

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 21-753

CHEMISTRY REVIEW(S)



NDA 21-753

**DIFFERIN® (adapalene) Gel,
0.3%**

GALDERMA LABORATORIES, L.P.

**J. S. Hathaway, Ph.D.
Division of Dermatologic and Dental Drug Products
HFD-540**

**Review #1
23-JAN-2005**



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Chemistry Review Data Sheet

1. NDA 21-753
2. REVIEW #: 1
3. REVIEW DATE: 21-DEC-2004
4. REVIEWER: J. S. Hathaway, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original NDA
Amendment (BL)

01-APR-2004
25-JUN-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Galderma Laboratories, L.P.
Address:	14501 North Freeway Ft. Worth, TX 76177
Representative:	Christine Shank Sr. Director, Regulatory Submissions
Telephone:	Phone (817) 961-5343 Fax (817) 961-0020

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	DIFFERIN®
b) Non-Proprietary Name (USAN):	Adapalene
c) Code Name/# (ONDC only):	N/A
d) Chem. Type/Submission Priority (ONDC only):	



CHEMISTRY REVIEW



Chemistry Review Data Sheet

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anti-acne

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 0.3% (w/w)

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

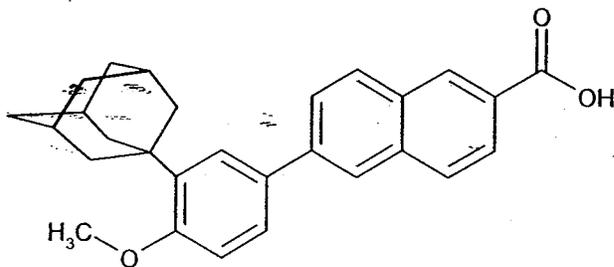
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid, or
2-naphthalenecarboxylic acid, 6-[4-methoxy-3-tricyclo[3.3.1.1^{3,7}]dec-1-ylphenyl]-

Molecular Formula: $C_{28}H_{28}O_3$

Molecular Weight: 412.53

CAS No.: 106685-40-9





CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
7 3	II	[]	[]	1	Adequate	21-DEC-2004	Adequate
7 3	III	[]	[]	3	Adequate	25-OCT-2002	Adequate

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 33,540	Adapalene Gel, 0.1% (w/w)
	IND []	Adapalene Gel, 0.3% (w/w)
	NDA 20-380	DIFFERIN (adapalene) Gel, 0.1% (w/w)
	NDA 20-748	DIFFERIN (adapalene) Cream, 0.1%
	NDA 20-338	DIFFERIN (adapalene) Solution, 0.1%

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CHEMISTRY REVIEW



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18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	17-MAY-2004	J. D'Ambrogio (HFD-322)
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Pending		
ODS/DMETS	Acceptable w/o "XP"	28-OCT-2004	C. Holquist, R.Ph. (HFD-420)
EA			J. S. Hathaway, Ph.D. (HFD-540)
Microbiology	N/A		

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On Original



The Chemistry Review for NDA 21-753

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA may be Approved for the chemistry, manufacturing and controls (CMC) as submitted in the application and supporting documents. No outstanding CMC regulatory issues exist at this time.

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 and Drug Substance

DIFFERIN® Gel, 0.3%, is indicated for the topical treatment of acne vulgaris. It is an aqueous gel formulation containing a suspension of the adapalene drug substance, and is a new strength of the existing approved dosage form. The formulation is

in the formulation. It is packaged in 45 gram tubes. The applicant has proposed a tentative expiration period.

Adapalene, the active ingredient, is the subject of the referenced NDA and its corresponding IND. It is also the subject of the applicant's approved NDAs 20-380, 20-388 and 20-748 for cream, gel and solution dosage forms, and the corresponding INDs 31,997, 33,540, 38,508 and 67,801 for these different dosage forms.

The applicant claimed categorical exclusion under 21 CFR 25.31(b), which was subsequently granted, since the Expected Introduction Concentration was less than 1.0 ppb.

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

The use of this drug product is indicated for the topical treatment of acne. Its directions for use call for once-daily application of a thin film of the gel to all areas. This



CHEMISTRY REVIEW



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higher strength is intended to provide more dosing options to physicians. Treatment duration is up to twelve weeks. The proposed expiration dating period is tentatively [] [] when stored at controlled room temperature, 20 - 25°C (68°-77°F) with excursions permitted between 15° - 30°C (59° - 86°F). The product should also be protected from freezing, as this has been demonstrated to adversely affect the drug product.

