

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-535

CORRESPONDENCE



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 25 July 2003

To: Paul Clark	From: Melinda Harris, M.S. Project Manager
Company: Galderma Laboratories	Division of Dermatologic & Dental Drug Products
Fax number: (817) 961-0020	Fax number: (301) 827-2091 or 2075
Phone number: (817) 961-5336	Phone number: (301) 827-2020
Subject: NDA 21-535 Clobex	

Total no. of pages including cover: 5

Comments: Minutes from the second tcon on July 18, 2003 are provided

Document to be mailed: YES NO

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MEMORANDUM OF TELECON

DATE: 7/18/03, 2:30 P.M.

APPLICATION NUMBER: NDA 21-535

DRUG PRODUCT: Clobex (clobetasol propionate) Lotion, 0.05%

BETWEEN:

Name: Paul Clark, Vice President, Regulatory Affairs
Phone: (817) 961-5336
Representing: Galderma Laboratories, L.P.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
Jonathan Wilkin, M.D., Division Director
Markham Luke, M.D., Ph.D., Clinical Team Leader, Dermatology
Melinda Harris, M.S., Regulatory Project Manager

SUBJECT: NDA 21-535

The teleconference was requested by the Agency as a continuation of the teleconference earlier in the day regarding the definition of efficacy endpoint parameters and HPA axis suppression parameters.

1. The Agency stated that the definition was described in the End-of-Phase 2 and pre-NDA meeting minutes. At the End-of-Phase 2 meeting (on page 8-9 of the minutes), it was agreed that the efficacy would be driven by using a static Global Severity Scale that would be described using an ordinal scale. A win is defined as clear or almost clear. The Sponsor chose to do a .5 scale. The Sponsor submitted protocols which were reviewed by the Agency and it was further stressed that a .5 scale was not recommended. Modifications to the Global Severity Scale were recommended.

Regarding HPA axis suppression parameters, in the pre-NDA minutes (#8 under Information needed for HPA axis suppression), it was stated that the Sponsor needed to use all 3 cortrosyn criteria and that if the patients fail on 1 criteria they are considered suppressed.

The Sponsor asked that if they do the studies requested in the Phase 4 commitments and the data shows different levels of HPA axis suppression, could the label be augmented or changed to reflect the new data sets.

The Agency responded that yes the label could be augmented or changed.

2. The Agency asked if the Sponsor still requests a meeting that would include the Ombudsman.

The Sponsor stated that they do not need a meeting that would include the Ombudsman.

The Sponsor agreed to have the revised label back on Monday morning. The conversation ended amicably.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Jonathan Wilkin
7/24/03 02:50:14 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 24 July 2003

To: Paul Clark	From: Melinda Harris, M.S. Project Manager
Company: Galderma Laboratories	Division of Dermatologic & Dental Drug Products
Fax number: (817) 961-0020	Fax number: (301) 827-2091 or 2075
Phone number: (817) 961-5336	Phone number: (301) 827-2020
Subject: NDA 21-535 Clobex	

Total no. of pages including cover: 5

Comments: Minutes from the first tcon on July 18, 2003 are provided

Document to be mailed: YES NO

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MEMORANDUM OF TELECON

DATE: 7/18/03, 1:00 P.M.

APPLICATION NUMBER: NDA 21-535

DRUG PRODUCT: Clobex (clobetasol propionate) Lotion, 0.05%

BETWEEN:

Name: Paul Clark, Vice President, Regulatory Affairs
Christian Loesche, Director, Global Clinical Development
Michael Graeber, M.D., Head, U.S. Clinical Development
Yin Liu, Head, U.S. Biometrics
Phone: (817) 961-5336
Representing: Galderma Laboratories, L.P.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
Markham Luke, M.D., Ph.D., Clinical Team Leader, Dermatology
Melinda Harris, M.S., Regulatory Project Manager

SUBJECT: NDA 21-535

The teleconference was requested by the Sponsor to discuss an issue in the Draft label sent to them by the Agency on July 16, 2003. The Sponsor wanted to know what definition of suppression was used to come up with some of the numbers the Agency used in the label, specifically in the Precautions Section.

