Glenmark has revised the package insert in accordance with the Agency's comments. In addition to the electronic (PDF) files, a single hard copy of the FPL of package insert is included in **Attachment 1** for reference. For ease of review, a side by side comparison of the previously submitted draft and proposed final insert label with all differences annotated and explained is also provided.

Glenmark Generics Inc., USA 750 Corporate Drive Mahwah, NJ 07430
Tel (201) 684-8000 Fax (201) 831-0080 www.glenmark-generics.com

This amendment is being submitted as archival and duplicate copies. Please note a CD-ROM containing electronic copies of package insert labeling and SPL is being submitted with the archival copy.

If I can provide any additional information or clarify the above, please do not hesitate to contact me directly at the number provided below.

Sincerely,
GLENMARK GENERICS INC., USA

Anthony M. Maffia, III
Director, Regulatory Affairs
Tel: (201) 684-8028
Fax: (201) 831-0080

Glenmark

January 9, 2009

VIA FEDERAL EXPRESS

Mr. Gary Buehler
Director, Office of Generic Drugs
OGD/CDER
Food and Drug Administration
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 90-633
Calcipotriene Ointment, 0.005%
Minor Amendment-Chemistry

Dear Sir or Madam:

Pursuant to **Code of Federal Regulations** Title 21 § 314.96, Glenmark Generics USA, Inc. herewith submits on their behalf this minor amendment response to the Agency's deficiency letter received on October 20, 2008.

Below we have restated the Agency's comments followed by Glenmark's response.

A. Chemistry Deficiencies:

1. ***Please provide an additional*** [redacted] (b) (4)

   As requested by the agency additional information from [redacted] (b) (4) on the [redacted] (b) (4) is enclosed in **Attachment 1.**

2. ***Please revise your proposed*** [redacted] (b) (4) ***revisions.***

Following this page, 3 pages withheld in full - (b)(4)

(b) (4)

11. Please provide (b) (4)

As recommended by the agency (b) (4) on Calcipotriene Ointment, 0.005%. (b) (4) are enclosed in **Attachment 9.**

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response.

1. ***The firms referenced in your application should be in compliance with cGMP at the time of approval.***

   We acknowledge the agency's comments. The firms referenced in the ANDA application would be in compliance with cGMP at the time of approval.

2. ***Please provide all available drug product room temperature stability data.***

   Please refer **Attachment 10** for 18 months long term stability data.

3. ***The bioequivalence information you have provided is pending review by our Division of Bioequivalence. After the review is completed, any deficiencies found will be communicated to you under a separate cover.***

   Glenmark notes and acknowledges that deficiencies on bioequivalence, if found, will be communicated under separate cover.

4. ***The labeling information you have provided is pending review. After the review is completed, any deficiencies found will be communicated to you under a separate cover.***

   On December 5, 2008 the agency notified Glenmark on the labeling deficiency of Calcipotriene Ointment, 0.005% and Glenmark responded to the agency on December 11, 2008. Glenmark notes and acknowledges that further deficiencies on labeling, if found, will be communicated under a separate cover.

This amendment is being submitted as archival, duplicate and field copies. If I can provide any additional information or clarify any of the above, please do not hesitate to contact me directly at the number provided below.

Calcipotriene Ointment, 0.005%
ANDA 90-633

Minor Amendment-Chemistry

Please be advised that, we, Glenmark Generics Inc. USA, are submitting this submission as paper submission. We are evaluating vendors for electronic submission software and will be able to finalise our vendor very soon. Once we are ready with the electronic software vendor, we will send our future submissions electronically with xml backbone. For the time being we are sending a scanned copy of the response on a CD-ROM Disk along with the paper copy.

Field Copy: This is to certify that the Field Copy, submitted in accord with 21 CFR 314.96(b), is a true copy of the technical section of this submission.

Sincerely,
GLENMARK GENERICS INC., USA

Anthony M. Maffia III
Director, Regulatory Affairs

Tel: (201) 684-8028
Fax: (201) 831-0080

January 23 2009

VIA FEDERAL EXPRESS

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855

SUBJECT: **ANDA #90-633**
Calcipotriene Ointment 0.005%
Telephone Amendment – Labeling.

