

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-852

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

1.2.1.1 Patent Information

LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) holds the following two US patents for the Dovobet® Ointment application:

- 4,866,048 drug substance patent, method of use patent
- 6,753,013 formulation patent, method of use patent

The FDA form 3542a for each patent is presented on the following pages.



1.2.1.2 Patent Certification

Not applicable



EXCLUSIVITY SUMMARY

NDA #21852

SUPPL #

HFD # 540

Trade Name: TACLONEX[®] Ointment

Generic Name: (calcipotriene 0.005% and betamethasone dipropionate 0.064%)

Applicant Name: LEO Pharmaceutical Products Ltd.

Approval Date: January 9, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505b(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

Betamethasone dipropionate received exclusivity not calcipotriene

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 17781 Diprosone[®] lotion (betamethasone dipropionate)
NDA# 18741 Diprolene[®] ointment (betamethasone dipropionate)
NDA# 18827 Lotrisone[®] ointment (betamethasone dipropionate\clotrimazole)
NDA# 19408 Diprolene[®] gel (betamethasone dipropionate)
NDA# 19555 Diprolene[®] cream (betamethasone dipropionate)
NDA# 20010 Lotrisone[®] lotion (betamethasone dipropionate\clotrimazole)
NDA# 19716 Diprolene[®] lotion (betamethasone dipropionate)
NDA# 20-273 Dovonex[®] ointment (calcipotriene)
NDA# 20-554 Dovonex[®] cream (calcipotriene)
NDA# 20-611 Dovonex[®] scalp solution (calcipotriene)

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of

the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

MCB 0003 INT (pivotal)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the

effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 MCB 0003 INT YES NO X

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 MCB 0003 INT YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

MCB 0003 INT (pivotal)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # 62,993 YES ! NO

! Explain:

Investigation #2

IND #

YES

!
!

! NO

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!
!

! NO

! Explain:

Investigation #2

YES

Explain:

!
!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Felecia Curtis

Title: RPM

Date: 12/30/05

Name of Office/Division Director signing form: Jill Lindstrom
Title: Acting Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Jill Lindstrom
2/24/2006 01:38:32 PM

1.2.1.3 Exclusivity Request

The applicant, LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S), believes that approval of the New Drug Application, Dovobet® Ointment, is entitled to a 3-year period of marketing exclusivity under the provision of 21 CFR 314.108, and is therefore claiming exclusivity.

Reference is made to 21 CFR 314.108 (b) (4) to support the claim for exclusivity for Dovobet® Ointment.

The applicant requests three years' exclusivity under the Hatch-Waxman amendments for Dovobet® Ointment in accordance with exclusivity under the Federal Food, Drug, and Cosmetic Act section 505(c)(3)(D) as the application contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the application.



PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-852 Supplement Type (e.g. SE5): _____ Supplement Number: _____

HFD-540 Trade and generic names/dosage form: (Calcipotriene, 0.005% & Betamethasone, _____)

Applicant: LEO Pharmaceutical Products Ltd Therapeutic Class: 3S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: For the topical treatment of psoriasis vulgaris in adults aged 18 years and above

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived: 0 to 11 years

Min _____ kg _____ mo. 0 yr. 0 Tanner Stage _____
Max _____ kg _____ mo. 0 yr. 11 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: Sponsor specified exact population to study.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred: 12 to 17 years

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other:

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. 0 _____ yr. 18 _____ Tanner Stage _____
Max _____ kg _____ mo. 0 _____ yr. 00 _____ Tanner Stage _____

Comments: 18 years and above

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Felecia Curtis, RN
Regulatory Project Manager

cc: NDA
HFD-960/Grace Carmouze
(revised 12-22-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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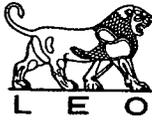
/s/

Felicia Curtis
5/17/05 11:59:19 AM

Brenda Carr
5/17/05 01:27:34 PM

Jill Lindstrom
5/20/05 03:57:54 PM

Jonathan Wilkin
6/2/05 06:09:37 PM



LEO Pharma A/S (LEO Pharmaceutical Products Ltd. A/S)

Debarment Certification

LEO Pharma A/S (LEO Pharmaceutical Products Ltd. A/S) hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this New Drug Application for Dovobet® Ointment.

Date: 10 Jan 2005

Jesper Kihl

Jesper Kihl
Vice President
Regulatory Affairs & Safety
LEO Pharma A/S (LEO Pharmaceutical Products A/S)
Industriparken 55
DK-2750 Ballerup, Denmark
Telephone: +45 44 94 58 88

Counter-signature:

Date: 7 Feb. 2005

Alberto Grignolo

Alberto Grignolo, Ph.D.
Corporate V.P. and General Manager
Drug Development Consulting Practise
PAREXEL International
195 West Street
Waltham, MA 02451-1163
Telephone: 781-434-9900

MEMORANDUM OF TELECON

DATE: January 9, 2006, 3:13 P.M.

APPLICATION NUMBER: NDA 21-852

DRUG PRODUCT: TRADENAME: Taclonex® Ointment

BETWEEN:

Name: Gail Gilfort, Regulatory Affairs Consultant

Phone: 919-294-5099

Representing: Parexel Consulting

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
Felecia Curtis, Regulatory Project Manager

SUBJECT: NDA 21-852

The Approval letter was sent via facsimile to the Applicant on January 9, 2006. The Applicant confirmed receipt of the fax via telephone on January 9, 2006 at 3:39 P.M

The teleconference ended amicably.

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/s/

Felicia Curtis
1/10/2006 02:24:47 PM
CSO

FDA Fax Memo

Date: January 5, 2006

Subject: NDA 21-852 Taclonex[®] Ointment

Hi Gail,

The following draft proposed Phase 4 commitment for NDA 21-852 for the topical treatment of psoriasis vulgaris in adults aged 18 years and above. Please provide your concurrence as soon as possible in order to finalize the action letter.

Pharmacology/Toxicology Phase 4 Study Request Commitment

The sponsor has committed to conduct the following nonclinical studies post-approval of the NDA:

1. Evaluation of the carcinogenicity of calcipotriene (this matter is currently being evaluated by the sponsor as a post-approval commitment to NDA 20-273) and study reports should be submitted when available.

Commitment Category: NON-CLINICAL TOXICOLOGY

Final Report Submission: Within 12 months after the study completion

2. Evaluation of the carcinogenicity of betamethasone dipropionate in mice. The sponsor should submit a protocol for this study with appropriate supporting documents for evaluation by the executive carcinogenicity assessment committee of CDER following approval of NDA 21-852.

Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission: Within 6 months of the date of this letter or by (insert date)

Study Start: Within 6 months of the date of the approval of the protocol
or by (insert date)

Final Report Submission: Within 12 months after the study completion by (insert date)

3. Evaluation of the carcinogenicity of betamethasone dipropionate in rats. The sponsor should submit a protocol for this study with appropriate supporting documents for evaluation by the executive carcinogenicity assessment committee of CDER following approval of NDA 21-852.

Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission: Within 6 months of the date of this letter or by (insert date)

Study Start: Within 6 months of the date of the approval of the protocol
or by (insert date)

Final Report Submission: Within 12 months after the study completion by (insert date)

4. Evaluation of betamethasone dipropionate for effects upon female fertility, including prenatal and postnatal function.

Commitment Category: NON-CLINICAL TOXICOLOGY

Study Start: Within 6 months of the date of this letter or by (insert date)

Final Report Submission: Within 6 months after the study completion by (insert date)

Clinical Phase 4 Study Request Commitment

1.

Study Start: (insert date)
Final Report Submission: (insert date)

If you have questions, please contact me at (301) 827-2043.

Respectfully,
Felecia Curtis

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/s/

Felicia Curtis
1/5/2006 12:28:02 PM
CSO

PAREXEL

PAREXEL International
2520 Meridian Parkway, Suite 200
Durham, North Carolina 27713
+1 919 544 3170 Fax: +1 919 544 3410
www.parexel.com

29 November 2005

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

**RE: NDA 21-852
Dovobet® Ointment .
Response to FDA Request for Information**

Dear Dr. Wilkin:

PAREXEL International (PAREXEL), acting as US Agent on behalf of LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S), is submitting additional information in response to comments issued by the Division regarding the Dovobet® ointment New Drug Application (NDA) submitted to FDA on 9 March 2005.

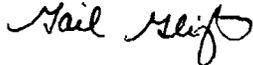
On 28 November 2005, a facsimile transmission from the Division was sent to the Sponsor requesting information regarding statements in the Summary of Product Characteristics included in the summary section of the application. In the fax, the clinical reviewer requested that the Sponsor provide the basis for the contraindication of use of Dovobet® ointment in patients with severe renal or hepatic insufficiency. A response to this request is contained in the following document.

— Dintment
NDA 21-852

Response to Request
Clinical Reviewer Request

If there is any additional documentation that the Division would like to further assist them with the review the NDA, please do not hesitate to contact me at 919-294-5099 (fax 919-544-3410) or via e-mail at gail.glifort@parexel.com. Thank you.

Sincerely,



Gail Glifort, RAC
Consultant
PAREXEL Consulting

cc: LEO Pharma A/S: Berit Mølby, Regulatory Affairs, Initial Filing
Nina Christiansen, Regulatory Affairs, Initial Filing

PAREXEL: Project Files

MEMORANDUM OF TELECON

DATE: November 18, 2005 10: 30 AM

APPLICATION NUMBER: NDA 21-852

DRUG PRODUCT: Dovobet Ointment

BETWEEN:

Division of Dermatology and Dental Products, HFD-540
Ramesh Sood, Ph.D., Chief, Branch 1, OPS/ONDQA
Ernest Pappas/Chemistry Reviewer, ONDQA
Felecia Curtis, Regulatory Project Manager

AND

Attendees via teleconference:

Gail Glifort, Regulatory Affairs Consultant for Parexel Consulting
Vibeke Jessen (Stability Testing department)
Jens Hansen (Vice President, Pharmaceutical Development)
Nina Christiansen, Berit Mølby and Gitte Schönwandt (Regulatory affairs)

Phone: 1-866-205-3978

SUBJECT: NDA 21-852

A teleconference was initiated by the Agency to request information from Parexel Consulting regarding the established name for Betamethasone Dipropionate, for NDA 21-852 (Dovobet Ointment).

The Agency informed Parexel Consulting of a concern regarding the use of Dovobet (calcipotriene, 0.005% and betamethasone, 0.0643%) Ointment. In this regard, the sponsor was requested to revise the labeling to replace Betamethasone with Betamethasone Dipropionate since Betamethasone Dipropionate is the established name as indicated by USAN. The revised labeling should reflect the following changes in the package insert, carton and tube labeling:

From: Dovobet (calcipotriene, 0.005% and betamethasone, 0.0643%) Ointment
To: Dovobet (calcipotriene, 0.005% and betamethasone dipropionate, 0.0643%) Ointment

Each gram of Dovobet Ointment should contain a calcipotriene hydrate (equivalent to 0.5 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in an ointment base of PPG-15 stearyl ether, dl-alpha tocopherol and

The Sponsor stated that they agreed with FDA's request for the labeling revision as stated above. However, they would have to receive final concurrence from their management, which they could give us on Monday.