1. The Agency responded that they applied the Cortrosyn labeling criteria to the three studies the Sponsor performed. If any one of the three criteria is not met, then the patient is considered suppressed. The adult study had weekly HPA axis suppression testing relying on Cortrosyn stimulation which may allow for underestimating the actual numbers of patients suppressed. It was noted by the Agency that patients were stimulated at 60 minutes instead of the recommended 30 minutes.
2. *The Sponsor asked how the Agency came up with 10 evaluable patients in Study 9708.*

The Agency responded that while 12 patients completed the study only 10 were evaluable. Two patients in each arm had evidence of HPA axis suppression before they began and were not considered evaluable. The Sponsor agreed that this was plausible.

- 3. The Sponsor requested a tcon be arranged between the Sponsor and Dr. Luke and Dr. Wilkin and possibly an ombudsman for the beginning of the week regarding efficacy issues.*

The Agency responded that they would look at the schedule and get back to the Sponsor.

The conversation ended amicably.

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/s/

Markham Luke
7/24/03 11:56:51 AM

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/s/

Melinda Harris
7/24/03 01:58:42 PM
CSO

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/s/

Melinda Harris
7/25/03 02:45:10 PM
CSO

GALDERMA

USA



July 24, 2003

Food and Drug Administration
Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
ATTENTION: Jonathan Wilkin, M.D.
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 21-535
CLOBEX™ (clobetasol propionate lotion) Lotion, 0.05%
Applicant Agreement to Labeling

Dear Dr. Wilkin:

The applicant agrees to the contents of the attached labeling as negotiated with the Division. In addition, the applicant acknowledges a minor revision to the Phase 4 commitments as indicated and agrees to these commitments.

Sincere regards,

Paul M. Clark
Vice President, Regulatory Affairs
Telephone: 817-961-5336
Fax: 817-961-0020

22 Draft Labeling Page(s) Withheld



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 22 July 2003

To: Paul Clark	From: Melinda Harris, M.S. Project Manager
Company: Galderma Laboratories	Division of Dermatologic & Dental Drug Products
Fax number: (817) 961-0020	Fax number: (301) 827-2091 or 2075
Phone number: (817) 961-5336	Phone number: (301) 827-2020
Subject: NDA 21-535	

Total no. of pages including cover: 4

Comments: CMC tcon minutes from 7/16/03

Document to be mailed: YES NO

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MEMORANDUM OF TELECON

DATE: 7/16/03, 3:00 P.M.

APPLICATION NUMBER: NDA 21-535

DRUG PRODUCT: Clobex (clobetasol propionate) Lotion, 0.05%

BETWEEN:

Name: Paul Clark, Vice President, Regulatory Affairs
Allen Brinkley, Director of Technical Affairs
Phone: (817) 961-5336
Representing: Galderma Laboratories, L.P.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
Wilson DeCamp, Ph.D./Chemistry Team Leader
Saleh Turujman, Ph.D., Chemistry Reviewer
Melinda Harris, M.S., Regulatory Project Manager

SUBJECT: NDA 21-535

The teleconference was requested by the Sponsor to discuss their submission of June 10, 2003, which stated that they need to change the manufacturer of their 1 oz. container. The Sponsor wanted to know what the status of that submission was and if it would need to be sent in as a supplement to the NDA after the action has been taken.

1. The Agency asked if the new manufacturer, _____, uses the same _____ as the previous manufacturer, _____.

The Sponsor responded that they both use _____.

2. The Agency stated that the initial advice of submitting a supplement given in the teleconference dated June 27, 2003 was incorrect. If the action taken on July 25, 2003 is an Approval action, the Sponsor can convey this information to the Agency in the Annual Report. If the action is Approvable, the Sponsor can submit this information to the Agency when they amend the application.

The conversation ended amicably.