Dear Mr. Buehler:

Pursuant to **Code of Federal Regulations** Title 21 § 314.96, Glenmark Generics Inc., USA herewith submits this Telephone amendment to the above noted pending application. Reference is made to the Labeling Amendment submitted on December 11, 2008. Further reference is made to the January 21, 2009 telephone contact from Ms. Beverly Weitzman, Project Manager, FDA, OGD.

The following was requested in the above referenced telephone contact:

- FPL of Container and Carton Labels

The Labeling Deficiency received December 5, 2008 stated that the container and carton labels were satisfactory in draft. Glenmark has since revised the website listed on the labels *from* "www.glenmark-generics.com" *to* "www.glenmarkgenerics.com". Glenmark is submitting the FPL for the container and carton labels electronically as PDFs and in hard copy, we are also submitting side-by-side comparisons of our previously submitted labeling, and the proposed labeling, with all differences annotated and explained. The hard copies of FPL for the container and carton labeling are followed by side-by-side comparisons for reference in **Attachment 1**.

Please note the CD-ROM containing all electronic files of labeling is being submitted with the Archival Copy.

If I can provide any additional information or clarify any of the above, please do not hesitate to contact me directly at the number provided below.

Sincerely,
GLENMARK GENERICS INC., USA

Danielle Ohlendorf for

Anthony M. Maffia, III
Director, Regulatory Affairs
Tel: (201) 684-8028
Fax: (201) 831-0080

February 5, 2009

VIA FEDERAL EXPRESS

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, Maryland 20855

SUBJECT: **ANDA #90-633**
Calcipotriene Ointment, 0.005%
Telephone Amendment

Dear Mr. Buehler:

Pursuant to **Code of Federal Regulations** Title 21 § 314.96, Glenmark Generics Inc., USA, U.S. Regulatory Agent for Glenmark Generics Limited, herewith submits on their behalf this Telephone Amendment for Calcipotriene Ointment, 0.005% in response to the February 3, 2008 telephone contact with Nashed Nashed, Chemistry Reviewer, OGD.

Glenmark received a deficiency letter from the Agency on October 20, 2008 and responded to this deficiency on January 9, 2009. Reviewing the deficiency response the Agency indicated the (b) (4) n Glenmark's response to Deficiency #10. The Agency asked for the (b) (4)

Glenmark has accepted the Agency's request to (b) (4) is enclosed in **Attachment 1**. amended as per the Agency's request is provided in **Attachment 2**.

This amendment is being submitted as archival, duplicate and field copies. An electronic copy of this amendment is also being provided and can be found in the **Archival** copy. If I can provide any additional information or clarify any of the above, please do not hesitate to contact me directly at the number provided below.

Field Copy: This is to certify that the Field Copy, submitted in accord with 21 CFR 314.96(b), is a true copy of the technical section of this submission.

Sincerely,
GLENMARK GENERICS INC., USA
U.S. Agent for Glenmark Generics Limited

Anthony M. Maffia, III
Director, Regulatory Affairs

Tel: (201) 684-8028
Fax: (201) 831-0080

BIOEQUIVALENCY COMMENTS

ANDA 090633

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Glenmark Generics Inc., USA TEL: 201-684-8028

ATTN: Anthony M. Maffia, III FAX: 201-831-0080

FROM: Nitin K. Patel PROJECT MANAGER: (240) 276-8887
(240) 276-8966 (fax)

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on May 20, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Calcipotriene Ointment, 0.005%.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has provided comments which are presented on the attached __1__ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

Please direct any questions concerning this communication to the Project Manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090633 APPLICANT: Glenmark Generics Inc., USA

DRUG PRODUCT: Calcipotriene Ointment, 0.005%

The Division of Bioequivalence has completed its review and has no further questions at this time.

The data submitted to ANDA 090633, using the primary endpoints of clinical success rate and treatment success rate at Visit 6, are adequate to demonstrate bioequivalence of Glenmark's Calcipotriene Ointment, 0.005%, with the reference listed drug, Dovonex® Ointment, 0.005%.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90633	ORIG-1	GLENMARK GENERICS INC USA	CALCIPOTRIENE

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/s/

NITIN K PATEL
02/01/2010

DALE P CONNER
02/16/2010

Dated: February 26, 2010.

