

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**21-852**

**CHEMISTRY REVIEW(S)**

**NDA 21-852**  
**Dovobet Ointment**

**Leo Pharmaceutical Products (Leo Pharm A/S)**

**Ernest G. Pappas**  
**Division of Dermatological and Dental Drug Products**



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# Chemistry Review Data Sheet

1. NDA 21-852
2. REVIEW #1
3. REVIEW DATE: 11/29/05
4. REVIEWER: Ernest G. Pappas
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

3/9/05

Amendment

8/2/05

Amendment

8/11/05

Amendment

9/12/05

Amendment

11/21/05

7. NAME & ADDRESS OF APPLICANT:

Name: Leo Pharmaceutical Products Ltd.(Leo Pharm  
A/S)



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

Industriparken 55  
Address: DK-2750 Ballerup  
Denmark

Telephone: +45 4494 5888

#### 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Dovobet
- b) Non-Proprietary Name (USAN): calcipotriene hydrate and betamethasone dipropionate
- c) Code Name/# (ONDC only): N.A.
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

#### 9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

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

11. DOSAGE FORM: Ointment

#### 12. STRENGTH/POTENCY:

calcipotriene hydrate: 0.005%

betamethasone dipropionate: —%

13. ROUTE OF ADMINISTRATION: Topical dermatologic

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

Not a SPOTS product



# CHEMISTRY REVIEW

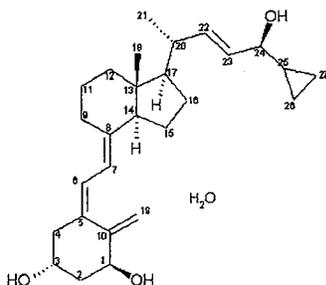


## Chemistry Review Data Sheet

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

Calcipotriol hydrate

Structural Formula:

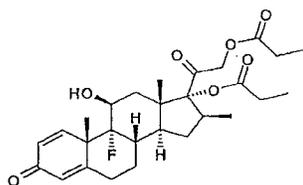


Molecular Formula: C<sub>27</sub>H<sub>40</sub>O<sub>3</sub>, H<sub>2</sub>O

Molecular Weight: 430.6

Betamethasone dipropionate

Chemical structure



Molecular formula  
C<sub>28</sub>H<sub>37</sub>FO<sub>7</sub>

Molecular weight  
504.6



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE <sup>1</sup> | STATUS <sup>2</sup> | DATE REVIEW COMPLETED | COMMENTS |
|-------|------|--------|-----------------|-------------------|---------------------|-----------------------|----------|
| [     |      |        |                 |                   | Adequate            | 1/4/05                |          |
|       |      |        |                 |                   | Adequate            |                       |          |
|       |      |        |                 |                   | Adequate            |                       |          |
|       |      |        |                 |                   | Adequate            |                       |          |
|       |      |        |                 |                   | Adequate            |                       |          |

<sup>1</sup> 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")

<sup>2</sup> 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 |
|----------|--------------------|-------------|
|          |                    |             |
|          |                    |             |
|          |                    |             |
|          |                    |             |



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

18. STATUS:

**ONDC:**

| <b>CONSULTS/ CMC<br/>RELATED<br/>REVIEWS</b> | <b>RECOMMENDATION</b> | <b>DATE</b> | <b>REVIEWER</b> |
|--|-----------------------|-------------|-----------------|
| EES  | Acceptable            | 9/5/05      | Adams           |
| DMETS  | Acceptable            | 7/25/05     | Best            |
| Microbiology                                 | Acceptable            | 7/29/05     | Lolas           |



# The Chemistry Review for NDA 21-852

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA can be approved from a Chemistry standpoint.

#### B. 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)

##### (1) Drug Product:

The drug product, Dovobet® Ointment is a topical product which is packaged in 3g, 15g, 30g, 60g and \_\_\_\_\_ collapsible aluminum tubes.

Dovobet® Ointment contains two active ingredients in the formulation, calcipotriene hydrate and betamethasone dipropionate. This product is manufactured with components that have a history in the pharmaceutical and cosmetic applications. These components have shown to be compatible through appropriate testing with each other and primary packages. Chemical testing of the product during stability has demonstrated that there are no adverse interaction between calcipotriene hydrate and betamethasone dipropionate and the excipients of the ointment base. Dovobet Ointment contains the excipients, \_\_\_\_\_ polyoxypropylene-15 stearyl ether, and \_\_\_\_\_  $\alpha$ -tocopherol (anti-oxidant).

During product development, it was imperative that an ointment be manufactured involving vehicle with no acid-alkaline properties since calcipotriol is very sensitive to acid and betamethasone dipropionate is sensitive to alkaline conditions.