The sponsor also requested clarification on the fax that was sent to them on November 17, 2005. In this regard, they asked for clarification for item 2. The FDA gave them this clarification. The sponsor indicated that they understood.

The conversation ended amicably.

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/s/

Felicia Curtis
11/21/2005 03:51:15 PM
CSO

Ramesh Sood
11/21/2005 04:00:39 PM
CHEMIST

PAREXEL International

2520 Meridian Parkway, Suite 200

Durham, North Carolina 27713

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www.parexel.com

PAREXEL

DESK COPIES

November 13, 2005

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatological and Dental Drug Products
Attn: Felecia Curtis, Project Manager
10903 New Hampshire Ave, Bldg. 22, Room 5176
Silver Spring, MD 20993-0002

Re: NDA 21-852
Dovobet® Ointment
Desk copies of the recent alternate trade name submission

Dear Felecia,

In the FDA Fax of August 31, 2005, which contained the comments from DMETS regarding the Dovobet ointment labelling, the Division requested the submission of alternate trade names for review. As requested, we are submitting two alternatives in a submission being sent to the Division this evening.

I am sending two desk copies of the submission to you because they contain the sound files on disk that I am not sure would be forwarded from the Central Document Room. One copy is your desk copy; the other is for the reviewers at the Office of Drug Safety (DMETS). I am sending 8 copies of the submission to the Central Document Room. The archive version contains a disk with the sound files; the others just contain the paper files (Safety and Promotional Assessments attached above). These are intended for the Division reviewers and extra copies for ODS reviewers. I hope this provides you with a sufficient number of copies for proper review.

Because it was stated in the August fax that review of the alternate names could take 3-4 months, we have asked for an expedited review of the proposed alternatives. It is our intent that this submission be included in the labelling review meeting scheduled for the end of the month.

If you have any questions or concerns regarding this submission, please do not hesitate to contact me. I will be out of the office tomorrow, but will return on Monday.

Thank you for your attention to this important issue.

Thank you.

Regards,



Gail Glifort, RAC
Consultant
PAREXEL Consulting

Enc (2)

PAREXEL International
2520 Meridian Parkway, Suite 200
Durham, North Carolina 27713
+1 919 544 3170 Fax: +1 919 544 3410
www.parexel.com

PAREXEL

ORIG AMENDMENT

DUPLICATE

BL

RECEIVED

NOV 04 2005

CDR/ODEP

3 November 2005

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

**RE: NDA 21-852, Dovobet[®] Ointment
Response to FDA Request for Information
Alternative Tradenames - Request for Expedited Review**

Dear Dr. Wilkin:

PAREXEL International (PAREXEL), acting as US Agent on behalf of LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S), is submitting additional information in response to comments issued by the Division regarding the Dovobet[®] ointment New Drug Application (NDA) submitted to FDA on 9 March 2005.

On 31 August 2005, a fax was sent to the Sponsor by the Division containing comments from the Division of Medication Errors and Technical Support (DMETS) concerning the tradename, Dovobet[®] ointment, and product labeling.

On 16 September 2005, a response to these comments was submitted to the Division along with revised product labels. In this response, LEO submitted a defense of the Dovobet[®] ointment tradename and also a proposal to modify the appearance of the tradename to _____ to help differentiate it orthographically from Dovonex[®].

It is our understanding that the Division is not expected to issue a decision on our defense of the tradename, _____, until their scheduled meeting on November 23, 2005. In view of the limited time remaining before our PDUFA Action Date for this application of January 9, 2006, LEO feels it is imperative that the application is approved with a tradename found acceptable by the Division. Therefore, we find it necessary to provide two alternative tradenames for consideration in the event that our defense of the tradename, _____, is not satisfactory.

Again, our first preference is the tradename _____. We strongly believe that Dovonex[®] has market recognition with the active ingredient calcipotriene; therefore, maintaining the association of "Dovo" for calcipotriene and introducing the _____ for

betamethasone will assist patients, physicians, pharmacists and nurses in recognizing the active ingredients of the product, and it will be a benefit to the healthcare community.

It is our hope that, after careful consideration, the Division accepts the tradename _____ for the product for the reasons given above and those included in the document submitted in September 2005.

Our second preference is the alternative tradename, _____. To facilitate the Division in their review of this alternative tradename, we are submitting an assessment with regard to the promotion and safety that was issued by the Brand Institute.

In the event that neither of our preferred names are selected by the Division, LEO asks that the Division consider the use of **Taclonex**® as the tradename of the ointment.

The Division has indicated that it may take up to 3-4 months to review additional tradenames, however, LEO respectfully requests that these alternative trade names may be reviewed on an expedited basis if necessary, in order to ensure that the product has an acceptable tradename by the PDUFA Action Date.

If there is any documentation that the Division would like to further assist them with the review of the tradename and the overall NDA, please do not hesitate to contact me at 919-294-5099 (fax 919-544-3410) or via e-mail at gail.glifort@parexel.com. We look forward to your response.

Sincerely,



Gail Glifort, RAC
Consultant
PAREXEL Consulting

cc: LEO Pharma A/S: Berit Mølby, Regulatory Affairs, Initial Filing
Nina Christiansen, Regulatory Affairs, Initial Filing

PAREXEL: Project Files

PAREXEL International

PAREXEL

2520 Meridian Parkway, Suite 200

Durham, North Carolina 27713

+1 919 544 3170 Fax: +1 919 544 3410

www.parexel.com

DUPLICATE

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NOV 03 2005

CDR / CDER

2 November 2005

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

N-000(0m)

ORIG AMENDMENT

RE: NDA 21-852
Dovobet[®] Ointment
Response to FDA Request for Information

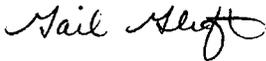
Dear Dr. Wilkin:

PAREXEL International (PAREXEL), acting as US Agent on behalf of LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S), is submitting a response to comments issued by the Division regarding the Dovobet[®] ointment New Drug Application (NDA) submitted to FDA on 9 March 2005.

On 1 November 2005, an FDA fax was sent to the sponsor with a request for clinical information. It was requested that a copy of the reference, British Medical Journal, 1997 March 5; 1(6061):598, be forwarded to the Division to facilitate the evaluation of the NDA. We hereby provide a copy of the reference as requested.

If there are any questions regarding this marketing application, please do not hesitate to contact me at 919-294-5099 (fax 919-544-3410) or via e-mail at gail.glifort@parexel.com.

Sincerely,



Gail Glifort, RAC
Consultant
PAREXEL Consulting

cc: LEO Pharma A/S: Berit Mølby: Regulatory Affairs, Initial Filing
Gitte Schönwandt: Regulatory Affairs, Initial Filing

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NOV 1 2005

CDR / CDER

31 October 2005

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 21-852
Dovobet[®] Ointment
Response to 483 Observation – Change in Specification

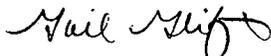
Dear Dr. Wilkin:

PAREXEL International (PAREXEL), acting as US Agent on behalf of LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S), is submitting a response to a Form 483 observation (FEI No. 3002807496) noted during the Pre-Approval Inspection (PAI) conducted for the Dovobet[®] ointment New Drug Application (NDA) submitted to FDA on 9 March 2005.

A PAI was conducted by the FDA in June 2005. During the inspection, it was observed that there were deviations from written specifications for the acceptance criteria for purified water. In response to this observation, LEO is introducing an action limit to the specifications for organisms in purified water. The documentation for this response and change are located on the following pages. This response was previously submitted to the Office of Compliance.

If there are any questions regarding this marketing application, please do not hesitate to contact me at 919-294-5099 (fax 919-544-3410) or via e-mail at gail.glifort@parexel.com.

Sincerely,



Gail Glifort, RAC
Consultant
PAREXEL Consulting

cc: LEO Pharma A/S: Gitte Schönwandt: Regulatory Affairs, Initial Filing
Nina Christianse: Head, Regulatory Affairs, Initial Filing

PAREXEL: Project Files

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ORIG AMENDMENT

RECEIVED

OCT 13 2005

CDR/CDER

12 October 2005

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

N-000(BM)

RE: NDA 21-852
Dovobet® Ointment
Response to FDA Request for Information

Dear Dr. Wilkin:

PAREXEL International (PAREXEL), acting as US Agent on behalf of LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S), is submitting a response to comments issued by the Division regarding the Dovobet® ointment New Drug Application (NDA) submitted to FDA on 9 March 2005.

On 11 October 2005, an FDA fax was sent to the sponsor with requests from the clinical reviewer. The reviewer requested information regarding the formula used by the sponsor to calculate the albumin-corrected serum calcium levels. We hereby provide a response with the formula requested.

If there are any questions regarding this marketing application, please do not hesitate to contact me at 919-294-5099 (fax 919-544-3410) or via e-mail at gail.glifort@parexel.com.

Sincerely,



Gail Glifort, RAC
Consultant
PAREXEL Consulting

cc: LEO Pharma A/S: Gitte Schönwandt: Regulatory Affairs, Initial Filing
Berit Mølby: Regulatory Affairs, Initial Filing

PAREXEL: Project Files

DUPLICATE

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PAREXEL

ORIGINAL

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SEP 23 2005

CDER White Oak DR 1

RECEIVED

SEP 22 2005

CDR / CDER

21 September 2005

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: **NDA 21-852**
Dovobet[®] Ointment
Response to FDA Request for Information

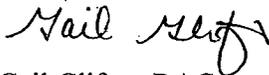
Dear Dr. Wilkin:

PAREXEL International (PAREXEL), acting as US Agent on behalf of LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S), is submitting a response to comments issued by the Division regarding the Dovobet[®] ointment New Drug Application (NDA) submitted to FDA on 9 March 2005.

On 13 September 2005, an FDA fax was sent to the sponsor with requests from the CMC and Biopharmacology reviewers. The reviewers requested information regarding the lots used in pivotal clinical and in vivo clinical pharmacology trials, including particle size and stability data. We hereby provide a response with the data requested.

If there are any questions regarding this marketing application, please do not hesitate to contact me at 919-294-5099 (fax 919-544-3410) or via e-mail at gail.glifort@parexel.com.