Maryam I. Daneshvar,

Acting Reports Clearance Officer, Centers for Disease Control and Prevention.

[FR Doc. 2010–4885 Filed 3–8–10; 8:45 am]

BILLING CODE 4163–18–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Administration for Children and Families

Proposed Information Collection Activity; Comment Request

Proposed Projects:

Title: Child Support Enforcement Program Expenditure Report (Form OCSE–396A) and the Child Support Enforcement Program Collection Report (Form OCSE–34A).

OMB No.: 0970–0181.

Description: State and Tribal agencies administering the Child Support Enforcement Program under Title IV–D of the Social Security Act are required to provide information each fiscal quarter to the Office of Child Support Enforcement (OCSE) concerning administrative expenditures and the receipt and disposition of child support payments from non-custodial parents. State title IV–D agencies report quarterly expenditures and collections using Forms OCSE–396A and OCSE–34A, respectively. Tribal title IV–D agencies report quarterly expenditures using Form SF–269, as prescribed in program regulations, and formerly reported quarterly collections using only a modified version of Form OCSE–34A. The information collected on these reporting forms is used to compute quarterly grant awards to States and Tribes, the annual incentive payments to States and provides valuable information on program finances. This information is also included in a published annual statistical and financial report, available to the general public.

Under Public Law 111–5, the "American Recovery and Reinvestment Act of 2009" (ARRA), enacted in February 2009, the availability of Federal funding to State administered child support enforcement programs was substantially increased with a change in methodology of calculating these funds. We propose to formally incorporate this necessary revision into the quarterly expenditure report and to update the existing quarterly collection report to enable the same version of that form to be used by both State and Tribal IV–D agencies. We also propose to review other data entry elements and the accompanying instructions in both data collection forms to assure that the financial information requested from States and Tribes remains relevant and will assure that OCSE collects the information needed in the most efficient format feasible.

Respondents: State agencies (including the District of Columbia, Puerto Rico, Guam and the Virgin Islands) administering the Child Support Enforcement Program. Tribal agencies with approved plans to administer the Child Support Enforcement Program.

ANNUAL BURDEN ESTIMATES

Instrument	Number of respondents	Number of responses per respondent	Average burden hours per response	Total burden hours
OCSE–396A	54	4	8	1,728
OCSE–34A	100	4	8	3,200

Estimated Total Annual Burden Hours: 4,928.

In compliance with the requirements of Section 506(c)(2)(A) of the Paperwork Reduction Act of 1995, the Administration for Children and Families is soliciting public comment on the specific aspects of the information collection described above. Copies of the proposed collection of information can be obtained and comments may be forwarded by writing to the Administration for Children and Families, Office of Administration, Office of Information Services, 370 L'Enfant Promenade, SW., Washington, DC 20447, *Attn:* ACF Reports Clearance Officer. *E-mail address: infocollection@acf.hhs.gov.* All requests should be identified by the title of the information collection.

The Department specifically requests comments on: (a) Whether the proposed collection of information is necessary for the proper performance of the functions of the agency, including whether the information shall have practical utility; (b) the accuracy of the agency's estimate of the burden of the proposed collection of information; (c) the quality, utility, and clarity of the information to be collected; and (d) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques or other forms of information technology. Consideration will be given to comments and suggestions submitted within 60 days of this publication.

Dated: March 3, 2010.

Robert Sargis,

Reports Clearance Officer.

[FR Doc. 2010–4895 Filed 3–8–10; 8:45 am]

BILLING CODE 4184–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket Nos. FDA–2008–P–0435 and FDA–2008–P–0554]

Determination That DOVONEX (Calcipotriene) Ointment, 0.005%, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its determination that DOVONEX (calcipotriene) Ointment, 0.005%, was not withdrawn from sale for reasons of safety or effectiveness. This determination will allow FDA to approve abbreviated new drug applications (ANDAs) for calcipotriene Ointment, 0.005%, if all other legal and regulatory requirements are met.

