# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-758**

# CHEMISTRY REVIEW(S)

# NDA 21-758

## Tradename (fluocinonide) Cream, 0.1%

## Medicis Pharmaceutical Corp.

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

# Table of Contents

# Chemistry Review Data Sheet

1. NDA 21-758

2. REVIEW #: 1

3. REVIEW DATE: 2/04/05

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 | 04/7/04 |
| Amendment (BZ) | 07/21/04 |
| Amendment (BZ) | 10/29/04 |
| Amendment (BC) | 12/20/04 |
| Amendment (BZ) | 12/28/04 |
| Amendment | 02/03/05 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Medicis Pharmaceutical Corporation |
| Address: | 8125 N. Hayden Rd.<br>Scottsdale, AZ 85258-2463 |
| Representative: | R.Todd Plott, M.D.<br>Vice President<br>Clinical Research and Regulatory Affairs |
| Telephone: | (602) 808-8800 |

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Tradename
b) Non-Proprietary Name (USAN):fluocinonide
c) Code Name/# (ONDC only): CAS 356-12-7
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Relief of the inflammatory and pruritic manifestations of corticosteroid- responsive dermatoses.

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 0.1%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: X Rx ___OTC

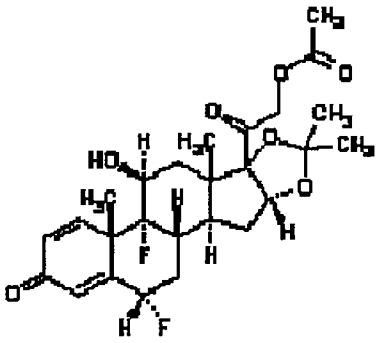
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

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

The chemical name is 6 alpha,9 alpha-difluoro-11 beta,21-dihydroxy-16 alpha,17 alpha-isopropylidenedioxypregna-1,4-diene-3,20-dione 21-acetate. Its chemical formula is $C_{26}H_{32}F_2O_7$, and its molecular weight is 494.58.

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] | 3 | Acceptable | 4/28/03 | Reviewed on 4/25/03 by Liang-Lii Huang, Ph.D. |
| [redacted] | III | | | 4 | Acceptable | | |

[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 |
|---|---|---|
| N.A. | | |

18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| EES | Acceptable | 6/24/04 | Adams |
| DMETS | [redacted] was found Unacceptable. | 6/7/04 | Holquist |

Appears This Way
On Original

# The Chemistry Review for NDA 21-758

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

This NDA can be **approved** from a Chemistry standpoint.
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### 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, Tradename (fluocinonide) 0.1% Cream is a topical product which is packaged in aluminum tubes with a white polypropylene, piecing screw cap. Tradename Cream, 0.1% has the same active component as in the currently marketed Lidex ® products including fluocinonide 0.05% cream, gel, ointment, and topical solutions, and Lidex-E emollient cream. Lidex ® (fluocinonide) 0.5% Cream was the first of its kind (Class II topical corticosteroid) to be manufactured in the United States by [redacted] in June, 1971. Like other topical corticosteroids it has anti-inflammatory, anti-pruritic and vasoconstrictive properties.

In addition, fluocinonide 0.1% products have been approved as generic equivalents and marketed world-wide. The names of the fluocinonide products marketed in Canada are Lidex Cream, Lidex Ointment, Lidemol Cream and Topsyn Gel.

The fluocinonide 0.1% drug product contains excipients that are commonly used in formulations and do not impact on the safety from a CMC standpoint. Five of the eight excipients are USP/NF monographs and must comply with the acceptance criteria as stipulated in the monographs. The NDA provided the testing standards for the ingredients not having a compendium monograph.

The drug product is an oil in water emulsion; a [redacted] phase system with a viscosity to classify it as a cream rather than a lotion. The [redacted] phase of fluocinonide 0.1% cream consists of glyceryl monostearate, which is contributed from [redacted] The [redacted] PEG stearate which is contributed as a component of [redacted] The [redacted] phase is comprised of propylene glycol, dimethyl isosorbide and water. Carbopol 980 [redacted] Citric acid [redacted] diisopropanolamine [redacted] Carbopol 980.

[redacted]

The sponsor proposed a 24-month expiration date for the product to be marketed in [redacted] packaging sizes ([redacted] 30g and 60 g). Up to [redacted] of room temperature data a [redacted] analysis were submitted in support of the proposed expiration date which found acceptable. Therefore, a 24-month expiry date has been granted for this drug product. [redacted]

The Tradenames, [redacted] Vanos are currently under review by the DMETS and DDMAC. To date, no recommendation has been given as to its acceptability. The labeling information, as well as the labels of the container and carton, is acceptable from a technical standpoint. The storage condition between $15^0$ C-$30^0$ C ($59^0$ F-$86^0$ F) was shown to be appropriate for drug product.

Establishment Inspection: All facilities, as indicated in the NDA, were found acceptable for CGMPs. An overall recommendation of approvable was received from the Office of Compliance on 6/24/04.

Environmental Assessment: The applicant's claim of categorical exclusion under

regulation 21 CFR 25.31 (b) is acceptable since the [redacted] was found to be at a level well below 1 ppb.

**(2) Drug substance:**

Fluocinonide is an API marketed in topical preparations worldwide under the trade names Betasone, Cortalar, Flucinar, Fluocinoclear, Fluonex, Lidex, Lidex-E, Lyderm, Metosyn, Straderm, Supracort, Tiamol, and Topsyn. It is the subject for DMF [redacted]. DMF [redacted] was reviewed and found acceptable by Liang-Lii Huang, Ph.D. dated 4/25/03. A certificate of Analysis was submitted for micronized fluocinonide; the assay results were found to fall within the acceptance criteria. The structure and physicochemical characteristic are adequately described in the DMF.
The NDA contained the HPLC method and Validation for the determination of Fluocinonide and related substances. The acceptance criteria and results were reported in the NDA.

The impurity profile was established for fluocinonide and is consistent throughout its manufacturing. The following known related impurities have been determined as follows: [redacted]. The acceptance criteria for the related substances have been tightened to reflect the manufacturing capability. The specifications specify these limits for the related impurities in order to assure consistent quality from batch to batch. These impurities were found to fall within the acceptance criteria.

Based on the evaluation of the primary stability data, the proposed retest date of [redacted] was deemed acceptable.

**B. Description of How the Drug Product is intended to be used**

Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Apply a thin layer of drug product to the affected skin once daily.

**C. Basis for Approvability or Not-Approval Recommendation- N/A as recommendation is approval.**

## III. Administrative

### A. Reviewer's Signature

### B. Endorsement Block

Chemist Name/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

### C. CC Block

44 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Chemistry-* 1

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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
2/4/05 02:31:46 PM
CHEMIST
My chemistry review for Tradename (fluocinonide) Cream, 0.1% is ready for signature.

Ramesh Sood
2/4/05 02:40:39 PM
CHEMIST