# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**NDA 22-185**

# CHEMISTRY REVIEW(S)

Chemistry Review Data Sheet

# NDA 22-185

## Taclonex Scalp (Calcipotriene 0.005% and Betamethasone dipropionate 0.064%) Gel
## LEO Pharmaceutical Products Ltd. A/S

## Division of Dermatology and Dental Products

**Zhengfang Ge, Ph.D.**

**Branch III, Division of Pre-Marketing Assessment II**
**Office of New Drug Quality Assessment**

# Table of Contents

# Chemistry Review Data Sheet

1. NDA # 22-185

2. REVIEW # 1

3. REVIEW DATE: Jan 16, 2008

4. REVIEWER: Zhengfang Ge

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Original submission | June 19, 2007 |
| Amendment | Aug 2, 2007 |
| Amendment | Aug 20, 2007 |
| Amendment | Sep 4, 2007 |
| Amendment | Dec 18, 2007 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Leo Pharma A/S |
| Address: | Industriparken 55<br>DK-2750 Ballerup<br>Denmark |
| Representative: | Alberto Grignolo Ph.D<br>Parexel Consulting<br>900 Chelmsford St, Suite 310<br>Lowell, MA 01851 |
| Telephone: | 978-275-0062 |

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Taclonex Scalp
b) Non-Proprietary Name (USAN): calcipotriene hydrate
c) CAS No: N/A
d) Code Name/# (ONDQA only): MC903, hydrate
e) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: This application was filed under the provisions of section 505(b)(1) of Federal Food, Drug and Cosmetic act and 21 CFR 314.50.

10. PHARMACOL. CATEGORY: Topical treatment of psoriasis vulgaris of the scalp in adults aged 18 years and above

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: Calcipotriene 0.005% and Betamethasone dipropionate 0.064%

13. ROUTE OF ADMINISTRATION: Topical dermatology

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X__Not a SPOTS product

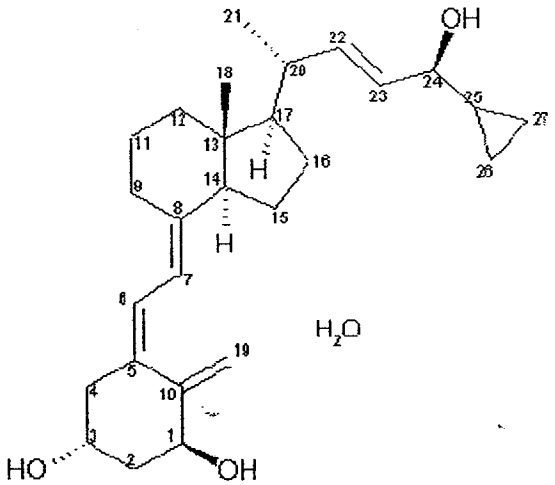
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**Calcipotriene hydrate:**

**Chemical Name:**

(1α ,3β ,5Z,7E,22E,24S)-24-Cyclo-propyl-9,10-seco-chola-5,7,10(19),22-tetraene-1,3,24-triol, hydrate

**Molecular Formula:** $C_{27}H_{40}O_3$, $H_2O$



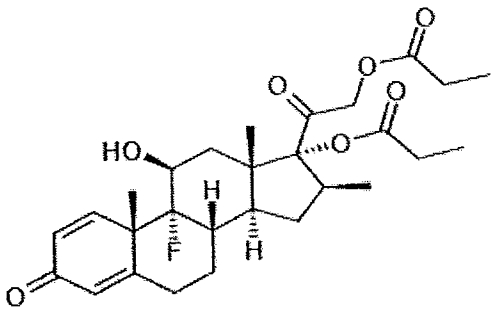

**Molecular Weight:** 430.6

**Betamethasone Dipropionate:**

**Chemical Name:**

Pregna-1,4-diene-3,20-dione-9-fluoro-11-hydroxy-16-methyl-17, 21-bis(1-oxypropoxy)-(11β ,16β )

**Molecular Formula:** $C_{28}H_{37}FO_7$



**Molecular Weight:** 504.6

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | II | | | 3 | Adequate | 17-May-2007 | Reviewed by L. Huang for |
| | III | | | 4 | Adequate | | See review in P.7. |
| | III | | | 4 | Adequate | | See review in P.7. |
| | III | | | 4 | Adequate | | See review in P.7. |

