# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-535**

## CHEMISTRY REVIEW(S)

# NDA 21-535

## CLOBEX (clobetasol propionate) Lotion 0.05%

## GALDERMA Laboratories, L.P.

**Saleh A. Turujman, Ph.D.**
**Division of Dermatologic and Dental Drug Products**
**HFD-540**

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# Chemistry Review Data Sheet

1. **NDA #** 21-535

2. **REVIEW:** # 1

3. **REVIEW DATE:** 15-June-2003

4. **REVIEWER:** Saleh A. Turujman, Ph.D.

5. **PREVIOUS DOCUMENTS:**

| Previous Documents | Document Date |
|---|---|
| NDA 21-535 Original Submission | 25-SEP-2002 |
| IR Letter (FAX) | 06 FEB-2003 |
| Amendment (BM)* | 11-FEB 2003 |
| Amendment (BS)** | 19-FEB 2003 |
| IR Letter (FAX) | 24 FEB-2003 |
| Amendment (BC) | 09-MAY 2003 |
| Amendment (BC)*** | 10-JUNE-2003 |

* Revised PPI

** Response to first IR letter; incorrectly coded (see NDA 21-535 e-mail of 3/17/03)

*** Not reviewed. [redacted] was informed that their amendment, to use a different manufacturer for their one-half ounce bottle, has been received too late in the review cycle to be included in the evaluation of the NDA.

6. **SUBMISSION(S) BEING REVIEWED:**

| Submission(s) Reviewed | Document Date |
|---|---|
| NDA 21-535 Original Submission | 25-SEP-2002 |
| Amendment (BM) | 11-FEB 2003 |
| Amendment (BS) | 19-FEB 2003 |
| Amendment (BC) | 09-MAY 2003 |

## 7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | GALDERMA Laboratories, L.P. |
| Address: | 14501 North Freeway<br>Fort Worth, Texas 76177 |
| Representative: | Paul Clark<br>Vice President, Regulatory affairs |
| Telephone: | (817) 961-5336 |

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

a) Proprietary Name: CLOBEX
b) Non-Proprietary Name (USAN): Clobetasol propionate
c) Code Name/#: 661.337
d) Chem. Type/Submission Priority:

- Chem. Type: 3
- Submission Priority: S

**9. LEGAL BASIS FOR SUBMISSION:** 505(b)(2) application 21 CFR 314.54; Listed drug: Temovate E (clobetasol propionate) Emollient Cream, 0.05% (NDA # 20-340) Glaxo-SmithKline

**10. PHARMACOL. CATEGORY:** Glucocorticoid anti-inflammatory

**11. DOSAGE FORM:** Lotion

**12. STRENGTH/POTENCY:** 0.05% (w/w)

**13. ROUTE OF ADMINISTRATION:**

**14. Rx/OTC DISPENSED:** _X__Rx ___OTC

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

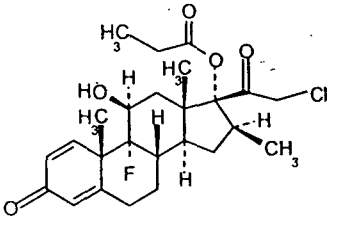
__X__ Not a SPOTS product

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

Clobetasol propionate, $C_{25}H_{32}ClFO_5$, MW ~ , CAS # -25122-46-7, is a synthetic fluorinated corticosteroid. The chemical name is 21-chloro-9-fluoro-11,17-dihydroxy-16-methylpregna-1,4-diene-3,20-dione 17 propionate. Other acceptable chemical names are:

- (11$\beta$,16$\beta$)-21-Chloro-9-fluoro-11$\beta$,17-dihydroxy-16$\beta$-methylpregna-1,4-diene-3,20-dione 17 propionate;
- (11$\beta$,16$\beta$)-21-Chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-pregna-1,4-diene-3,20-dione

The structural formula is shown below.



## 17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| [redacted] | II | [redacted] | [redacted] | 1 | Adequate<br>No changes<br>2 year Stability updated | Rev #3 March 22, 2001<br>Rev #4 May 15, 2003 | Update: 9 March 2001*<br>Update: 11 June 2002**<br>An Information Request letter was issued to DMF holder on May 16, 2003 |
| [redacted] | II | [redacted] | [redacted] | | Deficient | January 23, 2003 | Reviewed by Liang Huang for Deficiency letter issued February 14, 2003; Tcon 3-14-03 |
| [redacted] | III | [redacted] | [redacted] | 4 | | | |
| [redacted] | III | [redacted] | [redacted] | 4 | Adequate | 22 April 2002 | |
| [redacted] | III | [redacted] | [redacted] | 4 | | | |
| [redacted] | III | [redacted] | [redacted] | 4 | | | Update 21 May 2001 |
| [redacted] | III | [redacted] | [redacted] | 4 | | | Update: 3 August 2000 |

* Reviewed previously, as indicated by the review and review date in the Comis database. It was not verified whether any revisions were made since the last review. However for this NDA, sufficient information regarding the container/closure systems for the drug product was provided in the application as described in the review below
** Minor logistical reorganization changes + stability update; reviewed as indicated on May 15, 2003.