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/s/

Wilson H. DeCamp
7/21/03 02:51:14 PM
concur with minutes

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/s/

Melinda Harris

7/22/03 03:16:42 PM

CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 22 July 2003

To: Paul Clark	From: Melinda Harris, M.S. Project Manager
Company: Galderma Laboratories	Division of Dermatologic & Dental Drug Products
Fax number: (817) 961-0020	Fax number: (301) 827-2091 or 2075
Phone number: (817) 961-5336	Phone number: (301) 827-2020

Subject: NDA 21-535 Phase 4 commitments

Total no. of pages including cover: 3

Comments: Following are the revised Phase 4 commitments for your agreement

Document to be mailed: YES NO

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2020. Thank you.**

NDA 21-535 Phase 4 Commitments

Pharm/Tox Post-marketing Commitments

1. The Applicant commits to performing dermal carcinogenicity testing of the drug product.

Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission: Within 4 months of the date of this letter

Within 6 months of the date of the approval of the protocol

Final Report Submission: Within 12 months after the study completion

2. The Applicant commits to a study to evaluate the effects of the drug product on UV-induced skin cancers.

Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission: Within 4 months of the date of this letter

Study Start: Within 6 months of the date of the approval of the protocol

Final Report Submission: Within 12 months after the study completion

Draft Proposed Clinical Post-Marketing Commitment

1. The Sponsor commits to performing an HPA axis suppression study in no less than 60 evaluable patients using cosyntropin stimulation testing (conducted as labeled with stimulated serum cortisol levels at 30 minutes with any suppressed patients followed to recovery, stimulation should only be conducted at baseline and at the end of the two or four week treatment period) in adult patients with psoriasis or atopic dermatitis. Clobex Lotion should be applied to lesional skin at the maximum amounts permitted in labeling.

The minimum number of subjects (seperate cohorts for each) committed to are as follows:

- a) no less than 30 evaluable adult patients with psoriasis or atopic dermatitis of no less than 20% BSA after 2 weeks of treatment
- b) no less than 30 evaluable adult patients with psoriasis of no less than 10% BSA after 4 weeks of treatment

Commitment Category: CLINICAL SAFETY ASSESSMENT

Protocol Submission: Within 4 months of the date of this letter

Study Start: Within 6 months of the date of the approval of the protocol

Final Report Submission: Within 16 months after approval of the protocol

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/s/

Melinda Harris
7/22/03 09:46:29 AM
CSO

GALDERMA

U S A



July 22, 2003

Food and Drug Administration
Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
ATTENTION: Jonathan Wilkin, M.D.
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 21-535
CLOBEX™ (clobetasol propionate lotion) Lotion, 0.05%
Applicant Agreement to Phase 4 Commitments

Dear Dr. Wilkin:

The applicant agrees to perform the Phase 4 studies as described in the attached fax dated July 22, 2003. The applicant further agrees to comply with the timelines unless other provisions are agreed to by the Agency.

Sincere regards,

Paul M. Clark
Vice President, Regulatory Affairs
Telephone: 817-961-5336
Fax: 817-961-0020

NDA 21-535 Phase 4 Commitments

Pharm/Tox Post-marketing Commitments

1. The Applicant commits to performing dermal carcinogenicity testing of the drug product.

Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission: Within 4 months of the date of this letter

Within 6 months of the date of the approval of the protocol

Final Report Submission: Within 12 months after the study completion

2. The Applicant commits to a study to evaluate the effects of the drug product on UV-induced skin cancers.

Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission: Within 4 months of the date of this letter

Study Start: Within 6 months of the date of the approval of the protocol

Final Report Submission: Within 12 months after the study completion

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The minimum number of subjects (separate cohorts for each) committed to are as follows:

- a) no less than 30 evaluable adult patients with psoriasis or atopic dermatitis of no less than 20% BSA after 2 weeks of treatment
- b) no less than 30 evaluable adult patients with psoriasis of no less than 10% BSA after 4 weeks of treatment

Commitment Category: CLINICAL SAFETY ASSESSMENT

Protocol Submission: Within 4 months of the date of this letter

Study Start: Within 6 months of the date of the approval of the protocol

Final Report Submission: Within 16 months after approval of the protocol



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 18 July 2003

To: Paul Clark	From: Melinda Harris, M.S. Project Manager
Company: Galderma Laboratories	Division of Dermatologic & Dental Drug Products
Fax number: (817) 961-0020	Fax number: (301) 827-2091 or 2075
Phone number: (817) 961-5336	Phone number: (301) 827-2020
Subject: NDA 21-535 Phase 4 commitments	