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

**B. Other Documents:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

18. STATUS:

**ONDQA:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | Not Applicable | | |
| EES | Acceptable | 24-Sep-2007 | Office of Compliance |
| Pharm/Tox | Not Applicable | | |
| Biopharm | Not applicable | | |
| LNC | Not Applicable | | |
| Methods Validation | Not Applicable | | |
| DMETS | pending | | |
| EA | Adequate | | Section II/B of this review |
| Microbiology | Not applicable | | |

# The Chemistry Review for NDA 22-185

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

The sponsor has provided adequate resolution for all the CMC issues found during the review. Overall acceptable recommendations were reached for the inspections at the manufacturing facilities on 24-Sep-2007. The sponsor accepted the Agency's request to use "Suspension" instead of "Gel" for the dosage form, the presentation of the dosage form in the labeling will be confirmed during the labeling review. The NDA can be approved from CMC prospective.

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

None

## II. Summary of Chemistry Assessments

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

**Drug Substance:**

The proposed drug substances are calcipotriene hydrate and betamethasone dipropionate, USP. Both drug substances are used in the approved drug product Taclonex Ointment (NDA 21-852) with the same manufacturers . The sponsor cross referenced DMF , for the CMC information of betamethasone dipropionate. The DMF was previously reviewed by L. Huang, dated 17-May-2007, and was acceptable for The DMF has not been changed since then and therefore is acceptable to support this NDA. b(4)

The CMC information for calcipotriene hydrate is provided in this NDA. The manufacturer is LEO Pharmaceutical (NDA holder). The same drug substance is also used in four marketed drug products including Taclonex Ointment which is approved on 9-Jan-2006 (NDA 21-852, CMC reviewer E. Pappas). The sponsor reported in this NDA that the synthetic method used to manufacture the drug substance starting material, was changed to since approval of NDA 21-852. The same information was also s . The change was found adequate by Dr. Don Klein to support , and therefore, is adequate to support this NDA. b(4)

**Drug Product:**

The sponsor developed the drug product as a [redacted] gel containing two drug substances calcipotriol 50 mcg/g (as hydrate) and betamethasone dipropionate 0.643 mg/g in a fixed combination in a [redacted] vehicle and filled into 30 ml, 60 ml and 120 ml [redacted] bottles equipped with [redacted] nozzles and [redacted] screw caps, containing 15g, 30g and 60g product, respectively. Excipients paraffin and caster oil are Eur Ph/USP/NF compendial. Exicipient PPG-15 stearyl ether is a non-compendial, non-novel excipient and is used in the marketed product Taclonex® Ointment (NDA No. 21-852). b(4)

The sponsor used "Gel" for the dosage form. However, samples of the drug product provided by the sponsor clearly show that the product can freely flow which fits a dosage form of suspension instead of gel. Therefore, the sponsor was requested to use "Suspension" for the dosage form instead of "Gel". The sponsor accepted the request.

The drug product specification is in general similar to the approved ointment product except the physical specifications such as viscosity and particle size. The specification for total impurity of betamethasone dipropionate [redacted] is higher than the approved ointment product but is still under reasonable acceptable limit and supported by the stability results. The impurities from calcipotriol are increased during photo stability study when the drug product is stored without a secondary package, but not for the drug product stored with the secondary package. Therefore, the sponsor's proposal to store the drug products with the outer carton are acceptable. The sponsor provided sufficient stability data to support an expiration date of 24 months. b(4)

During the in-use stability study, a [redacted] were discovered after 6 months. The sponsor was requested to provide detailed information for the [redacted] in the in-use stability study ~~and the reason~~ [redacted] ~~In the amendment to respond the~~ Agency's requests, the sponsor provided supportive data that demonstrate [redacted] Since the [redacted] ~~ppeared after 6~~ months ~~of in-use stability study~~ and is not a result of [redacted] ~~the~~ sponsor's proposal for the product to be used within three months of opening is acceptable. b(4)

Satisfactory recommendation from facility inspections in the manufacture of the drug substance and drug product was reached on 24-Sep-2007.

The CMC portion of the labeling [redacted] b(4)

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

The drug product is indicated for the topical treatment of psoriasis vulgaris of the scalp in adults aged 18 years and above. It will be applied to the affected areas on the scalp once daily for up to 8 weeks and as needed thereafter under medical supervision. The maximum weekly dose should not exceed 100 g. The product needs to be shaken before use.

**C. Basis for Approvability or Not-Approval Recommendation**

The drug substances are USP compendial and have been used in approved drug products. The sponsor has adequately addressed all the CMC concerns for the drug product during the review. Overall acceptable recommendations were reached for the inspections at the manufacturing facilities on 24-Sep-2007. The sponsor accepted the Agency's request to use "Suspension" instead of "Gel" for the dosage form, the presentation of the dosage form in the labeling will be confirmed during the labeling review. The NDA can be approved from CMC prospective.