FOR FURTHER INFORMATION CONTACT: David Joy, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire

Ave., Bldg. 51, rm. 6358, Silver Spring, MD 20993–0002, 301–796–3601.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98–417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products approved under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed drug," which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA). The only clinical data required in an ANDA are data to show that the drug that is the subject of the ANDA is bioequivalent to the listed drug.

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products With Therapeutic Equivalence Evaluations," which is known generally as the "Orange Book." Under FDA regulations, drugs are removed from the list if the agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness, or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162). Under § 314.161(a)(1) (21 CFR 314.161(a)(1)), the agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before an ANDA that refers to that listed drug may be approved. FDA may not approve an ANDA that does not refer to a listed drug.

DOVONEX (calcipotriene) Ointment, 0.005%, is the subject of NDA 20–273, held by LEO Pharmaceutical Products Ltd. (LEO) and initially approved on December 29, 1993. DOVONEX is indicated for the treatment of plaque psoriasis in adults. In its annual report dated February 28, 2008, LEO notified FDA that DOVONEX (calcipotriene) Ointment, 0.005%, had been discontinued, and FDA moved the drug product to the "Discontinued Drug Product List" section of the Orange Book.

Lachman Consultant Services, Inc., submitted a citizen petition dated July 25, 2008 (Docket No. FDA–2008–P–0435), under 21 CFR 10.30, requesting that the agency determine whether DOVONEX (calcipotriene) Ointment, 0.005%, was withdrawn from sale for reasons of safety or effectiveness. A second citizen petition was submitted by Mya Thomae Consulting, Inc., dated October 13, 2008 (Docket No. FDA–2008–P–0554), requesting that the agency determine whether DOVONEX (calcipotriene) Ointment, 0.005%, was withdrawn from sale for reasons of safety or effectiveness.

FDA has reviewed its records and, under § 314.161, has determined that DOVONEX (calcipotriene) Ointment, 0.005%, was not withdrawn from sale for reasons of safety or effectiveness. The petitioners identified no data or other information suggesting that DOVONEX (calcipotriene) Ointment, 0.005%, was withdrawn for reasons of safety or effectiveness. FDA has independently evaluated relevant literature and data for possible postmarketing adverse events and has found no information that would indicate that this product was withdrawn from sale for reasons of safety or effectiveness. Accordingly, the agency will continue to list DOVONEX (calcipotriene) Ointment, 0.005%, in the "Discontinued Drug Product List" section of the Orange Book. The "Discontinued Drug Product List" delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. ANDAs that refer to DOVONEX (calcipotriene) Ointment, 0.005%, may be approved by the agency if all other legal and regulatory requirements for the approval of ANDAs are met. If FDA determines that labeling for this drug product should be revised to meet current standards, the agency will advise ANDA applicants to submit such labeling.

Dated: March 3, 2010.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2010–4925 Filed 3–8–10; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2010–N–0108]

Training Program for Regulatory Project Managers; Information Available to Industry

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) is announcing the continuation of the Regulatory Project Management Site Tours and Regulatory Interaction Program (the Site Tours Program). The purpose of this document is to invite pharmaceutical companies interested in participating in this program to contact CDER.

DATES: Pharmaceutical companies may submit proposed agendas to the agency by May 10, 2010 **Federal Register**].

FOR FURTHER INFORMATION CONTACT: Beth Duvall-Miller, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 6466, Silver Spring, MD 20993–0002, 301–796–0700, e-mail: *elizabeth.duvallmiller@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION:

I. Background

An important part of CDER's commitment to make safe and effective drugs available to all Americans is optimizing the efficiency and quality of the drug review process. To support this primary goal, CDER has initiated various training and development programs to promote high performance in its regulatory project management staff. CDER seeks to significantly enhance review efficiency and review quality by providing the staff with a better understanding of the pharmaceutical industry and its operations. To this end, CDER is continuing its training program to give regulatory project managers the opportunity to tour pharmaceutical facilities. The goals are to provide the following: (1) First hand exposure to industry's drug development processes and (2) a venue for sharing information about project management procedures (but not drug-specific information) with industry representatives.