Total no. of pages including cover: 3

Comments: Following are the Phase 4 commitments for your agreement

Document to be mailed: YES NO

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2020. Thank you.**

NDA 21-535 Phase 4 Commitments

Pharm/Tox Post-marketing Commitments

1. The Applicant commits to performing dermal carcinogenicity testing of the drug product.

Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission: Within 4 months of the date of this letter

Within 6 months of the date of the approval of the protocol

Final Report Submission: Within 12 months after the study completion

2. The Applicant commits to a study to evaluate the effects of the drug product on UV-induced skin cancers.

Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission: Within 4 months of the date of this letter

Study Start: Within 6 months of the date of the approval of the protocol

Final Report Submission: Within 12 months after the study completion

Draft Proposed Clinical Post-Marketing Commitment

1. The Sponsor commits to performing an HPA axis suppression study in no less than evaluable patients using cosyntropin stimulation testing (conducted as labeled with stimulated serum cortisol levels at 30 minutes with any suppressed patients followed to recovery, stimulation should only be conducted at baseline and at the end of the two week treatment period) in adult patients with psoriasis or atopic dermatitis. Clobex Lotion should be given at the maximum amounts permitted in labeling.

The minimum number of subjects (seperate cohorts for each) committed to are as follows:

- a) no less than evaluable adult patients with psoriasis or atopic dermatitis after 2 weeks of treatment
- b) no less than evaluable adult patients with psoriasis after 4 weeks of treatment

Commitment Category: CLINICAL SAFETY ASSESSMENT

Protocol Submission: Within 4 months of the date of this letter

Study Start: Within 6 months of the date of the approval of the protocol

Final Report Submission: Within 16 months after approval of the protocol

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/s/

Melinda Harris
7/18/03 02:20:39 PM
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 16 July 2003

To: Paul Clark	From: Melinda Harris, M.S. Project Manager
Company: Galderma Laboratories	Division of Dermatologic & Dental Drug Products
Fax number: (817) 961-0020	Fax number: (301) 827-2091 or 2075
Phone number: (817) 961-5336	Phone number: (301) 827-2020
Subject: NDA 21-535 Clobex	
Total no. of pages including cover: 25	
Comments: DRAFT labeling is provided. Please respond by the Monday July 21, 2003.	

Document to be mailed: YES NO

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/s/

Melinda Harris
7/16/03 04:04:08 PM
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JUL 09 2003

MEGA/CDER

July 7, 2003

Food and Drug Administration
 Division of Dermatological and Dental Drug Products (HFD-540)
 Center for Drug Evaluation and Research
 ATTENTION: Document Control Room
 9201 Corporate Blvd.
 Rockville, Maryland 20850

NC
 NEW CORRESP

RE: NDA 21-535
 CLOBEX™ (clobetasol propionate lotion) Lotion, 0.05%
 Grant of Permission to Refer to Confidential Information Supplied to FDA
 Original Submission Date: September 25, 2002

Dear Sir or Madam:

Please accept this letter as authorization for the Division of Dermatological and Dental Drug products to examine information listed below contained in NDA 21-535 on behalf of _____ in its discussion and submission to the Agency regarding IND . _____

STUDY TITLE	STUDY NUMBER	VOLUME	PAGES
Clobetasol Propionate Lotion Formulation – Preliminary Study of Embryo-Fetal Toxicity in the CD Rat by Dermal Administration	1.CG.03.SRE.12055	1.08	962-1145
Clobetasol Propionate Lotion Formulation – Study of Embryo-Fetal Toxicity in the CD Rat by Dermal Administration	1.CG.03.SRE.12081	1.08 1.09	1147 – 1354
Thirteen-week Topical Range Finding Study of Clobetasol 0.05% Lotion in Hairless Mice, with or without simulated sunlight	RDS.03.SRE.12258	1.7 1.8	416 – 925

Page 2
July 8, 2003
NDA 21-535 Clobetasol Propionate Lotion

Other information contained in this new drug application may not be disclosed unless previously authorized by Galderma Laboratories, L.P. If you have any questions, please feel free to contact me at 817 961 5336.