## III. Administrative

**A. Reviewer's Signature**

*In DFS*

**B. Endorsement Block**

Chemist: Zhengfang Ge
Chemistry Branch Chief: Moo-Jhong Rhee

**C. CC Block**

ProjectManager: Melinda Bauerlien
Pharmaceutical Assessment Lead: Shulin Ding

55 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Zhengfang Ge
2/6/2008 03:04:25 PM
CHEMIST

Moo-Jhong Rhee
2/7/2008 03:17:10 PM
CHEMIST
Chief, Branch III

# Initial Quality Assessment
# Branch III
# Pre-Marketing Assessment Division II

| | |
|---|---|
| **OND Division:** | Division of Dermatology and Dental Products |
| **NDA:** | 22-185 |
| **Applicant:** | Leo Pharmaceutical Products Ltd. |
| **Stamp Date:** | June 28, 2007 |
| **PDUFA Date** | April 28, 2007 |
| **Trademark:** | Taclonex Scalp® |
| **Established Name:** | Calcipotriene Hydrate and Betamethasone Dipropionate |
| **Dosage Form:** | Gel |
| **Route of Administration:** | Topical |
| **Indication:** | Psoriasis vulgaris of scalp in adults 18 years of age and older |
| **PAL:** | Shulin Ding |

| | YES | NO |
|---|---|---|
| **ONDQA Fileability:** | ☒ | ☐ |
| **Comments for 74-Day Letter** | ☐ | ☒ |

**Summary and Critical Issues:**

A. Summary

The proposed drug substances are calcipotriene hydrate and betamethasone dipropionate, USP. The CMC information for betamethasone dipropionate, USP, is referenced to DMF [redacted] The DMF has been reviewed multiple times and deemed adequate to support topical products. The CMC information for calcipotriene hydrate is provided in the NDA. Leo Pharmaceutical Products Ltd. (Ballerup, Denmark), is the manufacturer. These two drug substances with their corresponding manufacturers have been approved for Taclonex Ointment in January 2006 (NDA 21-852). b(4)

The proposed drug product, Taclonex Scalp® (calcipotriene 0.005% and betamethasone dipropionate 0.064%) gel is developed as a complement to Taclonex® Ointment, which contains the same drug substances in the same concentrations but for psoriasis vulgaris on the body. Taclonex Scalp gel is formulated in a [redacted] gel base in which [redacted] The formulation contains the following excipients: mineral oil, USP; PPG-15 stearyl ether; hydrogenated castor oil, NF; [redacted] There are no novel excipients in the formulation. The to-be-marketed formulation is the same formulation used in the Phase 3 clinical trials and registration stability batches. b(4)

Taclonex Scalp gel is packaged in [redacted] e bottles equipped with a [redacted] nozzle and [redacted] screw cap. The proposed b(4)

configurations are 15 g in 30 mL bottle, 30 g in 60 mL bottle, and 60 g in 120 mL bottle. The product needs to be shaken before use, and should be discarded three months after opening.

The designated commercial manufacturing site for Taclonex Scalp gel is the same site used for the manufacture of registration stability and all Phase 3 clinical batches. The proposed commercial scale manufacturing process (Process B) is the same process used in the manufacture of the registration stability batches and some of the Phase 3 supplies. Most of Phase 3 batches were manufactured using Process A, which has been shown to be equivalent to Process B through an in-vitro release study. The manufacturing process of the bulk gel consists of

b(4)

Drug product stability data provided in the initial submission to support the proposed expiry period of 24 months at 20-25°C with excursions permitted to 59-86°F (15-30°C) include long term (25°C/60% RH) data of 12 months for fill sizes of 15 g and 60 g from four primary batches in the to-be-marketed container/closure system. Also provided are the accelerated (40°C/75% RH) stability data of 6 months and the intermediate temperature (30°C/70% RH) data of 12 months from the four primary batches. Special stability studies provided to support the proposed product include low temperature (10°C), temperature cycling (-20°C to 40°C), photostability, and in-use stability. All registration stability batches were size, which is the proposed commercial scale.

b(4)

## B. Critical issues for review

Dosage Form Nomenclature

- The applicant proposes gel as the dosage form. If the product is confirmed to be a semi-solid as claimed by the applicant, the formulation fits both definitions of gel and ointment given by Buhse et al. (Topical drug classification, International Journal of Pharmaceutics, 295 (2005) 101-112). If it turns out to be a liquid, then the formulation does not fit gel/ointment definition; it fits the definition for suspension instead. To assist the assessment of dosage form nomenclature, the applicant should officially submit a representative sample to the NDA with rheograms.

b(4)

Drug Product Stability

- The applicant studied only the upright orientation. The inverted position and side-way were omitted in the registration stability protocol. It is uncertain if packaging integrity would be maintained upon long term storage in the inverted position or side-way. The concern is raised because the cap and the nozzle do not contact the formulation in the upright position but are expected to contact the

formulation when stored in the inverted position or side-way. Furthermore, the nozzle is made of a different material from bottle.