II. The Site Tours Program

In this program, over a 2- to 3-day period, small groups (five or less) of regulatory project managers, including a senior level regulatory project manager, can observe operations of pharmaceutical manufacturing and/or packaging facilities, pathology/toxicology laboratories, and regulatory affairs operations. Neither this tour nor any part of the program is intended as a mechanism to inspect, assess, judge, or perform a regulatory function, but is meant rather to improve mutual understanding and to provide an avenue for open dialogue. During the Site Tours Program, regulatory project managers

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90633	ORIG-1	GLENMARK GENERICS INC USA	CALCIPOTRIENE

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/s/

EUNJUNG E CHUH

03/10/2010

Feder Register Notice issued on 3/9/2010 - Determination that Dovonex (Calcipotriene) Ointment was not withdrawn from sale for reasons of safety or effectiveness

Glenmark

March 11, 2010

VIA FEDERAL EXPRESS

Mr. Gary Buehler
Director, Office of Generic Drugs
OGD/CDER
Food and Drug Administration
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 90-633
Calcipotriene Ointment, 0.005%
Telephone Amendment-Chemistry

Dear Sir or Madam:

Pursuant to **Code of Federal Regulations** Title 21 § 314.96, Glenmark Generics Inc., USA, herewith submits on their behalf this telephone amendment for Calcipotriene Ointment 0.005% in response to the telephone conversation with Mr. Nashed Nashed and Dr. Paul Schwartz from OGD on March 09, 2010.

Below we have restated the above referenced conversation, followed by Glenmark's response.

A. Chemistry Deficiencies:

1. (b) (4) ***are required.***

As requested by the Agency, the revised (b) (4) (b) (4) is enclosed in **Attachment 1.**

The data for the (b) (4) is also enclosed in **Attachment 1**.

Following this page,1 page withheld in full - (b)(4)

Glenmark's proposed (b) (4)

(b) (4)

3. ***Please provide the*** (b) (4)

(b) (4)

(b) (4)

are included in **Attachment 2**.

This amendment is being submitted as archival, duplicate and field copies. If I can provide any additional information or clarify any of the above, please do not hesitate to contact me directly at the number provided below.

Field Copy: This is to certify that the Field Copy, submitted in accord with 21 CFR 314.96(b), is a true copy of the technical section of this submission.

Sincerely,
GLENMARK GENERICS INC., USA

(for)

Anthony M. Maffia III
Director, Regulatory Affairs

Tel: (201) 684-8028
Fax: (201) 831-0080

March 16, 2010

VIA FEDERAL EXPRESS

Mr. Gary Buehler
Director, Office of Generic Drugs
OGD/CDER
Food and Drug Administration
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Re: ANDA 90-633
Calcipotriene Ointment, 0.005%
Telephone Amendment-Chemistry

Dear Sir or Madam:

Pursuant to **Code of Federal Regulations** Title 21 § 314.96, Glenmark Generics Inc., USA, herewith submits on their behalf this telephone amendment for Calcipotriene Ointment 0.005% in response to the telephone conversation with Dr. Paul Schwartz from OGD on March 15, 2010.

Below we have restated the above referenced conversation, followed by Glenmark's response.

A. Chemistry Deficiencies:

1. ***Please list the*** (b) (4)

   As requested by the Agency, the (b) (4)

   included in **Attachment 1.**

This amendment is being submitted as archival, duplicate and field copies. If I can provide any additional information or clarify any of the above, please do not hesitate to contact me directly at the number provided below.

Glenmark Generics Inc., USA 750 Corporate Drive Mahwah, NJ 07430
Tel (201) 684-8000 Fax (201) 831-0080 www.glenmark-generics.com

Field Copy: This is to certify that the Field Copy, submitted in accord with 21 CFR 314.96(b), is a true copy of the technical section of this submission.