Sincere regards,



Paul M. Clark
Vice President, Regulatory Affairs
Telephone: 817-961-5336
Fax: 817-961-0020

c:



Food and Drug Administration
 Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 2 July 2003

To: Paul Clark	From: Melinda Harris, M.S. Project Manager
Company: Galderma Laboratories	Division of Dermatologic & Dental Drug Products
Fax number: (817) 961-0020	Fax number: (301) 827-2091 or 2075
Phone number: (817) 961-5336	Phone number: (301) 827-2020

Subject: NDA 21-535 Submission 000

Total no. of pages including cover: 5

Comments: Minutes from the 6/27/03 tcon are provided

Document to be mailed: YES NO

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MEMORANDUM OF TELECON

DATE: 6/27/03, 2:00 P.M.

APPLICATION NUMBER: NDA 21-535

DRUG PRODUCT: Clobex (clobetasol propionate lotion) 0.05%

BETWEEN:

Name: Paul Clark, Vice President, Regulatory Affairs
Phone: (817) 961-5336
Representing: Galderma Laboratories, L.P.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
Wilson DeCamp, Ph.D./Chemistry Team Leader
Saleh Turujman, Ph.D., Chemistry Reviewer
Melinda Harris, M.S., Regulatory Project Manager

SUBJECT: NDA 21-535

The teleconference was requested by FDA to convey specific information to the Sponsor concerning the submitted NDA.

1. The Agency stated that DMF _____, held by the Sponsor's alternate _____ supplier, _____, has been found to be inadequate. The DMF holder has not responded to the deficiency letter issued by the Agency in February 2003. An NDA cannot be approved if a Type II DMF is inadequate (deficient). The Agency recommended that the Sponsor withdraw _____ as the alternate _____ supplier. A postapproval supplement may be submitted proposing an alternate _____ supplier. The Agency recommended that the Sponsor delay the supplement requesting _____ to be the alternate supplier until they have been notified by _____ that they have responded to the deficiency letter.

The Sponsor stated that they will send a letter stating that they are withdrawing _____ today.

2. *The Sponsor asked if the Agency was able to consider the submission regarding the 1 oz bottle.*

The Agency responded that the submission came in too late in the review process for it to be included in the review. The amendment was dated June 10, 2003, and received on

June 11, 2003. The PDUFA goal date for this NDA is July 27, 2003. The Sponsor was advised to submit the amendment as a supplement.

The conversation ended amicably.

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/s/

Wilson H. DeCamp
6/30/03 05:31:29 PM
concur

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/s/

Melinda Harris
7/2/03 08:53:33 AM
CSO



July 1, 2003

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Food and Drug Administration
Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
ATTENTION: Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

NEW CORRESP

RE: NDA 21-535
Clobetasol Propionate Topical Lotion 0.05%
Withdrawal of _____ Supplier

RECEIVED

JUL 03 2003

MEGA/CDER

Dear Sir or Madam:

In response to FDA's communication that one of the _____ suppliers, _____, has not responded to a DMF deficiency letter issued by the agency, the applicant hereby requests that the reference to DMF _____ pertaining to _____ be withdrawn from consideration for the approval of the application.

The applicant has been in contact with the management of _____ and they have indicated that they are preparing a response to the DMF deficiency letter. Unfortunately, the response will not be available before the PDUFA review date.

If I can be of assistance with any questions or concerns, please contact me.

Sincere regards,

Paul M. Clark
Vice President, Regulatory Affairs
Telephone: 817-961-5336
Fax: 817-961-0020

DUPLICATE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

Dermata Laboratories, L.P.

DATE OF SUBMISSION

June 10, 2003

TELEPHONE NO. (Include Area Code)

1-961-5000

FACSIMILE (FAX) Number (Include Area Code)

817-961-0020

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code,
U.S. License number if previously issued):

101 North Freeway
Worth, TX 76177

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State,
ZIP Code, telephone & FAX number) IF APPLICABLE

RECEIVED

JUN 11 2003

PRODUCT DESCRIPTION

DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

535

MEGA/CDER

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

betasol Propionate Lotion

PROPRIETARY NAME (trade name) IF ANY

Clobex Lotion

GENERIC/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)

betasol Propionate

CODE NAME (If any)

CP Lotion

DOSE FORM:

Lotion

STRENGTHS:

0.05%

ROUTE OF ADMINISTRATION:

Topical

INDICATED INDICATION(S) FOR USE:

the treatment of steroid responsive dermatosis.