- A thin layer of oil would form during the shelf-life of the proposed product. The oil is low in betamethasone content. To mitigate this non-uniformity issue, the applicant proposes "shake before use" before dosing and also b(4) . Although shake-before-use may resolve the dosing problem with betamethasone

- It was noted in the in-use stability study that at 6 month time point. To circumvent the problem, the applicant proposes to limit the use period of the product to three months. The acceptability of this proposal will need to be carefully reviewed b(4)

b(4)

b(4)

Extractables

- The applicant does not provide test results for the packaging qualification studies on container/closure system such as USP<661> studies. Additionally, the applicant uses a or the extraction study described in USP<661> b(4)

Due to the potential of leachables from label/adhesive should be investigated in addition to the leachables from the bottle. The applicant, however, did not include label/adhesive in the qualification studies on container/closure system. All stability samples do not have labels on the bottles either. In light of the noted in the in-use stability study, the concern with a significant leaching can not be eliminated without additional data. b(4)

Drug Product assay methods

- The specificity of the two assay methods [redacted] is not adequately established. The method validation on specificity does not include [redacted] b(4)

Drug Product Related Substances methods and acceptance criteria

- The specificity of the two related substance methods [redacted] is not adequately established. [redacted] b(4)

Drug Product Post Approval Stability Protocol

- The applicant proposed to test the product every 6 months for two years. The adequacy of the testing frequency will need to be reviewed.

Calcipotriene Hydrate Drug Substance

- Some impurities are quantitated by HPLC but some by TLC. The adequacy of the TLC method needs to be carefully reviewed.
- The GC method for [redacted] b(4)

C. Comments for 74-Day Letter: None

D. Comments/Recommendation:

The application is fileable from the CMC and quality perspective.

The major review issues of this NDA include dosage form nomenclature, drug product stability, [redacted] extractables, method specificity for assays and related substances, and drug product post approval stability protocol.

Drug product facilities are located in Europe. GMP inspection requests have been submitted.

Shulin Ding
Pharmaceutical Assessment Lead

Moo Jhong Rhee
Chief, Branch III

# Filing Checklists

## A. Administrative Checklists

| YES | NO | | Comments |
|---|---|---|---|
| x | | On its face, is the section organized adequately? | |
| x | | Is the section indexed and paginated adequately? | |
| x | | On its face, is the section legible? | |
| x | | Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs? | |
| x | | Has an environmental assessment report or categorical exclusion been provided? | |

## B. Technical Checklists

### 1. Drug Substance: Calcipotriene Hydrate

| | | | |
|---|---|---|---|
| x | | Does the section contain synthetic scheme with in-process parameters? | |
| x | | Does the section contain structural elucidation data? | |
| x | | Does the section contain specifications? | |
| x | | Does the section contain information on impurities? | |
| x | | Does the section contain validation data for analytical methods? | |
| x | | Does the section contain container and closure information? | |
| x | | Does the section contain stability data? | |

### 2. Drug Substance: Betamethasone Dipropionate Referenced to DMF 4148.

| | | | |
|---|---|---|---|
| | | Does the section contain synthetic scheme with in-process parameters? | Not applicable |
| | | Does the section contain structural elucidation data? | Not applicable |
| x | | Does the section contain specifications? | |
| | | Does the section contain information on impurities? | Not applicable |
| | | Does the section contain validation data for analytical methods? | Not applicable |
| x | | Does the section contain container and closure information? | |
| | | Does the section contain stability data? | Not applicable |

### 3. Drug Product

| | | | |
|---|---|---|---|
| x | | Does the section contain manufacturing process with in-process controls? | |
| x | | Does the section contain quality controls of excipients? | |
| x | | Does the section contain information on composition? | |
| x | | Does the section contain specifications? | |
| x | | Does the section contain information on degradation products? | |
| x | | Does the section contain validation data for analytical methods? | |
| x | | Does the section contain information on container and closure systems? | |