Sincerely,



Gail Glifort, RAC
Consultant
PAREXEL Consulting

cc: LEO Pharma A/S: Gitte Schönwandt: Regulatory Affairs, Initial Filing
Nina Christiansen: Regulatory Affairs, Initial Filing

PAREXEL: Project Files

_____ Ointment
DMETS Review Comments for _____[®] Tradename
Fax of August 31, 2005

LEO request for DMETS reconsideration of the proprietary name

DMETS COMMENT

DMETS does not recommend the use of the proprietary name, Dovobet. In reviewing the proprietary name, the primary concerns related to look-alike and sound-alike confusion with Dovonex. Dovonex was identified to have look and sound-alike similarities to the proposed name, Dovobet. Dovonex is indicated for the treatment of moderate plaque psoriasis and is available in 0.005% ointment, 0.005% cream, and 0.005% solution. Dovonex is applied to affected area(s) twice daily. Dovonex contains Calcipotriene as the single active ingredient while _____ contains Calcipotriene in combination with the corticosteroid Betamethasone. The identical beginning letters shared between Dovonex and Dovobet ("Dovo") is the principal contribution to the look-alike and sound-alike similarities of the two names. Additionally, the auditory similarities are compounded by the three syllable count and orthographic similarities by the shared seven letter count. Furthermore, the letter "x" in Dovonex can look similar to the letter "t" in Dovobet, depending on how it is scripted. However, Dovobet contains the upstroke letter "b" which, if scripted prominently, may help differentiate the names orthographically. Additionally, the differing last syllable "-nex" vs. "-bet") may help to distinguish the names from each other when pronounced. Dovonex is supplied in multiple dosage forms (ointment, cream, and solution). Thus, the intended dosage form will either be stated on the order or obtained from the prescriber prior to dispensing. This dosage form designation will help to differentiate the two names on a prescription and help to minimize the potential for medication errors. However, both products are available as ointments and thus, inclusion of the dosage form on an order may not help to minimize the confusion between the name pair. While the frequency of application (twice daily vs. once daily) is another product characteristic that may help to distinguish Dovonex from Dovobet, it is not unlikely to have topical products ordered with "as directed" directions for use.



Furthermore LEO suggests utilizing "[redacted]" letters as a risk management tool to highlight the different portion of the two names. This technique has been used to differentiate approved proprietary and non-proprietary names by the FDA. An example includes [redacted], when medication errors were reported with Lamisil. We propose the appearance as "[redacted]", which will appear on the labels and labeling of the product. LEO believes that this along with the other actions taken, as described below, will indeed differentiate the "[redacted]" name from Dovonex® and therefore kindly request the Agency to reconsider its recommendation not to use the proprietary name [redacted].

DMETS COMMENT

If Dovobet is inadvertently dispensed instead of Dovonex, the patient would be exposed a high potency corticosteroid (i.e., betamethasone dipropionate) and may experience the local (e.g., atrophy and hypopigmentation) and systemic (e.g., hypothalamic-pituitary-adrenal axis (HPA) suppression) adverse effects associated with topical corticosteroids. If Dovonex is inadvertently dispensed instead of Dovobet, the patient will not receive the benefits of the corticosteroid the prescriber intended the treatment to include and thus, the patient's condition may fail to improve or worsen.

LEO RESPONSE

Physicians, pharmacists and patients are in our opinion able to recognize and distinguish the two products from each other. Both active substances are used for treatment of psoriasis in sequential therapy. Typically, for initial or acute treatment of psoriasis plaques [redacted] or a steroid alone is used followed by Dovonex®. For treatment outcome or safety reasons, both products can be used at any phase of psoriasis treatment. The products may also be used in an alternating fashion in pulse therapy. Treatment efficacy and safety have been shown in several studies for both products alone, and also for sequential or pulse combination regimes of both products.

Both products are effective and safe treatments for patients with psoriasis vulgaris amenable to topical treatment [redacted] reduces symptoms faster than Dovonex® and therefore presents a convenience benefit during acute disease phases. However, the patient's condition is not expected to fail to improve or worsen if Dovonex® is used instead of [redacted].



The safety profile of _____⁶ is based on data from more than 3,000 patients treated with _____ ointment. Regarding risk of local adverse effects, skin atrophy was infrequent (0.1%) and hypopigmentation reported in less than 1% (NDA 21-852, Module 2, Clinical Overview; 2.5.5.14). These effects are known to be associated mainly with prolonged use of potent topical steroids and _____ ointment has been shown to be safe also when used as required for up to 52 weeks (NDA 21-852, Module 2, Clinical Overview; 2.5.5.9). Systemic effects have been investigated in terms of HPA axis suppression and no cases were reported for _____ ointment, even in patients with very extensive psoriasis (NDA 21-852, Module 2, Clinical Overview; 2.5.3.1). Thus, the risk of steroid-related effects if _____ was accidentally used instead of Dovonex[®] for a limited treatment period is very small.

DMETS COMMENT

Furthermore, whether the drugs are stored by proprietary name or by route of administration (topical), they will likely be stored next to each other on the pharmacy shelves. This may lead to selection errors among these products due to their similar names. Moreover, Dovonex and Dovobet have many overlapping product characteristics including prescriber population (dermatologists), ordered quantity (30 grams, 60 grams, and 100 grams), treatment duration (chronic), product strength (0.005%), indication for use (psoriasis), route of administration (topical), dosage formulation (ointment), and patient population (patients with psoriasis). The orthographic similarities overlapping product characteristics, and potential for similar prescribing directions (use as directed), increase the potential for confusion involving this name pair.

LEO RESPONSE

The outer packaging of _____⁶ ointment differs significantly from the outer packaging of Dovonex[®] ointment which helps distinguish the two products from each other. As shown below, the Dovonex[®] ointment carton is presented in the colors of green/turquoise and white, whereas the proposed carton package for _____⁶ ointment is a neutral white package with black text and red stripes. Even if the two products are located next to each other on pharmacy shelves, the design of the packaging material will help differentiate the products from each other, thus minimizing the potential user error.



DMETS state that the many overlapping product characteristics between Dovonex[®] and — may increase the potential for confusion; however, LEO finds that many of these product characteristics may be of benefit for both the prescriber and the patients. The fact that the prescriber and patient population is identical for the two products may be beneficial as doctors and patients are well introduced to “Dovo” nex[®], which in the US is well known, established and perceived as calcipotriene, an effective treatment of psoriasis vulgaris. Doctors are - and eventually patients will also be - able to recognize and separate the two products from each other. The — name emphasizes with its last syllable — ne other active compound betamethasone dipropionate, which is also used for the treatment of psoriasis and has been available on the US market in several topical formulations (such as Alphatrex[®], and Betamethasone dipropionate from various manufacturers). This intuitive perception of two active compounds associated with the product name — supports patients and doctors in the distinction of the two products. Furthermore, and because of the steroid compound which is associated with the name, efficacy expectations from doctors and patients towards the two products is different. This is, at least, our experience from other countries in Europe where both names do co-exist with each other. This has also been confirmed in market analyses performed to monitor the immediate association of doctors to the name Dovobet[®] — in countries where Dovonex[®]/Dovobet[®] and Daivonex[®] — co-exist (see appendix I and II for lists of countries where the two names co-exist).

The strength of the active ingredient, calcipotriol, is identical in the two products; however, — also contains the active ingredient, betamethasone, which clearly distinguishes the two products. The names of the active ingredients will also be printed on the packaging materials of Dovonex[®] ointment and — ointment (see below).

Indication for use, route of administration and dosage formulation are similar for both products, Dovonex[®] ointment and —[®] ointment, however, this again may eventually ensure correct use of both products used by the same patient for the same disease.

DMETS COMMENT

Additionally, DMETS reviewed the container labels, carton, and insert labelling from a safety perspective.



LEO RESPONSE

LEO has taken these comments into consideration and has followed most of DMETS suggestions to alter the container labels and carton in order to differentiate the packaging material for the two products further. Please see our separate response submitted on September 16, 2005 and the proposed outer packaging for [redacted] ointment above. Furthermore LEO has added a barcode to the proposed carton for [redacted] ointment which we believe will help minimize medication/dispensing errors.

EXPERIENCE FROM EUROPE

Dovobet[®] ointment was first launched in Denmark in October, 2001, under the tradename Daivobet[®] and has, since then, been launched for the treatment of psoriasis vulgaris in most European countries, in Asia, in South America and in Canada. In all these countries LEO has also marketed its calcipotriene monocomponent product for psoriasis treatment under the tradenames Dovonex[®] or Daivonex[®]. Reference is made to appendix I listing the countries in which Dovonex[®]/Daivonex[®] ointment and Dovobet[®]/Daivobet[®] ointment are approved and marketed.

As seen in appendix I, the tradename Dovobet[®] co-exists with the name Dovonex[®] in Canada, Ireland, Greece, Cyprus and the United Kingdom. During the last four years where the tradenames have co-existed in these markets LEO has not received any reports, nor are LEO aware of any reports on medication errors made due to the similarity of the tradenames. Furthermore, LEO has recently asked the health authorities in Canada, Greece and United Kingdom if they have received or registered any pharmacovigilance reports caused by confusion of mix-ups between Dovonex[®] and Dovobet[®].

As seen in the table below there has been no reporting of any mix-ups between Dovonex[®] and Dovobet[®] in those countries. In order to emphasize that many patients have been using Dovobet[®] ointment while it has co-existed with Dovonex[®] we have also listed the number of prescriptions sold of each product the last two years on the particular market.



| | Co-existence of trade-names since | Number of prescriptions | | | | Extract from the Health Authority Response |
|----------------|-----------------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---|
| | | Dovonex [®] 2003 | Dovobet [®] 2003 | Dovonex [®] 2004 | Dovobet [®] 2004 | |
| Canada | December 2001 | } | } | } | } | <i>No reports of Dovobet[®] being mixed-up with Dovonex[®]</i> |
| Greece | November 2002 | | | | | <i>No such reporting has been made.</i> |
| Ireland | April 2002 | | | | | <i>Has not received any reports of mix-up errors between Dovonex[®] and Dovobet[®]</i> |
| United Kingdom | May 2002 | | | | | <i>Have not received any reports of medication error associated with the products Dovobet[®] and Dovonex[®]</i> |

Co-existence of the tradename with Daivonex[®] is very common in the European countries as in the rest of the world (see appendix II). As for the markets with the Dovobet[®]/Dovonex[®] tradenames the markets with co-existence of /Daivonex[®] have not experienced any mix-ups between the tradenames that have resulted in a safety reporting. LEO has asked the health authorities in Switzerland, Sweden, Finland, Germany and Norway, if they have received or registered any pharmacovigilance reports caused by confusion of mix-ups between and [®]. Please see the below table for extracts of the responses received from the Health Authorities (full responses from all Health Authorities are available upon request).



| | | Number of prescriptions | | | | Extracts from the Health Authority Response | |
|-------------|-----------------------------------|-------------------------|------------------------|----------------|------------------------|--|--|
| | Co-existence of trade-names since | Daivonex® 2003 | <u> </u> 2003 | Daivonex® 2004 | <u> </u> 2004 | | |
| Switzerland | July 2002 | } | | | | } No reports of medication error or confusion between Daivonex® and <u> </u> | |
| Sweden | April 2002 | | | | | | } No reports indicating that a mix-up between Daivonex® and <u> </u> as resulted in any adverse reaction. |
| Finland | April 2002 | | | | | | |
| Germany | November 2002 | } | | | | } Authorities have not recorded any mix-ups in connection with Daivonex® and <u> </u> | |
| Norway | May 2002 | | | | | | } Have not received any information on adverse events in connection with confusing the two trademarks. |

CONCLUSIONS

The suggested new way of writing and the proposed packaging material for ointment differentiates ointment from Dovonex® ointment thereby minimizing the potential user error at pharmacies.



A large number of patients have already been using Dovobet® ointment for several years while it has co-existed with the Dovonex® products without any reports of mix-ups between the two products.

The above information illustrates that LEO has extensive experience of having both tradenames co-existing in several markets with no reporting of medication errors due to confusion between the two tradenames. This may be due to the fact that both products are prescribed by dermatologists and used by the same patient population who knows these products.