[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 |
|---|---|---|
| IND* | 54,230 | Clobetasol Propionate lotion, 0.05% |

* Document date: 30 SEP 1997

18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | N/A | N/A | |
| EES | Acceptable | 10-Oct-2002 | Janine D'Ambrogio |
| EES | Acceptable | 8-Oct-2002 | Janine D'Ambrogio |
| EES (DPT Laboratories) | Acceptable | 10-Oct-2002 | Janine D'Ambrogio |
| Pharm/Tox | N/A | N/A | |
| Biopharm | N/A | N/A | |
| LNC | N/A | N/A | |
| Methods Validation | Not submitted yet | N/A | |
| DMETS | Approval | 19-Nov-2002 | Jennifer Fan |
| EA | Categorical exclusion | N/A | N/A |
| Microbiology | N/A | N/A | N/A |

APPEARS THIS WAY
ON ORIGINAL

# The Chemistry Review for NDA 21-535

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing and controls standpoint is approvable pending action by the applicant to withdraw [redacted] as an alternate [redacted] supplier.

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

None recommended.

## II. Summary of Chemistry Assessments

### A. Description of the Drug Substance and the Drug Product

The drug substance, clobetasol propionate, USP, a synthetic analog of prednisolone, is a well-established, super potent corticosteroid which is currently approved for topical use in the US in five different dosage forms (31 drug products): cream, ointment, gel, solution, and foam (aerosol). All dosage forms use the same strength of 0.05% clobetasol propionate proposed by the applicant.

The applicant refers most of the chemistry, manufacturing and controls information regarding clobetasol propionate, to Type II DMF [redacted] held by [redacted]

Clobetasol propionate lotion was formulated as a [liquid] oil-in-water emulsion , with the drug substance [redacted] (called the [redacted] by the applicant) using the following excipients: hydroxypropylmethylcellulose, polyoxyethylene glycol 300 isostearate [redacted] Carbomer [redacted] mineral oil, propylene glycol, sodium hydroxide, purified water. All the excipients are compendial except for polyoxyethylene glycol 300 isostearate : [redacted] , a [redacted] , for which the applicant provides a comprehensive manufacturing and control information.

Propylene glycol is used to [redacted] However, the large amount of propylene glycol used ( [redacted] is a cause of concern from a clinical point of view because of its penetration enhancing properties in conjunction with this super potent corticosteroid drug substance (see clinical review).

Propylene glycol is also a [redacted]. The applicant does provide confirmatory tests for the [redacted] of propylene glycol in the drug product.

[redacted]

The applicant intends to market Clobex lotion in a professional physician's sample bottle (0.5 oz) and three commercial package sizes (1 oz, 2 oz and 4 oz bottles). All the bottle sizes are made from High Density Polyethylene (HPDE). The professional physician's sample bottle (0.5 oz) and the 1.0 oz size commercial bottle are provided with a [redacted] closure. The 1 oz and 2 oz size bottles are provided with a [redacted] closure. The amount of active ingredient per unit application (dose) is provided in the next section.

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

Clobetasol propionate, a synthetic fluorinated corticosteroid for topical dermatologic use, has anti-inflammatory, antipruritic, and vasoconstrictive properties. Clobex (clobetasol propionate) lotion, 0.05% is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses as well as for the treatment of moderate to severe plaque-type psoriasis. Clobex should be applied to the affected skin areas twice daily and rubbed in gently and completely. For inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, application should be limited to two consecutive weeks while for moderate to severe plaque-type psoriasis, treatment should be limited to four consecutive weeks. The total dosage should not exceed 50 g (approximately 2 fl. oz) per week. This drug product will be supplied in 1 fl. oz ( ), 2 fl. oz ( ) and 4 fl. oz ( ) bottles. The maximum human dose of clobetasol propionate per day (50 g lotion per week) is approximately 7.1 g lotion per day, giving a daily exposure of 3.6 mg of clobetasol propionate per day. An expiration dating period of 36 months is approved, based on 36 months of long-term stability data for [redacted] stability batches of [redacted] each.

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

After evaluation for GMP compliance, all three manufacturing and testing facilities were found to be acceptable. Clobetasol propionate, is a well-established chemical whose

structure has been fully elucidated. It is characterized through the USP monograph, and listed in USAN and in the Merck Index (additional data). The DMF of the [redacted] supplier has been updated, reviewed and found to be adequate. The NDA submission and its amendments (responses to information request letters) provide adequate information on the chemistry, manufacturing and controls for the production of Clobex (clobetasol propionate) lotion, 0.05%.

## III. Administrative

### A. Reviewer's Signature

### B. Endorsement Block

Chemist: Saleh A. Turujman/6/27/03
Chemistry TL: Wilson H. DeCamp/
Project Manager: Melinda Harris/

### C. CC Block

Cc: NDA 21-535
HFD-540/Division File
HFD-540/Chem/SATurujman
HFD-540/ChemTL/WHDeCamp
HFD-540/ProjMgr/MHarris
HFD-540/MedOff/DCook
HFD-540/Pharm/PBrown
HFD-540/BioPharm/CChaurasia
HFD-540/Biometrics/SLee

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36 Page(s) Withheld

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/s/

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Saleh Turujman
6/27/03 02:33:12 PM
CHEMIST

For your concurrence

Wilson H. DeCamp
6/27/03 04:57:40 PM
CHEMIST
concur with review