The critical manufacturing parameters in the product development are (1) Dissolution of Calcipotriol Hydrate, and (2) \_\_\_\_\_ Betamethasone dipropionate. In this regard, polyoxypropylene-15 stearyl ether was selected because of the high solubility of calcipotriol hydrate in this solvent. Some needle shape crystals of calcipotriol were observed under the microscopic examination in the final product; however they found to be few in quantity for some batches. It was important that calcipotriol hydrate remained soluble in the oil-in-water base.



## Executive Summary Section

These crystals are controlled from batch to batch during manufacturing by a tight acceptance specification for these crystals.

Betamethasone dipropionate particles (99 % < 15  $\mu\text{m}$ ) are dispersed in the oil/water phase base. Under the microscope the betamethasone dipropionate is seen as small plate shaped particles. The particle size of betamethasone dipropionate distribution is controlled by a tight acceptance specification at the drug substance and as well as drug product level.

The drug regulatory release and stability specification contains the acceptance criteria for testing Dovobet Ointment. These specifications were reviewed and found acceptable. The process validation studies for 27 batches ensured the homogeneity of calcipotriol hydrate and betamethasone dipropionate in the Dovobet Ointment. The assay of calcipotriol hydrate and betamethasone dipropionate content and control of particle size distribution ensures batch-to-batch reproducibility of future commercial lots. In addition, particle size distribution data were presented for batches used in toxicological, clinical, and stability studies. No change was observed for these studies.

Stability data were submitted on eleven production batches of the Dovobet Ointment as packaged in the container/closure system proposed for the marketplace. Up to 36 months of room temperature data were submitted in support of the proposed 24 month expiration date. The stability data were found acceptable to support an expiration date of 24 months.

The labeling was reviewed and found acceptable from a technical standpoint. However, the proprietary name Dovobet is pending acceptance by DMETS and DDMAC for naming the finished product as Dovobet Ointment. The storage condition of "Store at controlled room temperature 25  $^{\circ}\text{C}$  has been recommended on the packaging labeling.

Establishment Inspections: All facilities as indicated in the NDA are found acceptable for CGMPs. An overall recommendation of "acceptable" was received from the Office of Compliance on 9/8/05.

Environmental Assessment: The applicant's claim of categorical exclusion under regulation 21 CFR 25.31 (b) is acceptable since the EIC projection was found to be at a level well below 1ppb.

### (2) Drug Substance(s):

The drug substance, Betamethasone Dipropionate, is manufactured and supplied to the NDA holder (Leo) by \_\_\_\_\_ . Betamethasone Dipropionate is the subject of approved marketed products, e.g., Diprolene Ointment (NDA 18-741), Diprolene Cream (NDA 19-555), Diprosone Lotion (NDA 17-781), Betamethasone Ointment (NDA 19-143), Betamethasone Cream (NDA 19-138), etc. The details of the method of manufacture, controls, and packaging of the drug substance have been also reported in these NDAs and ANDAs. However, the CMC information for betamethasone dipropionate for this NDA has been referred to DMF \_\_\_\_\_ .

Executive Summary Section

Information as to the description, characterization/proof of structure, synthesis, process controls, reference standard, purity profile, container/closure and stability of the betamethasone dipropionate is also reported in the NDA.

The following impurities were identified by —————

[ ]

The acceptance criteria for these impurities were found to be acceptable.

The stability data have been found acceptable for betamethasone dipropionate drug substance.

**Calcipotriene Hydrate:**

The drug substance, Calcipotriene Hydrate, is manufactured, tested and approved by Leo Pharmaceutical Products Ltd, A/S (Leo Pharma A/S). Calcipotriene Hydrate is the subject of approved marketed products, e.g., Dovonex Cream (NDA 20-554); Dovonex Ointment (NDA 20-273), and Dovonex Scalp Solution (NDA 20-611). The details of the method of manufacture, controls, and packaging of the drug substance have been reported in these NDAs.

Information as to the description, characterization/proof of structure, synthesis, process controls, reference standard, purity profile, container/closure and stability of the calcipotriene drug substance can be referenced in these NDAs.

The following potential impurities were identified by Leo:

[ ]

The acceptance criteria have been found acceptable.

The stability data have been found acceptable for calcipotriol hydrate drug substance.



Executive Summary Section

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

Dovobet Ointment is indicated for topical treatment of psoriasis vulgaris in adults aged 18 years and above. The dosage regimen should be applied once daily.

**C. Basis for Approvability or Not-Approval Recommendation: N/A**

**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

ChemistName/Date: Same date as draft review  
ChemistryTeamLeaderName/Date  
ProjectManagerName/Date

**C. CC Block**

94 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Chemistry-1a

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

11/30/2005 08:47:45 AM

CHEMIST

My chemistry is ready for signature. Recommend approval of  
the NDA.

Ramesh Sood

11/30/2005 08:50:34 AM

CHEMIST