CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-644

CHEMISTRY REVIEW(S)

NDA 21-644

CLOBEX (Clobetasol Propionate) Shampoo, 0.05%

GALDERMA Laboratories, L.P.

Saleh A. Turujman, Ph.D.
Division of Dermatologic and Dental Drug Products

Table of Contents

Chemistry Review Data Sheet

1. **NDA #** 21-644

2. **REVIEW #** 1

3. **REVIEW DATE:** 19 December, 2003

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

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 21-644 Original Submission	6-MAY-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 21-644 Original Submission	6-MAY-2002

7. **NAME & ADDRESS OF APPLICANT:**

Name:	GALDERMA Laboratories, L.P.
Address:	14501 North Freeway Fort Worth, Texas 76177
Representative:	Paul Clark 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/#: 662.066
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: Shampoo

12. STRENGTH/POTENCY: 0.05%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

__X__Not a SPOTS product

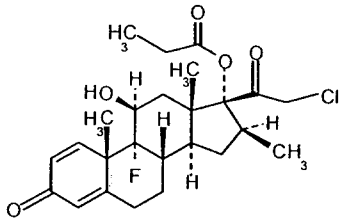
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Clobetasol propionate, $C_{25}H_{32}ClFO_5$, MW 466.97, 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:

- 21-Chloro-9-fluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17 propionate;

- (11β,16β)-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 Adequate	Rev #4 May 15, 2003 Rev #5 Dec. 1, 2003	Update: 11 June 2002
[redacted]	II				Deficient Deficient **Adequate**	Rev #1 Jan. 23, 2003 Rev #2 Aug 26, 2003 Rev #3 Nov 07, 2003	Reviewed by Liang Huang for ANDA 75368; Deficiency letter 2/14/03; Tcon 3-14-03. Amendments: 7/8/03; 10/31/03
[redacted]	III			4			
[redacted]	III			4	Adequate	22 April 2002	
[redacted]	III			4			
[redacted]	III			2	Inadequate	2/21/2003	Type I DMF per NSager
[redacted]	III			3	Adequate	10/23/2003	STso/HFD-550
[redacted]	III			3	Adequate	10/23/2003	STso/HFD-550
[redacted]	III			3	Adequate	4/14/1998	Higgins/HFD-540
[redacted]	III			4			
[redacted]	III			4			
[redacted]	III	[redacted]	[redacted]	3	Adequate	9/17/2003	Bertha/HFD-570

[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	[redacted]	Clobetasol propionate lotion

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	
EES	Acceptable	23 June 2003	Janine D'Ambrogio
EES	Acceptable	23 June 2003	Janine D'Ambrogio
EES	Acceptable	23 June 2003	Janine D'Ambrogio
Pharm/Tox	N/A	N/A	
Biopharm	N/A	N/A	
LNC	N/A	N/A	
Methods Validation	Not yet submitted	N/A	
OPDRA			
EA	Categorical exclusion	N/A	
Microbiology	N/A	N/A	

The Chemistry Review for NDA 21-644

The Executive Summary

I. Recommendations

- **A. Recommendation and Conclusion on Approvability**

The recommendation for this NDA is approval from a chemistry, manufacturing and controls standpoint.

- **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 Drug Product**

The drug substance, clobetasol propionate, 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 the 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 DMFs from contract manufacturers.

Clobetasol propionate shampoo was formulated as a solution. The rationale is provided in this review under "**III. INVESTIGATIONAL FORMULATIONS**".

Clobetasol propionate shampoo, 0.05% contains three compendial excipients, *viz.*, alcohol (ethanol [redacted]), sodium citrate dihydrate, citric acid monohydrate, purified water, three non-compendial excipients, *viz.*, coco-betaine, polyquaternium-10 and sodium laureth sulfate. All three have been widely used in topical cosmetic preparations over the last 20 years. Complete manufacturing and control information for each of these excipients is provided in the NDA. Each was reviewed and found acceptable.

The applicant proposes to market Clobex Shampoo in a professional physician's sample bottle (0.5 fl. oz) and one commercial package size (4 fl. oz bottle). Both size bottles are made from [redacted]. The professional physician's sample bottle (0.5 oz) and the 4.0 fl. oz size commercial bottle are combined with a dispensing system/closure, which is a low density polyethylene dropper tip closure. In addition, the 4 fl. oz size bottle is provided with an alternative polyethylene disc-top 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) Shampoo, 0.05% is indicated for [redacted] the treatment of moderate to severe scalp psoriasis.
  - Clobex Shampoo should be applied to the affected scalp areas once daily and rubbed in gently and completely into the dry scalp. Application is limited to four consecutive weeks or when the indication clears.
  - The total dosage should not exceed 50 g of the drug product (approximately 2 fl. oz) per week. This drug product will be supplied in a 4 fl. oz (113 g, 118 mL) bottle.
  - The maximum human dose of clobetasol propionate per day is approximately 7.1 g shampoo per day (50 g shampoo per week), giving a daily exposure of 3.6 mg of clobetasol propionate per day.
  - An expiration dating period of 24 months is supported by [redacted] of long-term stability data and [redacted] of accelerated stability data for [redacted] stability batches [redacted] each.

- **C. Basis for Approvability or Not-Approval Recommendation**
  - After evaluation for GMP compliance, all 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 DMFs of the drug substance suppliers have 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) Shampoo, 0.05%.

III. Administrative

- **A. Reviewer's Signature**

- **B. Endorsement Block**

Chemist: Saleh A. Turujman/
Chemistry TL: Wilson H. DeCamp/
Project Manager: Jacquelyn Smith/

- **C. CC Block**

Cc: NDA 21-644
HFD-540/Division File
HFD-540/Chem/SATurujman
HFD-540/ChemTL/WHDeCamp
HFD-540/ProjMgr/JSmith
HFD-540/MedOff/JLindstrom
HFD-540/Pharm/PBrown
HFD-540/BioPharm/CChaurasia
HFD-540/Biometrics/SThomson

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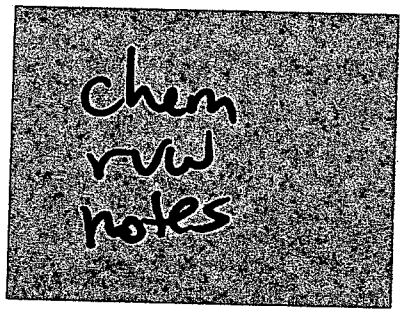

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Saleh Turujman
12/19/03 06:35:07 PM
CHEMIST

For your concurrence

Wilson H. DeCamp
12/19/03 06:37:02 PM
CHEMIST
concur with review; NDA is approvable

APPEARS THIS WAY
ON ORIGINAL