We therefore kindly ask the FDA to reconsider its recommendation not to use the tradename

~~_____®~~



APPENDIX I

Countries where Dovobet[®] and Dovonex[®] is approved



THIS DOCUMENT CONTAINS TRADE SECRETS, OR COMMERCIAL OR FINANCIAL INFORMATION, PRIVILEGED OR CONFIDENTIAL, DELIVERED IN CONFIDENCE AND RELIANCE THAT SUCH INFORMATION WILL NOT BE COPIED OR MADE AVAILABLE TO ANY THIRD PARTY WITHOUT THE WRITTEN CONSENT OF LEO PHARMA A/S - LEO PHARMACEUTICAL PRODUCTS LTD. A/S

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COUNTRIES IN WHICH DOVOBET® OINTMENT IS APPROVED

| Country | Trade Name | Approval Date | Launch Date |
|------------------|------------|---------------|-------------|
| Belgium | Dovobet® | 15-Jul-2002 | Apr-2004 |
| Canada** | Dovobet® | 11-Jul-2001 | Dec-2001 |
| Cyprus** | Dovobet® | 30-Apr-2004 | Nov-2004 |
| Greece** | Dovobet® | 05-Mar-2002 | Nov-2002 |
| Ireland** | Dovobet® | 08-Feb-2002 | Apr-2002 |
| Italy | Dovobet® | 16-Jun-2003 | Jul-2003 |
| Luxembourg | Dovobet® | 13-Feb-2002 | Jan-2004 |
| Netherlands | Dovobet® | 11-Jun-2002 | Apr-2003 |
| United Kingdom** | Dovobet® | 18-Dec-2001 | May-2002 |

* Indicates countries with co-existing tradenames Daivonex® and Daivobet®

** Indicates countries with co-existing tradenames Dovonex® and Dovobet®



COUNTRIES IN WHICH DOVONEX® OINTMENT IS APPROVED

| Country | Trade Name | Approval Date | Launch Date |
|------------------|------------|---------------|-------------|
| Canada** | Dovonex® | 27-Oct-1992 | Nov-1992 |
| Cyprus** | Dovonex® | 27-Jun-1991 | Nov-1991 |
| Greece** | Dovonex® | 10-Sep-1992 | May-1993 |
| Ireland** | Dovonex® | 25-Feb-1991 | Apr-1991 |
| Japan | Dovonex® | 18-Jan-2000 | Jun-2000 |
| South Africa | Dovonex® | 02-Feb-1993 | Apr-1993 |
| United Kingdom** | Dovonex® | 10-Jan-1991 | Apr-1991 |
| USA | Dovonex® | 29-Dec-1993 | Jan-1994 |

* Indicates countries with co-existing tradenames Daivonex® and Daivobet®

** Indicates countries with co-existing tradenames Dovonex® and Dovobet®



APPENDIX II

Countries where Daivobet[®] and Daivonex[®] is approved



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O:REP

ADIVERSEIDOVOBET USIDOVOBET TRADENAME DEFENCE 16-09-2005.DOC

COUNTRIES IN WHICH DAIVOBET® OINTMENT IS APPROVED

| Country | Trade Name | Approval Date | Launch Date |
|---------------------|------------------|---------------|-----------------------------|
| Australia* | Daivobet® 50/500 | 11-Aug-2004 | Sep-2004 |
| Bahrain* | Daivobet® | 17-Aug-2003 | May-2004 |
| Bulgaria* | Daivobet® | 08-May-2003 | |
| Brazil* | Daivobet® | 10-Dec-2004 | |
| Colombia* | Daivobet® | 03-Feb-2004 | Jun-2004 |
| Costa Rica* | Daivobet® | 07-May-2002 | May-2003 |
| Czech Republic* | Daivobet® | 31-Mar-2004 | Planned for 3/4 QRT 2005 |
| Denmark* | Daivobet® | 20-Mar-2001 | Oct-2001 |
| Dominican Republic* | Daivobet® | 28-Jun-2002 | Nov-2002 |
| El Salvador* | Daivobet® | 29-May-2002 | Nov-2002 |
| Estonia* | Daivobet® | 06-Dec-2002 | May-2003 |
| Finland* | Daivobet® | 11-Feb-2002 | Apr-2002 |
| France* | Daivobet® | 12-Feb-2003 | May-2004 |
| Germany* | Daivobet® | 17-Jun-2002 | Nov-2002 |
| Guatemala* | Daivobet® | 13-Feb-2002 | Nov-2002 |
| Honduras* | Daivobet® | 09-Apr-2002 | Nov-2002 |
| Hong Kong* | Daivobet® | 23-Jan-2003 | Sep-2003 |
| Hungary* | Daivobet® | 27-Apr-2004 | Planned for 3/4 QRT 2005 |
| Iceland* | Daivobet® | 05-Feb-2002 | Apr-2002 |
| Indonesia* | Daivobet® | 15-Dec-2003 | Jul-2004 |
| Israel* | Daivobet® | 10-Feb-2003 | Feb-2004 |
| Jordan* | Daivobet® | 13-Jan-2004 | Jun-2004 |
| Korea* | Daivobet® | 14-Sep-2004 | |
| Kuwait* | Daivobet® | 03-Mar-2004 | May-2004 |
| Latvia* | Daivobet® | 12-Feb-2003 | May-2003 |
| Lebanon* | Daivobet® | 28-Apr-2004 | Jun-2004 |
| Lithuania* | Daivobet® | 28-Aug-2002 | May-2003 |

continues



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CONFIDENTIAL - MENT DIVERSE DAIVOBET US DAIVOBET TRADENAME DEFENCE 16-09-2005.DOC

COUNTRIES IN WHICH DAIVOBET® OINTMENT IS APPROVED (CONTINUED)

| Country | Trade Name | Approval Date | Launch Date |
|----------------------|------------------|---------------|------------------|
| Malaysia* | Daivobet® | 27-Apr-2004 | Est. Oct-2004 |
| Malta* | Daivobet® | 28-Jan-2003 | May-2003 |
| Mexico* | Daivobet® | 08-Jun-2004 | |
| Norway* | Daivobet® | 14-Feb-2002 | May-2002 |
| Oman* | Daivobet® | 11-May-2004 | Nov-2004 |
| Pakistan* | Daivobet® | 26-Jul-2004 | |
| Panama* | Daivobet® | 02-Aug-2002 | Nov-2002 |
| Philippines* | Daivobet® | 12-Jun-2003 | Nov-2003 |
| Poland* | Daivobet® | 13-Feb-2003 | Apr-2004 |
| Portugal* | Daivobet® | 19-Feb-2002 | Nov-2003 |
| Qatar* | Daivobet® | 06-Nov-2003 | May-2004 |
| Romania* | Daivobet® | 04-Aug-2003 | Apr-2004 |
| Russia* | Daivobet® | 07-May-2004 | Not marketed |
| Saudi Arabia | Daivobet® | 08-Mar-2005 | Not marketed yet |
| Singapore* | Daivobet® | 27-Mar-2003 | Nov-2003 |
| Slovenia* | Daivobet® | 30-Dec-2002 | Mar-2004 |
| Spain* | Daivobet® Pomada | 04-Feb-2002 | Sep-2003 |
| Sri Lanka* | Daivobet® | 16-Jun-2003 | Oct-2003 |
| Sweden* | Daivobet® | 06-Feb-2002 | Apr-2002 |
| Switzerland | Daivobet® | 18-Mar-2002 | Jul-2002 |
| Syria | Daivobet® | 29-Dec-2002 | Not marketed |
| Taiwan | Daivobet® | 11-Mar-2004 | Not marketed yet |
| Thailand | Daivobet® | 01-Oct-2003 | May-2004 |
| United Arab Emirates | Daivobet® | 12-Jan-2004 | May-2004 |
| Vietnam | Daivobet® | 31-Dec-2004 | Oct-2004 |

- * Indicates countries with co-existing tradenames Daivonex® and Daivobet®
 ** Indicates countries with co-existing tradenames Dovonex® and Dovobet®



COUNTRIES IN WHICH DAIVONEX[®] OINTMENT IS APPROVED

| Country | Trade Name | Approval Date | Launch Date |
|---------------------|-----------------------|---------------|-------------|
| Algeria | Daivonex [®] | 23-May-1998 | 1998 |
| Argentina | Daivonex [®] | 16-Jul-1992 | Feb-1993 |
| Australia* | Daivonex [®] | 26-Apr-1994 | Jun-1994 |
| Bahrain* | Daivonex [®] | 20-May-1992 | Oct-1992 |
| Bangladesh | Daivonex [®] | 09-Jan-1994 | Apr-1995 |
| Belgium | Daivonex [®] | 16-Mar-1993 | Oct-1993 |
| Bolivia | Daivonex [®] | 10-Oct-1991 | Aug-1996 |
| Brazil | Daivonex [®] | 24-Feb-1992 | Sep-1992 |
| Bulgaria* | Daivonex [®] | 06-Jun-2000 | Dec-2001 |
| Chile | Daivonex [®] | 12-May-1993 | Jul-1993 |
| China | Daivonex [®] | 16-Jun-1995 | Oct-1995 |
| Colombia* | Daivonex [®] | 30-Dec-1994 | Yes |
| Costa Rica* | Daivonex [®] | 18-Jan-1993 | Mar-1993 |
| Curacao | Daivonex [®] | 03-Jan-1992 | Mar-1992 |
| Czech Republic* | Daivonex [®] | 12-Feb-1997 | No |
| Denmark* | Daivonex [®] | 07-Nov-1990 | Mar-1991 |
| Dominican Republic* | Daivonex [®] | 22-Mar-1994 | Mar-1992 |
| Ecuador | Daivonex [®] | 11-Jun-1993 | Sep-1996 |
| Egypt | Daivonex [®] | 30-Jul-1996 | 1998 |
| El Salvador* | Daivonex [®] | 08-May-1992 | Jun-1992 |
| Estonia* | Daivonex [®] | 06-May-1994 | Sep-1994 |
| Finland* | Daivonex [®] | 09-Aug-1993 | Oct-1993 |
| France* | Daivonex [®] | 25-May-1992 | Apr-1993 |
| Germany* | Daivonex [®] | 17-Jul-1992 | Oct-1992 |
| Guatemala* | Daivonex [®] | 22-Aug-1991 | Feb-1992 |
| Honduras* | Daivonex [®] | 04-Oct-1991 | Mar-1992 |
| Hong Kong* | Daivonex [®] | 17-Mar-1992 | Oct-1992 |
| Hungary* | Daivonex [®] | 11-Dec-1997 | No |

continues



THIS DOCUMENT CONTAINS TRADE SECRETS, OR COMMERCIAL OR FINANCIAL INFORMATION, PRIVILEGED OR CONFIDENTIAL, DELIVERED IN CONFIDENCE AND RELIANCE THAT SUCH INFORMATION WILL NOT BE COPIED OR MADE AVAILABLE TO ANY THIRD PARTY WITHOUT THE WRITTEN CONSENT OF LEO PHARMA A/S - LEO PHARMACEUTICAL PRODUCTS LTD. A/S