Sincerely,
GLENMARK GENERICS INC., USA

Anthony M. Maffia III
Director, Regulatory Affairs

Tel: (201) 684-8028
Fax: (201) 831-0080

OGD APPROVAL ROUTING SUMMARY

ANDA # 090633 Applicant Glenmark Generics Inc., USA
Drug Calcipotriene Ointment Strength(s) 0.005%

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date 23 February 2010 Date 3/24/10
Chief, Reg. Support Branch Initials MHS Initials rlw

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = Dovonex Oint NDA# 20-273
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked N/A
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.
Comments: ANDA submitted on 5/23/2008, BOS=Dovonex Oint NDA 20-273, PII cert provided. ANDA ack for filing on 5/23/2008(LO dated 8/26/2008). CP submitted on behalf of Glenmark by Lachman requesting that the Agency determine whether NDA 20-273 was D/C'd for reasons of S/E. The Agency's formal determination for this product issued on 3/9/10. ANDA is eligible for Full Approval.

2. Project Manager, Esther Chuh Team 2 Review Support Branch Date 2/22/2010 Date _____
Initials EC Initials _____

Original Rec'd date 5/23/2008
Date Acceptable for Filing 5/23/2008
Patent Certification (type) P II

Date Patent/Exclus.expires n/a - Expired
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 11/12/2008
Date of Office Bio Review Clinical Bio AC 2/1/2010
Date of Labeling Approv. Sum 2/6/2009
Date of Sterility Assur. App. n/a
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer: Labeling Team Leader:
Date 2/22/2010 Date 2/22/2010
Name/Initials Beverly Weitzman Name/Initials John Grace
Comments:

From: Grace, John F
Sent: Monday, February 22, 2010 2:06 PM
To: Weitzman, Beverly
Cc: Chuh, Esther
Subject: RE: Labeling Sign-Off: ANDA 90-633 Glenmark's Calcipotriene Ointment

concur.

From: Weitzman, Beverly
Sent: Monday, February 22, 2010 2:05 PM
To: Grace, John F
Cc: Chuh, Esther
Subject: RE: Labeling Sign-Off: ANDA 90-633 Glenmark's Calcipotriene Ointment

The labeling review done by Beverly Weitzman 2/14/09 and signed off by John Grace 2/16/09 remains acceptable. There are no new changes to the RLD labeling at this time. No changes noted

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 3/24/10
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials rlw/for
Comments:N/A. There are no patents listed in the current "Orange Book" for this drug product.

5. Div. Dir./Deputy Dir. Date3/4/10
Chemistry Div. I Initials PS

Comments:CMC OK.

6. Frank Holcombe **First Generics Only** Date3/22/2010
Assoc. Dir. For Chemistry Initials RMP Comments: (First generic drug review)
Satisafatory for FGAA.

7. Vacant Date_____ Deputy Dir., DLPS
Initials_____

RLD = Dovonex Ointment, 0.005%
Leo Pharmaceutical Products, Ltd. NDA 20-273 (In discontinued section of "Orange Book".

8. Peter Rickman Date 3/24/10
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐ Comments: Bioequivalence study with Clinical Endpoints (plaque psoriasis) found acceptable 2/1/10. Statistical review also foubnd acceptable 12/8/09.

Final-printed labeling (FPL) found acceptable for approval 2/6/09; as endorsed 2/22/10.

CMC found acceptable for approval (Chemistry Review #2, as revised 3/19/10).

OR

8. Robert L. West Date 3/24/10
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EES dated 11/12/08 (Verified 3/24/10). No "OAI" Alerts noted.

There are no patents or exclusivity listed in the current "Orange Book" for this drug product.

On March 9, 2010, the agency's determination that the reference drug product, Leo's Dovonex Ointment was not withdrawn from sale for reasons of safety or effectiveness published in the Federal Register (Volume 75, No. 45).

This ANDA is recommended for approval.

9. Gary Buehler Date 3/24/10
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Esther Chuh Team 2 Date3/24/2010

Review Support Branch Initials EC
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
10:15 AM Time notified of approval by phone
10:30 AM Time approval letter faxed

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90633	ORIG-1	GLENMARK GENERICS INC USA	CALCIPOTRIENE

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/s/

EUNJUNG E CHUH
03/24/2010