C. Basis for Approvability or Not-Approval Recommendation

Not applicable.

III. Administrative

A. Reviewer's Signature

(see attached electronic signature page)

Joel S. Hathaway, Ph.D.

B. Endorsement Block

JSHathaway/Date: 23-JAN-2005

RSood/

MAWright/

C. CC Block

cc: Original NDA 21-753

HFD-540/DivDir/JKWilkin

HFD-540/DermTeamLdr/MLuke

HFD-540/MedOffr/JPorres

HFD-540/PharmTox/DMainigi

HFD-540/ProjMgr/MAWright

HFD-540.Chem/JSHathaway

HFD-540/ChemTeamLdr/

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Chemistry Review #1

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this page is the manifestation of the electronic signature.**

/s/

Steve Hathaway
1/28/05 02:44:52 PM
CHEMIST
AP recommended for CMC
For your concurrence

Ramesh Sood
1/28/05 03:31:04 PM
CHEMIST

NDA 21-753

DIFFERIN® (adapalene) Gel, 0.3%

Galderma Laboratories, L.P.

Jane L. Chang, Ph.D.

Review Chemist

**Division of Dermatologic and Dental Drug Products
HFD-540**

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1. NDA 21-753
2. REVIEW #: 2
3. REVIEW DATE: May 10, 2007
4. REVIEWER: Jane Chang
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original NDA	01-APR-2004
Amendment (BL)	25-JUN-2004

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (AZ)	18-DEC-2006
Amendment (BL)	11-JAN-2007
Amendment (BC)	24-JAN-2007
Amendment (BC)	02-FEB-2007
Amendment (BL)	02-FEB-2007
Amendment (BC)	28-MAR-2007
Amendment (BL)	04-MAY-2007

7. NAME & ADDRESS OF APPLICANT:

Name: Galderma Laboratories, L.P.
 Address: 14501 North Freeway
 Ft. Worth, TX 76177
 Representative: Christine Shank
 Sr. Director, Regulatory Submissions
 Telephone: Phone (817) 961-5343
 Fax (817) 961-0020

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: DIFFERIN
b) Non-Proprietary Name (USAN): Adapalene
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5 (new formulation, per the new MAPP 7500.3)
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of acne vulgaris

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 0.3% (w/w)

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

Chemical name: 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid,
or

2-naphthalenecarboxylic acid, 6-[4-methoxy-3-tricyclo[3.3.1.1.3,7]dec-1-ylphenyl]-

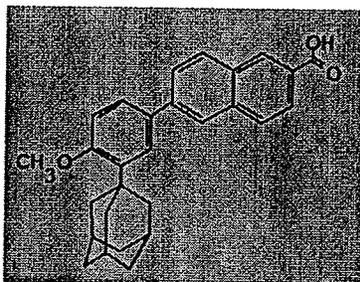
Molecular Formula: $C_{28}H_{28}O_3$

Molecular Weight: 412.53

CAS No.: 106685-40-9

Chemical structure:

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
C]	II	[]	[]	1	adequate	29-JAN-2007	by J. Chang
C]	III	[]	[]	3	adequate	25-OCT-2002	By J. S. Hathaway

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	33,540	Adapalene Gel, 0.1% (w/w)
IND	C]	Adapalene Gel, 0.3% (w/w)
NDA	20-380	DIFFERIN (adapalene) Gel, 0.1% (w/w)
NDA	20-748	DIFFERIN (adapalene) Cream, 0.1%
NDA	20-338	DIFFERIN (adapalene) Solution, 0.1%

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending*		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A**		
Office of Drug Safety	Acceptable w/o "XP"	28-Oct-2004	C. Holquist
EA	Categorical exclusion (see review #1)	28-Jan-2005	J. S. Hathaway
Microbiology	N/A		

*At the completion of this review, inspection for the is still pending. The other manufacturing facility, DTP Laboratories Inc., is acceptable.

**In Review #1 by Dr. J. S. Hathaway, it was stated that the drug product shares the analytical methods used in NDA 20-380. No further evaluation is necessary as these methods have been shown to be adequate.