COUNTRIES IN WHICH DAIVONEX[®] OINTMENT IS APPROVED (CONTINUED)

| Country | Trade Name | Approval Date | Launch Date |
|--------------|-----------------------|---------------|-------------|
| Iceland* | Daivonex [®] | 04-Mar-1992 | Apr-1992 |
| India | Daivonex [®] | 06-Oct-1995 | 3 QRT 1995 |
| Indonesia* | Daivonex [®] | 11-Feb-2004 | |
| Iraq | Daivonex [®] | 10-Sep-1997 | |
| Israel* | Daivonex [®] | 30-Jun-1994 | Dec-1994 |
| Italy | Daivonex [®] | 01-Feb-1993 | Mar-1993 |
| Jordan* | Daivonex [®] | 29-Mar-1993 | Apr-1993 |
| Korea* | Daivonex [®] | 17-Dec-1993 | Apr-1993 |
| Kuwait* | Daivonex [®] | 31-Jul-1992 | Sep-1992 |
| Latvia* | Daivonex [®] | 25-May-1995 | Aug-1994 |
| Lebanon* | Daivonex [®] | 31-Mar-1992 | 1994 |
| Lithuania* | Daivonex [®] | 05-Jul-1994 | Sep-1994 |
| Luxembourg | Daivonex [®] | 09-Aug-1993 | Oct-1993 |
| Malaysia* | Daivonex [®] | 01-Jan-1993 | Feb-1993 |
| Malta* | Daivonex [®] | 18-Nov-1990 | Jul-1994 |
| Mexico* | Daivonex [®] | 19-Jul-1995 | Mar-1993 |
| Morocco | Daivonex [®] | 20-Jan-1993 | 1994 |
| Netherlands | Daivonex [®] | 12-May-1992 | Aug-1992 |
| New Zealand | Daivonex [®] | 20-May-1991 | Sep-1991 |
| Norway* | Daivonex [®] | 04-Mar-1992 | Apr-1992 |
| Oman* | Daivonex [®] | 22-May-1993 | Mar-1992 |
| Pakistan* | Daivonex [®] | 05-Sep-1994 | Jul-1995 |
| Panama* | Daivonex [®] | 06-Jul-1992 | Apr-1995 |
| Peru | Daivonex [®] | 03-Jul-2001 | No |
| Philippines* | Daivonex [®] | 12-Oct-1992 | Dec-1992 |
| Poland* | Daivonex [®] | 14-Feb-1997 | Feb-1998 |
| Portugal* | Daivonex [®] | 20-Jan-1993 | Nov-1993 |
| Qatar* | Daivonex [®] | 30-Jun-1992 | Apr-1992 |
| Romania* | Daivonex [®] | 12-Jul-2000 | Sep-2000 |

continues



THIS DOCUMENT CONTAINS TRADE SECRETS, OR COMMERCIAL OR FINANCIAL INFORMATION, PRIVILEGED OR CONFIDENTIAL, DELIVERED IN CONFIDENCE AND RELIANCE THAT SUCH INFORMATION WILL NOT BE COPIED OR MADE AVAILABLE TO ANY THIRD PARTY WITHOUT THE WRITTEN CONSENT OF LEO PHARMA A/S - LEO PHARMACEUTICAL PRODUCTS LTD. A/S

O:\RE\OINTMENT\DIVERSE\DOVOBET US\DOVOBET TRADENAME DEFENCE 16-09-2005.DOC

COUNTRIES IN WHICH DAIVONEX[®] OINTMENT IS APPROVED (CONTINUED)

| Country | Trade Name | Approval Date | Launch Date |
|----------------------|------------------------------|---------------|-------------|
| Russia* | Daivonex [®] | 22-Sep-1993 | No |
| Saudi Arabia | Daivonex [®] | 15-May-1993 | Jan-1996 |
| Singapore* | Daivonex [®] | 27-Sep-1991 | Apr-1994 |
| Slovak Republic | Daivonex [®] | 22-Aug-1996 | No |
| Slovenia* | Daivonex [®] | 13-Mar-1998 | Jan-1994 |
| Spain* | Daivonex [®] Pomada | 24-May-1993 | May-1993 |
| Sri Lanka* | Daivonex [®] | 04-Jul-1991 | Apr-1992 |
| Sweden* | Daivonex [®] | 24-Jan-1992 | Jan-1992 |
| Switzerland | Daivonex [®] | 23-Mar-1992 | Apr-1992 |
| Syria | Daivonex [®] | 08-Feb-1994 | Apr-1994 |
| Taiwan | Daivonex [®] | 22-Dec-1993 | Jun-1995 |
| Thailand | Daivonex [®] | 28-Sep-1993 | Feb-1994 |
| Tunisia | Daivonex [®] | 07-Apr-1994 | 1994 |
| United Arab Emirates | Daivonex [®] | 14-Jan-1992 | Apr-1993 |
| Vietnam | Daivonex [®] | 29-Oct-1996 | Jun-1999 |
| Yemen Arab Republic | Daivonex [®] | 06-Jul-1999 | May-2000 |

- * Indicates countries with co-existing tradenames Daivonex[®] and Daivobet[®]
 ** Indicates countries with co-existing tradenames Dovonex[®] and Dovobet[®]



PAREXEL International

2520 Meridian Parkway, Suite 200
Durham, North Carolina 27713
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www.parexel.com

PAREXEL

RECEIVED
SEP 19 2005
CDR / CDER

16 September 2005

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

N-000(BL)
ORIG AMENDMENT

RE: NDA 21-852
Dovobet® Ointment
Response to FDA Request for Information

RECEIVED

SEP 21 2005

CDER White Oak DR 1

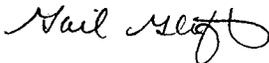
Dear Dr. Wilkin:

PAREXEL International (PAREXEL), acting as US Agent on behalf of LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S), is submitting a response to comments issued by the Division regarding the Dovobet® ointment New Drug Application (NDA) submitted to FDA on 9 March 2005.

On 31 August 2005, a fax was sent to the sponsor by the Division containing comments from the Division of Medication Errors and Technical Support (DMETS) concerning the proprietary name, Dovobet® ointment, and product labeling. We hereby submit a defense of the Dovobet® ointment tradename in which we propose to modify the appearance of the tradename to . We also submit responses to the DMETS comments with revised labeling including a newly designed label for the 3 g sample for review.

If there are any questions regarding this marketing application, please do not hesitate to contact me at 919-294-5099 (fax 919-544-3410) or via e-mail at gail.glifort@parexel.com. We look forward to your response.

Sincerely,



Gail Glifort, RAC
Consultant
PAREXEL Consulting

DUPLICATE

cc: LEO Pharma A/S: Gitte Schönwandt: Regulatory Affairs, Initial Filing
Anne Jensen, Regulatory Affairs, Initial Filing
PAREXEL: Project Files

PAREXEL International

PAREXEL

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www.parexel.com

N-000(BC)

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SEP 13 2005

CDR / CDER

12 September 2005

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

ORIG AMENDMENT

RE: NDA 21-852
Dovobet® Ointment
Response to FDA Request for Information

RECEIVED

SEP 14 2005

CDER White Oak DR 1

Dear Dr. Wilkin:

PAREXEL International (PAREXEL), acting as US Agent on behalf of LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S), is submitting a response to an FDA request for information regarding the Dovobet® ointment New Drug Application (NDA) submitted to FDA on 9 March 2005.

On 29 August 2005, the project manager, Felecia Curtis, and the chemistry reviewer, Ernie Pappas, requested that the sponsor provide data derived from the microscopic examination for particle size distribution of the manufactured lots, including those lots placed on stability studies. We hereby submit the aforementioned information.

If there are any questions regarding this marketing application, please do not hesitate to contact me at 919-294-5099 (fax 919-544-3410) or via e-mail at gail.glifort@parexel.com.

Sincerely,

Gail Glifort

Gail Glifort, RAC
Consultant
PAREXEL Consulting

DUPLICATE

cc: LEO Pharma A/S: Gitte Schönwandt: Regulatory Affairs, Initial Filing
Anne Jensen, Regulatory Affairs, Initial Filing

PAREXEL: Project Files

PAREXEL International

PAREXEL

2520 Meridian Parkway, Suite 200

Durham, North Carolina 27713

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www.parexel.com

29 August 2005

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 21-852
Dovobet[®] Ointment
Response to FDA Request for Samples and Information

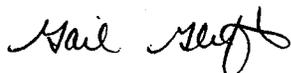
Dear Dr. Wilkin:

PAREXEL International (PAREXEL), acting as US Agent on behalf of LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S), is submitting a response to an FDA request for samples of and information regarding the Dovobet[®] ointment New Drug Application (NDA) submitted to FDA on 9 March 2005.

On 23 August 2005, the project manager, Felecia Curtis, and the chemistry reviewer, Ernie Pappas, requested that five (5) random samples of the finished product be sent to the Division. Dr. Pappas also requested clarification on the methods used to test the product for particle size. We hereby submit the aforementioned information.

If there are any questions regarding this marketing application, please do not hesitate to contact me at 919-294-5099 (fax 919-544-3410) or via e-mail at gail.glifort@parexel.com.

Sincerely,



Gail Glifort, RAC
Consultant
PAREXEL Consulting

cc: LEO Pharma A/S: Gitte Schönwandt: Regulatory Affairs, Initial Filing
Anne Jensen, Regulatory Affairs, Initial Filing

PAREXEL: Project Files

PAREXEL International

PAREXEL

DUPLICATE

2520 Meridian Parkway, Suite 200

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www.parexel.com

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AUG 12 2005

MEGA / CDER

11 August 2005

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850

N-600 (Bm)
ORIG AMENDMENT

RE: NDA 21-852
Dovobet® Ointment
Response to FDA Request for Information

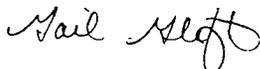
Dear Dr. Wilkin:

PAREXEL International (PAREXEL), acting as US Agent on behalf of LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S), is submitting a response to an FDA request for information regarding the Dovobet® ointment New Drug Application (NDA) submitted to FDA on 9 March 2005.

On 4 August 2005, the project manager, Felecia Curtis, faxed a request for a summary of batches of Dovobet® ointment used in the clinical development program by phase. The summary was to identify the study protocol, batch number and batch size used for clinical studies. The summary was also to indicate the differences, if any, in formulation between these clinical batches and batches intended for market. We hereby submit the aforementioned information.

If there are any questions regarding this marketing application, please do not hesitate to contact me at 919-294-5099 (fax 919-544-3410) or via e-mail at gail.glifort@parexel.com.

Sincerely,



Gail Glifort, RAC
Consultant
PAREXEL Consulting

cc: LEO Pharma A/S: Gitte Schönwandt: Regulatory Affairs, Initial Filing
Anne Jensen, Regulatory Affairs, Initial Filing

PAREXEL: Project Files

PAREXEL International

PAREXEL

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www.parexel.com

2 August 2005

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 21-852
Dovobet® Ointment
Response to FDA Request for Information

Dear Dr. Wilkin:

PAREXEL International (PAREXEL), acting as US Agent on behalf of LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S), is submitting a response to an FDA request for information regarding the Dovobet® ointment New Drug Application (NDA) submitted to FDA on 9 March 2005.