APPLICATION INFORMATION

APPLICATION TYPE

(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF ANDA, IDENTIFY THE APPROPRIATE TYPE

505 (b)(1)

505 (b)(2)

IF ANDA, OR 505 (B)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug: Holder of Approved Application

TYPE OF SUBMISSION
(check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

IF PREVIOUS SUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION
SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

IF SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION

IF SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

CBE

CBE-30

PRIOR APPROVAL (PA)

REASON FOR SUBMISSION

Submission of new bottle specification

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

List the locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

BEST POSSIBLE COPY

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)



May 9, 2003

Food and Drug Administration
Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
ATTENTION: Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 21-535
CLOBEX™ (clobetasol propionate lotion) Lotion, 0.05%
Response to CMC Request for Information

Dear Sir or Madam:

Reference is made to the New Drug Application for Clobetasol Propionate Lotion 0.05%. This submission amends the application with information requested by FDA CMC reviewers in a facsimile date 24 February, 2003.

If I can be of assistance with any questions or concerns, please contact me.

Sincere regards,

A handwritten signature in black ink that reads "Paul Clark".

Paul M. Clark
Vice President, Regulatory Affairs
Telephone: 817-961-5336
Fax: 817-961-0020

c: Archival
CMC
Desk Copy
Fax of Cover Letter to Melinda Harris, FDA Project Manager



April 24, 2003

Food and Drug Administration
Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
ATTENTION: Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 21-535
CLOBEX™ (clobetasol propionate lotion) Lotion, 0.05%
4-Month Safety Update

Dear Sir or Madam:

Reference is made to the New Drug Application for Clobetasol Propionate Lotion 0.05%. This submission amends the application with the 4-month safety update required by 21 CFR 314.50 (d)(5)(vi)(b).

Sincere regards,

Paul M. Clark
Vice President, Regulatory Affairs
Telephone: 817-961-5336
Fax: 817-961-0020

c: Archival
CMC
Desk Copy
Fax of Cover Letter to Melinda Harris, FDA Project Manager



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 27 March 2003

To: Paul Clark	From: Melinda Harris Project Manager
Company: Galderma Laboratories	Division of Dermatologic & Dental Drug Products
Fax number: (817) 961-0020	Fax number: (301) 827-2091 or 2075
Phone number: (817) 961-5336	Phone number: (301) 827-2020
Subject: NDA 21-535 Submission date 25 September 2002 Clinical Request for Information	

Total no. of pages including cover: 2

Comments:

Please send the final study report and protocols for the HPA axis suppression studies and the European study on an electronic disk as a desk copy to my attention Room N241.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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/s/

Melinda Harris
3/27/03 09:43:01 AM
CSO

NDA 21-535 Clobetasol Propionate Lotion 0.05%

Clarification of 15 January Telecon Minutes

February 27, 2003

Page 2

During the teleconference, the applicant did not intend to convey to the Division that the studies conducted and submitted in support of NDA 21-535 did not meet FDA's requirements for substantial evidence that the drug product was safe for its intended use both in adults and adolescents. The sponsor stresses the point that the pediatric HPA-axis function study was initiated with the objective to increase the number of adolescent subjects, providing HPA-axis function data, in the submission and not because the two adult HPA-axis function studies were not meeting the objective to provide adequate safety data for the adult population.

In our submission of 5 February 2003, the applicant has provided justification for both the interim cosyntropin stimulation and 60-minute collection interval. The applicant maintains that the two adult and one pediatric HPA-axis function studies in the submission are valid and support the safety of the drug.

The applicant respectfully requests that this clarification be amended to the official minutes of the teleconference held on 15 January 2003.

Sincere regards,



Paul M. Clark

Vice President, Regulatory Affairs

Telephone: 817-961-5336

Fax: 817-961-0020

c: Melinda Harris, FDA Project Manager



RECEIVED

FEB 20 2003

MEGA/CDER

NANDA
DC
3/3/03
N-005(ES)

ORIG AMENDMENT

February 19 2003

Food and Drug Administration
Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
ATTENTION: Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 21-535
CLOBEX™ (clobetasol propionate lotion) Lotion, 0.05%
Response to Information Request (Facsimile 6 February 2003)

Dear Sir or Madam:

Reference is made to the New Drug Application for Clobetasol Propionate Lotion 0.05%. This submission amends the application with information requested by FDA Statistical reviewers concerning the sequence of enrollment for several patients in two studies, 18001, 2651.