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The Chemistry Review for NDA 21-753

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing, and controls review perspective, this NDA may be approved pending an acceptable recommendation from the Office of Compliance for the establishment inspections. At the completion of this review, the inspection at Sylachim Finorga Division facility is still pending.

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

DIFFERIN® Gel, 0.3%, is indicated for the topical treatment of acne vulgaris. It is an aqueous gel formulation containing a suspension of the adapalene drug substance, and is a new strength of the existing approved dosage form. The formulation is

in the formulation. It is packaged in 145 gram tubes. Only 45 g package sizes are intended to be manufactured for initial launch of the drug product.

(2) Drug Substance

The drug substance, adapalene, is also the drug substance for the approved drug products, Differin Gel, 0.1% (NDA 20-380) and Differin Cream, 0.1% (NDA 20-748). CMC information for adapalene has been referred to DMF This DMF has been reviewed by this reviewer and found to be adequate to support this NDA.

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

The drug product is indicated for the topical treatment of acne. Its directions for use call for once-daily application of a thin film of the gel to all areas. This higher strength is intended to provide more dosing options to physicians. Treatment duration is

Executive Summary Section

up to twelve weeks. The proposed expiration dating period is tentatively] when stored at controlled room temperature, 20 - 25°C (68°-77°F) with excursions permitted between 15° - 30°C (59° - 86°F). The product should also be protected from freezing, as this has been demonstrated to adversely affect the drug product.

C. Basis for Approvability or Not-Approval Recommendation

There was no CMC deficiencies in the previous review (see Review #1 by Dr. J. S. Hathaway). In this review, labeling was reviewed and all labeling issues have been resolved. The inspection of [] which is the [] [] is still pending. Therefore, from a CMC standpoint, this new drug application may be approved pending an acceptable recommendation from the Office of Compliance for the establishment inspection.

III. Administrative

- A. Reviewer's Signature electronically signed in DFS
- B. Endorsement Block electronically signed in DFS
- C. CC Block entered electronically in DFS

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Chemistry Review #2

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/s/

Jane Chang
5/10/2007 03:48:23 PM
CHEMIST

Moo-Jhong Rhee
5/11/2007 11:57:00 AM
CHEMIST
Chief, Branch III

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Chemistry Review #4

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 14, 2007
TO: NDA 21-753
FROM: Jane Chang
Review Chemist, ONDQA
SUBJECT: Update of EES Status
NDA 21-753, Differin (adapalene) Gel

Recommendation and Conclusion on Approvability:

From a chemistry, manufacturing, and controls review perspective, this NDA may be approved.

All manufacturing and testing facilities were found to be acceptable by the Office of Compliance as recommended by C. Cruz on June 14, 2007. The EER Summary Report is attached.

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ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21753/000 Sponsor: GALDERMA LABS
 Org Code : 540 14501 NORTH FREEWAY
 Priority : 3S FORT WORTH, TX 76177

Stamp Date : 01-APR-2004 Brand Name : DIFFERIN XE (ADAPALENE GEL
 FDOPA Date : 19-JUN-2007 0.3% GEL

Action Goal : Estab. Name:
 District Goal: 03-DEC-2004 Generic Name: ADAPALENE GEL 0.3% GEL
 Dosage Form: (GEL)
 Strength : 0.3%

FDA Contacts: M. WRIGHT Project Manager 301-796-1027
 J. HATHAWAY Review Chemist 301-796-1677
 N. SCHMUFF Team Leader 301-796-1454

Overall Recommendation: ACCEPTABLE on 14-JUN-2007 by C. CRUZ (HFD-323) 301-827-9013
 ACCEPTABLE on 17-MAY-2004 by J. D. AMBROGIO (HFD-322) 301-827-
 9073

Establishment : CFN : 1628114 FEI : 1000117684
 DPT LABORATORIES INC
 200/307 E JOSEPHINE STREET
 SAN ANTONIO, TX 78215

DMF No: NADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : OIN OAI Status: NONE

Last Milestone: QC RECOMMENDATION

Milestone Date: 29-JAN-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [] FEI : []
 [] []
 38670

DMF No: []

AADA:

Responsibilities: []

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-JUN-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

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/s/

Jane Chang
6/14/2007 05:37:17 PM
CHEMIST

Moo-Jhong Rhee
6/14/2007 05:40:40 PM
CHEMIST
Chief, Branch III