On 22 July 2005, the project manager, Felecia Curtis, and the chemistry reviewer, Ernie Pappas, requested a statement regarding the changes, if any, to the quality section for the drug substance calcipotriene in the Dovobet® ointment NDA since the submission of the Bristol-Myers, Squibb (BMS) NDAs for Dovonex® ointment, cream and scalp solution, NDA 20-273 using the drug substance calcipotriol, NDA 20-554 using the drug substance calcipotriol hydrate and NDA 20-611 using the drug substance calcipotriol hydrate, respectively. We hereby submit a listing of the changes that have occurred since the filing and approval of the last BMS NDA for scalp solution (NDA 20-611).

If there are any questions regarding this marketing application, please do not hesitate to contact me at 919-294-5099 (fax 919-544-3410) or via e-mail at gail.glifort@parexel.com.

Sincerely,



Gail Glifort, RAC
Consultant
PAREXEL Consulting

cc: LEO Pharma A/S: Gitte Schönwandt: Regulatory Affairs, Initial Filing
Berit Mölby, Regulatory Affairs, Initial Filing
PAREXEL: Project Files

RECEIVED

AUG 03 2005

MEGA / CDER

N-000(BC)

ORIG AMENDMENT

DUPLICATE

MEMORANDUM

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

DATE: July 25, 2005

TO: Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Products
HFD-540

VIA: Felecia Curtis, Regulatory Health Project Manager
Division of Dermatologic and Dental Products
HFD-540

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCs Review of Patient Labeling for Dovobet Ointment
(calciptriene, 0.005% and betamethasone, 0.001%)
NDA 21-852

Background and Summary

The following is the revised Patient Labeling (PPI) for Dovobet Ointment (calciptriene, 0.005% and betamethasone, 0.001%), NDA 21-852. We have simplified the wording, made it consistent with the PI, and removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications). We have put this PPI in the patient-friendly format that we are recommending for all patient information, although, this format is not required for voluntary PPIs. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on draft labeling submitted by the sponsor on May 20, 2005. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

Comments to the review Division in the attached patient label are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division. Please let us know if you have any questions.

3 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 1b

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

/s/

Jeanine Best
7/25/05 02:50:38 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
7/25/05 04:00:44 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

PAREXEL International

PAREXEL

DUPLICATE

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Durham, North Carolina 27713
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www.parexel.com

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JUL 14 2005

MEGA / CDER

13 July 2005

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850

N-000 (01)
ORIG AMENDMENT

RE: NDA 21-852
Dovobet[®] Ointment
Response to FDA Request for Information

Dear Dr. Wilkin:

PAREXEL International (PAREXEL), acting as US Agent on behalf of LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S), is submitting a response to an FDA request for information regarding the Dovobet[®] ointment New Drug Application (NDA) submitted to FDA on 9 March 2005.

On 29 and 30 June 2005, we received e-mail correspondence from Anastasia Lolos, the review microbiologist, requesting procedures for microbiological testing, validation of these methods, raw microbiological data and a sampling plan for testing raw materials and drug product for microorganisms. This response includes the official FDA copy of the response to the above request in paper; a scanned version has been sent to Ms. Lolos and the project manager, Felecia Curtis, via e-mail earlier today.

If there are any questions regarding this marketing application, please do not hesitate to contact me at 919-294-5099 (fax 919-544-3410) or via e-mail at gail.glifort@parexel.com.

Sincerely,



Gail Glifort, RAC
Consultant
PAREXEL Consulting

cc: LEO Pharma A/S: Gitte Schönwandt: Regulatory Affairs, Initial Filing
Berit Mølby, Regulatory Affairs, Initial Filing

PAREXEL: Project Files

PAREXEL International

PAREXEL

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DUPLICATE

05 July 2005

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JUL 06 2005

MEGA / CDER

ORIG AMENDMENT

N-000-(SU)

Jonathan Wilkin, MD, Division Director
Food and Drug Administration
Center for Drugs Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

**Re: DOVOBET[®] Ointment (calcipotriol/betamethasone dipropionate)
NDA 21-852 – 120-Day Safety Update**

Dear Dr. Wilkin:

Reference is made to New Drug Application (NDA) 21-852 for Dovobet[®] Ointment. In accordance with the responsibilities transferred to PAREXEL International Corporation (PAREXEL) by LEO Pharmaceutical Products (LEO), PAREXEL is hereby submitting in triplicate a 120-Day Safety Update.

The appendices to this 120-Day Safety Update include the protocol for a preclinical toxicity study (LOP/052) entitled, "Calcipotriol Toxicity Study by Oral Gavage Administration to Han Wistar Rats for 13 Weeks," and the Periodic Safety Update Report for the period 01 April 2004 to 31 March 2005.

Please contact me directly at (919) 294-5099 or via e-mail at gail.glifort@parexel.com if you have any questions regarding this submission.

Sincerely,

Gail Glifort

Gail Glifort
Consultant
PAREXEL Consulting

cc: LEO Pharmaceutical Products: Berit Mølby, MSc Pharm, Regulatory Affairs
PAREXEL International: Project Files

PAREXEL International

PAREXEL

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Durham, North Carolina 27713
+1 919 544 3170 Fax: +1 919 544 3410
www.parexel.com

DUPLICATE

23 June 2005

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850

RECEIVED

JUN 24 2005

MEGA / CDER

ORIG AMENDMENT

2000-02

RE: NDA 21-852
Dovobet® Ointment
Response to FDA Request for Information

Dear Dr. Wilkin:

PAREXEL International (PAREXEL), acting as US Agent on behalf of LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S), is submitting a response to an FDA request for information regarding the Dovobet® ointment New Drug Application (NDA) submitted to FDA on 9 March 2005.

On 15 June 2005, we received a facsimile from the Division in which the medical officer requested that a patient package insert (PPI) be submitted in Word to facilitate review. This response includes the official FDA copy of the PPI in paper; a Word version has been sent to the project manager, Felecia Curtis, via e-mail earlier today.

If there are any questions regarding this marketing application, please do not hesitate to contact me at 919-294-5099 (fax 919-544-3410) or via e-mail at gail.glifort@parexel.com.

Sincerely,

Gail Glifort

Gail Glifort, RAC
Consultant
PAREXEL Consulting

cc: LEO Pharma A/S: Gitte Schönwandt: Regulatory Affairs, Initial Filing
Berit Mølby, Regulatory Affairs, Initial Filing

PAREXEL: Project Files

| | | | | |
|--|---|--------------------------------------|--|--------------------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION | | REQUEST FOR CONSULTATION | | |
| TO (Division/Office): David Hussong, Associate Director for Microbiology (CMC MICRO), PKLN RM 18B08 HFD-805 | | | FROM: Felecia Curtis PM/ HFD-540, Derm and Dental Ext. 72043 | |
| DATE: May 23, 2005 | NDA NO. 21-852 | NDA NO. | TYPE OF DOCUMENT : CMC Micro briefing package | DATE OF DOCUMENT: May 23, 2005 |
| NAME OF DRUG: Dovobet Ointment (Calcipotriene, 0.005% & Betamethasone, | PRIORITY CONSIDERATION PDUFA target date 11/1/05 | CLASSIFICATION OF DRUG: 4s | DESIRED COMPLETION DATE September 1, 2005 | |
| NAME OF FIRM: LEO Pharmaceutical Products Ltd | | | | |
| REASON FOR REQUEST | | | | |
| I. GENERAL | | | | |
| <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): | | | | |
| II. BIOMETRICS | | | | |
| STATISTICAL EVALUATION BRANCH | | | STATISTICAL APPLICATION BRANCH | |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): | | | <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): CMC Micro Review | |
| III. BIOPHARMACEUTICS | | | | |
| <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES | | | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST | |
| IV. DRUG EXPERIENCE | | | | |
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | | | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS | |
| V. SCIENTIFIC INVESTIGATIONS | | | | |
| <input type="checkbox"/> CLINICAL | | | <input type="checkbox"/> PRECLINICAL | |
| COMMENTS/SPECIAL INSTRUCTIONS: A hard & electronic copy is being forwarded please provide comments. Thank You. | | | | |
| SIGNATURE OF REQUESTER Felecia Curtis | | | METHOD OF DELIVERY (Check one) x <input type="checkbox"/> MAIL <input type="checkbox"/> HAND | |
| SIGNATURE OF RECEIVER | | | SIGNATURE OF DELIVERER | |

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this page is the manifestation of the electronic signature.**

/s/

Felicia Curtis
5/23/05 08:53:22 AM

REQUEST FOR CONSULTATION

TO (Division/Office):
**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
PKLN Rm. 6-34**

FROM: **Felecia Curtis PM/
HFD-540, Derm and Dental
Ext. 72043**

| | | | | |
|----------------------|---------|-------------------|-----------------------------|----------------------------------|
| DATE May 19, 2005 | IND NO. | NDA NO. 21-852 | TYPE OF DOCUMENT New NDA | DATE OF DOCUMENT May 19, 2005 |
|----------------------|---------|-------------------|-----------------------------|----------------------------------|

| | | | |
|---|--|------------------------------|--|
| NAME OF DRUG Dovobet Ointment (Calcipotriene, 0.005% & Betamethasone, - o) | PRIORITY CONSIDERATION PDUFA target date 11/1/05 | CLASSIFICATION OF DRUG 4s | DESIRED COMPLETION DATE August 15, 2005 |
|---|--|------------------------------|--|

NAME OF FIRM: : LEO Pharmaceutical Products Ltd

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

| | |
|---|--|
| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW): |

III. BIOPHARMACEUTICS

| | |
|---|--|
| <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST |
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IV. DRUG EXPERIENCE

| | |
|---|---|
| <input type="checkbox"/> PHASE IV SUR VEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

| | |
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| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
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COMMENTS/SPECIAL INSTRUCTIONS: Attached is a copy of the proposed label being forwarded. I will also send a hard copy.

PDUFA DATE: 1/6/2006
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA 21-852
 HFD-540/Division File
 HFD-540/Felecia Curtis
 HFD-540/Reviewers and Team Leaders

| | |
|--|---|
| NAME AND PHONE NUMBER OF REQUESTER Felecia Curtis 301-827-2043 | METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS ONLY <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND |
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this page is the manifestation of the electronic signature.**

/s/

Felicia Curtis
5/19/05 02:18:31 PM

PAREXEL International

PAREXEL

DUPLICATE

2520 Meridian Parkway, Suite 200
Durham, North Carolina 27713
+1 919 544 3170 Fax: +1 919 544 3410
www.parexel.com

RECEIVED

MAY 24 2005

MEGA / CDER

23 May 2005

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850

N-000 (B2)
ORIG AMENDMENT

**RE: NDA 21-852
Dovobet® Ointment
NEW DRUG APPLICATION – Response to FDA Request for Information**

Dear Dr. Wilkin:

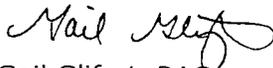
PAREXEL International (PAREXEL) is submitting a response to a request for information received as part of the Filing Communication faxed on 18 May 2005. PAREXEL is acting as US Agent on behalf of LEO Pharmaceutical Products-Ltd. A/S (LEO Pharma A/S) (LEO). The Dovobet® ointment New Drug Application was originally submitted to FDA on 9 March 2005.

In the Communication of 18 May, the Clinical and Biostatistics reviewers identified potential review issues regarding the NDA that LEO has addressed in the attached response. As part of the issues, the Clinical reviewer reminded LEO that a 120-day safety update should be submitted to the NDA. To this end, we would like to discuss the contents, format and data cut-off date(s) for the update with the Division at your earliest convenience.

Please note that the Biostatistics reviewer has requested that LEO provide details of the randomization for study MCB-0003-INT in electronic format, thus, we have included a disk with this information in pdf format for review.

If there are any questions regarding this submission or additional requests for information for the NDA, please do not hesitate to contact me at 919-294-5099 (fax 919-544-3410) or via e-mail at gail.glifort@parexel.com.

Sincerely,



Gail Glifort, RAC
Consultant
PAREXEL Consulting

cc: LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S): Berit Mølby,
Regulatory Affairs, Initial Filing

PAREXEL International

2520 Meridian Parkway, Suite 200

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PAREXEL

DUPLICATE

4 May 2005

N-000(Bm)
ORIG AMENDMENT

RECEIVED

MAY 05 2005

MEGA / CDER

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, MD 20850

**RE: NDA 21-852
Dovobet[®] Ointment
Response to FDA Request for Information**

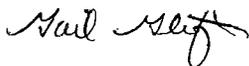
Dear Dr. Wilkin:

PAREXEL International (PAREXEL), acting as US Agent on behalf of LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S), is submitting a response to an FDA request for information regarding the Dovobet[®] ointment New Drug Application (NDA) submitted to FDA on 9 March 2005.

On 3 May 2005, we received a facsimile from the Division in which the clinical reviewer(s) requested indices for Individual Patient Data Listings for each clinical study report. This response gives the location of the indices for the individual patient data listings submitted within the study reports in the NDA. Those study listings for which indices were not included in the NDA (i.e., MCB 0003 INT, MCB 9905 INT, MCB 9802, MCB 0001 INT, MCB 9904 INT, MCB 0102 INT, MHO 0201 FR and MBL 0201 FR) are hereby provided in this submission.

If there are any questions regarding this marketing application, please do not hesitate to contact me at 919-294-5099 (fax 919-544-3410) or via e-mail at gail.glifort@parexel.com.

Sincerely,



Gail Glifort, RAC
Consultant
PAREXEL Consulting

cc: LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S): Berit Mölby, Regulatory Affairs, Initial Filing

MEMORANDUM OF MEETING MINUTES



Meeting Date: June 9, 2003 **Time:** 10:00 AM
Location: 9201 Corporate Blvd. Rm. S400A
Application: IND 62, 993, Dovobet® Ointment
Subject: Regulatory Guidance Meeting
Meeting ID: 10148
Sponsor: Parexel International
Meeting Chair: Jonathan K. Wilkin, M.D., Director, DDDDP, HFD-540
Meeting Recorder: Jacquelyn Smith, Regulatory Project Manager, DDDDP, HFD-540

FDA Attendees, Titles, and Office/Division:

Jonathan K. Wilkin, M.D., Director, DDDDP, HFD-540
Markham Luke, M.D., Ph.D., Team Leader, Clinical, DDDDP, HFD-540
Brenda Carr, M.D., Clinical reviewer, DDDDP, HFD-540
Ernest Pappas, Chemistry Reviewer, DNDCIII, HFD-830
Norman See, Ph.D., Pharmacology Reviewer, DDDDP, HFD-540
Mohamed Al-Osh, Ph.D., Team Leader, Biostatistics, DBIII, HFD-725
Mohamed Moustapha, Ph.D. Biostatistics, DBIII, HFD-725
Abi Adebawale, Ph.D., Acting Pharmacokinetics Team Leader, DPEIII, HFD-880
Donald Hare, R Ph., Special Assistant to the Director, OGD, HFD-604
Shaw T. Chen, M.D. Ph.D., Associate Director for Special Product Review - Botanical Drug Products HFD-105
Virginia Giroux, Regulatory Project Manager, DDDDP, HFD-540
Leonthana Carrington, Regulatory Project Manager, DDDDP, HFD-540
Jacquelyn Smith, Regulatory Project Manager, DDDDP, HFD-540

External Constituent Attendees and Titles:

Janet Rae, RAC, Regulatory Affairs Consultant
David Pizzi, MS, RAC, Director, Regulatory Affairs
Sandy Eisen, M.D., Principal Medical Consultant
Anders Ljungqvist, Vice President, Regulatory Affairs, QA/QC
Ann Christine Korsgaard, M.Sc., Pharm, Regulatory Affairs Initial Filing
Malene Kjaer Muller, Regulatory Affairs Initial Filing
Erick Kirkegaard, M.D., Vice President, Medical Department
Jette Traulsen, M.D., Director, Dermatological Medical Department
Claus Bay, M.Sc., Head, Statistics Department
Jens Thing Mortensen, DVM, DABT, Head, Department of Toxicology
Jorgen Schutzsack, DVM, Toxicologist
Janet Logsted Nielsen, M.Sc., Pharm, Head, Pharmacokinetics and Metabolism
Gert Hoy, M.Sc., Pharm, Project Manager, Pharmaceutical Formulation

Purpose:

To provide general guidance on content and format of the Investigational New Drug Application under 21 CFR 312. The pre-meeting briefing document provides background and questions for discussion.

Administrative:

Question #1

As LEO has right of reference to all data from investigations conducted with calcipotriene by Bristol-Myers Squibb (BMS) and is conducting a comprehensive toxicological program with betamethasone dipropionate in support of the Dovobet® ointment NDA, **does the FDA agree that the NDA for Dovobet® ointment can be submitted according to section 505(b)(1) of the Federal Food, Drug and Cosmetic Act ?**

Response: It appears that the NDA for Dovobet® ointment could be submitted via the 505(b)(1) route.

Chemistry, Manufacturing and Controls:

The amended meeting package contained five (5) chemistry questions or comments. They are the following:

- **FDA Comment # 1:**

Letters of authorization for the Drug Master Files (DMFs) referenced should accompany the IND.

- **Leo Response # 1:**

Leo indicated that, since they are the owner of DMF _____ and that the manufacture of calcipotriene hydrate is described in this DMF, no authorization letter was provided in the DMF.

FDA's comment to Leo #1:

Since DMF _____ is owned by Leo, they should identify this DMF number on Form 1571H, but no letter of authorization is necessary.

- **FDA Comment # 2:**

The analytical assay methods by HPLC for the actives, Calcipotriene hydrate and Betamethasone dipropionate should be described in detail. Assurance should be given that both of the actives do not interfere with the assay of the individual active components for the finished product.

- **Leo Response # 2:**

The HPLC analytical assay methods and method validation reports for calcipotriene hydrate and betamethasone dipropionate used in the finished product specification were

provided in the original IND submitted on July 27, 2001, and in the IND CMC Amendment on December 17, 2002 (serial #12). The method validation reports demonstrate that no interference occurs between the two actives.

FDA's comment to Leo # 2:

These assay methods were reviewed and found to be stability indicating. They were found to identify and assay calicipotriene hydrate, betamethasone dipropionate, and related substances without interference from these components. The methods validation provided information on the accuracy, precision, specificity, sensitivity and robustness of the HPLC methods.

- **FDA Comment # 3:**

The stability studies that were conducted on 6 batches of the ointment as described in your meeting package (pg.24) are acceptable, providing that you submit this data and they are found to be acceptable. In addition, please provide the stability protocol prior to Phase 3.

- **Leo Response # 3:**

Leo indicated that accelerated and long term stability data were submitted in the original IND on July 27,200 and in the IND amendment dated December 17, 2002. They also indicated that the stability testing protocol for the ongoing and post approval batches was submitted in the December 17, 2002, IND CMC amendment. In addition, they indicated that a revised stability protocol was submitted in the May 2, 2003, meeting package (serial # 30), and it also enclosed with the May 12, 2003, amendment.

FDA's comment to Leo # 3:

The stability data, as submitted in the December 17, 2002, amendment and the May 2, 2003, Meeting Briefing Document, are adequate to support Phase 3 studies. These stability studies are performed according to ICH guidelines. In addition, an acceptable stability protocol was submitted for an NDA submission.

The Sponsor asked for clarification on the previous statement.

- **FDA Comment # 4:**

The same CMC information as submitted in your CMC portion of the meeting package should be submitted with the IND submission with detailed information for each section.

- **Leo Response # 4:**

Leo indicated that the CMC information described in the June 26, 2000, meeting package was also provided in the original IND submission on July 27,2001.

FDA's comment to Leo # 4:

This CMC information is the same as submitted in the July 27, 2001, IND. In addition, a brief description of the CMCs was submitted in the May 2, 2003 Meeting Briefing Document. This description summarizes the CMC information that was submitted in the original IND submission and updated stability protocol that will be used during Phase 3 studies. This information was reviewed and found acceptable.

- **FDA Comment # 5:**

"Dovobet" may not be an acceptable tradename. We recommend that the sponsor prepare alternative tradenames in advance.

Agency will consult the Office of Drug Safety on the trade name "Dovobet" upon NDA submission.

- **Leo Response # 5:**

Leo indicated that a Certificate of Registration for Dovobet by the U.S. Patent and Trademark Office was received on January 28, 2003. They would consider using an alternative tradename but still prefers to use the current name Dovobet. Please clarify why the Division believes that the name Dovobet would not be acceptable.

FDA's comment to Leo # 5:

Our position is unaltered. Any drug trademark will be submitted to the Office of Drug Safety.

Additional CMC Comments:

We have following comments and requests regarding the CMC information that was submitted in the meeting package:

Regarding the "Specifications and Analytical Methods for Drug Product" (page 16):

1. Under the test for "Betamethasone related substances", please (1) list all of the related substances above the identification threshold as specified identified or specified unidentified impurities, and (2) include any unspecified impurity with an acceptance criterion of NMT the identification threshold, This is recommended for impurities in drug products by ICH guidance.
2. Please provide an upper limit specification for the particle size specifications since the specification as submitted, is open ended.

Pharmacology/Toxicology:

Question #2

Polyoxypropylene-15-stearyl ether is also chemically listed as polypropylene glycol (PPG)-15-stearyl ether (CAS 25231-21-4). PPG-15-stearyl ether is listed on CDER's list of inactive

ingredients for approved topical drug products with an allowed maximum exposure of — Polyoxypropylene-15-stearyl ether is an ingredient used in the approved product Psorcon E Ointment by Dermik Laboratories under NDA 19,260. In Dovobet® ointment, — polyoxypropylene-15-stearyl ether is used as solvent for calcipotriene.

Does the FDA agree that the use of polyoxypropylene-15-stearyl ether in Dovobet® ointment is adequately supported by safety data for the purpose of submitting an NDA for Dovobet® ointment?

Response: The fact that a given excipient is a component of an approved product does not necessarily mean that excipient will be deemed safe for other uses. The safety database associated with polyoxypropylene-15-stearyl ether should be evaluated and, if necessary, brought up to current standards. The sponsor is referred to CDER's draft guidance for industry, "Nonclinical Studies for Development of Pharmaceutical Excipients", for information concerning the current standard. Note that nonclinical and clinical safety data from studies conducted with formulations of the product that contain polyoxypropylene-15-stearyl ether may address some of the issues associated with use of this excipient (e.g., carcinogenicity, chronic toxicology). It is recommended that nonclinical studies conducted with the drug product include both untreated control animals and vehicle-treated control animals such that the potential of the vehicle (i.e., the excipients) to induce toxicity may be assessed, although additional studies (conducted with individual excipients) may be needed if the vehicle was found to be toxic. The potential of polyoxypropylene-15-stearyl ether to induce reproductive toxicity or genetic toxicity should also be adequately addressed under a NDA.

Question #3

Given the widespread use of betamethasone dipropionate for more than 20 years for topical treatment of many conditions, including psoriasis, the FDA request that LEO provide new carcinogenicity studies to current standards is accepted, but is not considered to be an urgent need in the context of risk management.

For this reason LEO proposes to provide the new data as a post-approval commitment. Does the FDA find this acceptable?

Response: The sponsor's proposal is acceptable. Data from carcinogenicity studies conducted with betamethasone may be submitted post-approval ("Phase 4"), provided the initial submission contains protocols for suitable carcinogenicity studies, adequate data to support the dosage selection for the proposed carcinogenicity studies, and a clear commitment to submit carcinogenicity data within a specific time frame.

Question #4

Preliminary data from ongoing photocarcinogenicity study in hairless mice on Dovonex® (calcipotriene) Scalp Solution conducted by Bristol-Myers Squibb (Dovonex® NDA 20,611) indicate that calcipotriene may cause a slight enhancement of photocarcinogenesis when used at the highest concentration tolerated by the mice.

LEO proposes to await the final evaluation of the BMS study with Dovonex® Scalp Solution and to perform a photocarcinogenicity study with Dovobet® ointment as a post-approval commitment. Does the FDA agree?

Response: It is recommended that the photosafety issues associated with the drug product be addressed in a manner consistent with CDER's guidance for industry on photosafety testing. It may not be necessary to conduct a photocarcinogenicity study in hairless mice. The NDA should

include (or reference) the final photocarcinogenesis data from the study conducted with calcipotriene and include information about the effect of the to-be-marketed formulation of Dovobet on the optical properties of the skin. Further photo data may be requested as a Phase 4 commitment.

Question #5

The reproductive toxicity of calcipotriene has been fully evaluated in all segments and no evidence of reproductive toxicity has been found. Betamethasone dipropionate has been investigated in teratology studies in rats, mice and rabbits and shown to be a teratogen which is a well-known class effect of potent steroids.

In view of these well-established findings LEO considers that the conduct of further reproductive toxicity studies would provide no additional information for use in defining the risk management profile for Dovobet® ointment. Does the FDA agree?

Response: A NDA for Dovobet ointment should be adequately supported with respect to effects of both calcipotriene and betamethasone on fertility, reproductive function, or early embryonic development (please see the ICH S5A document, section 4.1.1), as well as for effects on prenatal and postnatal development, including maternal function (please see section 4.1.2 of the ICH S5A document). If suitable data concerning the effects of betamethasone dipropionate on fertility and perinatal development are not currently available, submission of those data will be regarded as a Phase 4 commitment.

Biopharmaceutics:

Question #7

Psoriasis patients with more than 15% involvement of Body Surface Area are considered “worst case” of the category “amenable to topical therapy”.

[]

Response: In a general sense the study as outlined appears to be adequate.

Question #8

Data show that there is no difference between the absorption of calcipotriene through healthy skin compared with psoriatic skin. Currently available clinical data show no evidence of significant systemic exposure to either calcipotriene or betamethasone dipropionate. In addition, further clinical data specifically addressing the potential for HPA axis suppression will become available before submission of the NDA.

In view of this, LEO does not propose additional absorption studies. Does the FDA agree?

Response: The sponsor should put their information together as a package and submit it under the IND for review as ultimately it is an issue of our determination that the standards for bioavailability testing/determination have been met.

Addendum: At the meeting the FDA agreed that the sponsor will advance their arguments with regards to the systemic exposure of calcipotriene hydrate and betamethasone dipropionate as further clinical data become available.

Clinical:

Question #6

Full formal dose-ranging studies have not been conducted with ointment. The product contains two well-established, approved active ingredients at the same concentration in which they are currently marketed for the same indication. The safety profile of ointment is excellent at twice daily administration and the product is now proposed for once daily use. Efficacy data show clinical equivalence between once and twice daily administration. The data do suggest that any further reduction in the dosing may result in lower efficacy. In conclusion, the most favorable risk/benefit ratio has been found with the proposed once daily dosage.

For these reasons, LEO considers that the conduct of further dose-ranging studies will not provide any information leading to improved patient benefit. Does the FDA agree?

Response: No additional dose-ranging studies are requested for the Sponsor's product under the currently proposed usage of once daily for 4 weeks.

Question #7

Psoriasis patients with more than 15% involvement of Body Surface Area are considered "worst case" of the category "amenable to topical therapy"

 **Response:** This approach appears to be acceptable if it reflects proposed maximal use conditions for the Sponsor's product. See biopharmaceutics comments. 

Question #9

The FDA guidance "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" includes several situations where a single pivotal study may be sufficient to support an NDA. These include the use of a drug, known to be effective in monotherapy, when combined with another therapy in a fixed combination product. LEO has conducted a double blind, multi-center, pivotal trial (MCB 0003 INT) including 1,603 patients and using endpoints and treatment arms recommended by the FDA. (Strong supporting data are also available from 4 additional large studies which included nearly 4,000 patients).

Does the FDA accept that these phase III data are sufficient to support the NDA for Dovobet[®] ointment once daily dosage?

Response: The Sponsor's supportive data are noted, and, as the Sponsor has indicated, there are circumstances under which a single pivotal trial might be sufficient to support an NDA. Ultimately, however, whether or not data are sufficient to support approval of an NDA is a review

issue. Generally, two adequate and well-controlled studies are required in support of a 505(b)(1) application. The design of study MCB 0003 INT appears to be consistent with that suggested by the Agency to support a 505(b)(1) application. Specifically, the trial compared the combination product to each active ingredient in the study substance vehicle (the trial also included a vehicle arm). This design is also consistent with that recommended for study of a combination product (21 CFR. Sec. 300.50).

It is noted that the Sponsor's pivotal trial, MCB 0003 INT, was conducted in Canada and Europe. The Sponsor would need to either provide data to support that these patient populations are reflective of the U.S. population, or conduct a trial in the U.S. The Sponsor is referred to the E1A "Guideline for Industry." The Sponsor indicates that, "Dovobet® is unlikely to be sensitive to ethnic factors due to its non-systemic mode of action and minimal absorption..." (p. 67). However, this statement does not consider local events that could correlate with "ethnic factors" e.g., hypopigmentation.

Discussion during meeting: The Sponsor proposed to do a Phase 4 study to address the Agency's

C

Question #10

LEO has developed Dovobet® ointment as a safe and effective therapy for adults suffering from psoriasis vulgaris. Psoriasis is not generally considered to be a pediatric indication and most clinicians would prefer to avoid the use of potent corticosteroid medications in young children. **For these reasons, LEO does not propose to develop Dovobet® ointment for the pediatric population and intends to submit a full pediatric waiver. Does the FDA agree with this approach?**

Response: As psoriasis can occur in the pediatric age group, a partial pediatric waiver would seem more appropriate. It is recommended that subjects 12 years and older be studied with the Sponsor's product.

Discussion during meeting: The Sponsor agreed to study their product in subjects down to 12 years of age, and proposed this study be conducted as a Phase 4 commitment. The request for a partial waiver and for deferral of the study will be included in the NDA.

Biostatistics:

Question #9

Does the FDA accept that these Phase 3 data are sufficient to support the NDA for Dovobet Ointment once daily dosage?"

The sponsor has provided summary of efficacy results of their clinical trials, the following are general comments related to the issues raised by the sponsor:

- 1) The sponsor indicated that based on the results of previous studies the once daily (QD) dose is the appropriate dose. The sponsor argued that no additional dose-finding study is justified. In response the Division indicated that the sponsor dose-range finding was based on the mean percentage change in the Psoriasis Area and Severity Index (PASI) as the primary efficacy

endpoint and was not based on the primary efficacy endpoint recommended for Phase 3 trials (Physician's Global Assessment (PGA)). Assuming that PASI is highly correlated with the PGA, the sponsor's finding that the once daily dose regimen might be acceptable. The sponsor's comparisons between the QD and twice daily (BID) were carried out across several studies. It should be noted that results from different studies are subject to study-to-study variability, which could be relatively large when the studies have different designs as in this submission.

- 2) The sponsor presented a summary of efficacy results of their pivotal study (MCB 0003 INT) comparing Dovobet Ointment once daily against the Calcipotriol, Betamethasone and Dovobet vehicle. Based on their reported highly significant p-values for primary comparison of Dovobet vs. the two actives (p-values<0.00125), the sponsor desires to submit a single study NDA submission. The Division raised the following points related to the reported efficacy results:
 - a) Results of the sponsor's analysis are based on fitting the logistic regression model with presumably center and treatment as covariates. However it appears that no center-by-treatment interaction term is included in the fitted model, consequently it is not clear the extent of the center-to-center variability in the efficacy results. In addition, efficacy results based on the logistic regression model is not the method of analysis recommended by the Division, where the Division recommended at the joint June 26, 2000 meeting the Cochran-Mantel-Haenszel (CMH).

During the meeting the sponsor indicated that they carried out analysis using the CMH test approach and the results were similar to those of the logistic regression model and that the fitted logistic regression would include interaction terms as well. In response the Division stated that for establishing efficacy all analysis methods need to be pre-specified as post-hoc analysis should not be used for superiority efficacy claim. The sponsor should provide in the NDA submission the original statistical analysis plan in the protocol and any amendment to their plan along with dates. The sponsor agreed to provide the full protocol analysis plan and any protocol change, the statistical methodology, the corresponding efficacy results and the agency recommended analysis (CMH) for review.

- a) The study was carried out in Europe, generalization of the efficacy results from this study to US population need to be evaluated.
- b) There are several regulatory requirements for a single study submission to be supportive of an NDA application, such as:
 - Persuasive statistical finding, and
 - Consistency of efficacy results across centers and subgroups.

Based on the sponsor's information summary provided it is difficult to draw conclusion about consistency of the efficacy results, and the strength of evidence for the sponsor pivotal study.

Administrative Comments:

1. For applications submitted after February 2, 1999, per 21CFR 54.3 and 21CFR 54.4, an NDA

applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.

2. Comments shared today with the Sponsor are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the IND might identify additional comments or informational requests.
3. It is recommended that the Sponsor request and attend a pre-NDA meeting to obtain comments regarding format and content prior to submission of NDA.

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/s/

Jonathan Wilkin
6/30/03 01:00:54 PM