If I can be of assistance with any questions or concerns, please contact me.

Sincere regards,

Paul M. Clark
Vice President, Regulatory Affairs
Telephone: 817-961-5336
Fax: 817-961-0020

c: Archival
Statistical
Desk Copy
Fax of Cover Letter to Melinda Harris, FDA Project Manager

ORIGINAL



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 24 February 2003

To: Paul Clark	From: Melinda Harris Project Manager
Company: Galderma Laboratories	Division of Dermatologic & Dental Drug Products
Fax number: (817) 961-0020	Fax number: (301) 827-2091 or 2075
Phone number: (817) 961-5336	Phone number: (301) 827-2020
Subject: NDA 21-535	

Total no. of pages including cover: 3

Comments: CMC request for information

Document to be mailed: YES NO

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2020. Thank you.

A. Drug Substance

- You state that the size of the particles of the drug substance do not have an impact on the bioavailability of the drug product, because the drug substance is _____ (Vol 1.3 item 4 page 578). However, particle size has an impact on solubility. Are you asserting that particle size has no effect on the rate of dissolution of the drug substance? If the answer is in the affirmative, you are requested to provide data to support that assertion. Otherwise an acceptance criterion for particle size [range] should be qualified for the drug substance.
- Why is there a tentative range for the melting point of the drug substance (_____ which is broader than that of USP (196°). The melting point is generally regarded as an indicator of purity. The fact that initially, during development, the melting point range of the drug substance was _____ (Vol. 1.1.1 Item 3 page 45) simply indicates that the drug substance was not as pure as (contained more impurities than) the compendial reference.
- The _____ is a potential _____ impurity which is generally removed during subsequent purification. The specifications you provided for the drug substance in the NDA (Vol. 1.3 Item 4 page 578), which generally reflect the USP monograph for clobetasol propionate, do not directly address the potential presence of this _____ impurity. Please comment on how you ascertain the absence of this potential _____ impurity (_____).

B. Drug Product

- Please provide the function of each of the components (excipients) of your drug product.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Melinda Harris
2/24/03 11:14:23 AM
CSO

Feb 19th
356 H

February 18, 2003

Food and Drug Administration
Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
ATTENTION: Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 21-535
CLOBEX™ (clobetasol propionate lotion) Lotion, 0.05%
Response to Information Request (FAX 6 Jan 2003)

Dear Sir or Madam:

Reference is made to the New Drug Application for Clobetasol Propionate Lotion 0.05%. This submission amends the application with information requested by FDA in the fax dated 6 February, 2003.

As requested, the applicant has provided the original French language labeling for Dermoval, clobetasol propionate, Cream 0.05% and its English translation.

Sincere regards,



Paul M. Clark
Vice President, Regulatory Affairs
Telephone: 817-961-5336
Fax: 817-961-0020

c: Archival
CMC
Desk Copy
Fax of Cover Letter to Melinda Harris, FDA Project Manager

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Galderma Laboratories, L.P.	DATE OF SUBMISSION February 19, 2003
TELEPHONE NO. (Include Area Code) 817-961-5000	FACSIMILE (FAX) Number (Include Area Code) 817-961-0020
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 14501 North Freeway Fort Worth, TX 76177	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

RECEIVED

FEB 20 2003

MEGA/CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-535		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Clobetasol Propionate Lotion	PROPRIETARY NAME (trade name) IF ANY Clobex Lotion	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Clobetasol Propionate	CODE NAME (If any) CP Lotion	
DOSAGE FORM: Lotion	STRENGTHS: 0.05%	ROUTE OF ADMINISTRATION: Topical

PROPOSED INDICATION(S) FOR USE:

for the treatment of steroid responsive dermatosis.

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505 (B)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRE-SUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> PRIOR APPROVAL (PA)
REASON FOR SUBMISSION Response to request for information - English translation of French Dermoval labeling
PROPOSED MARKETING STATUS (check one) <input type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

DUPLICATE



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 6 February 2003

To: Paul Clark	From: Melinda Harris Project Manager
Company: Galderma Laboratories	Division of Dermatologic & Dental Drug Products
Fax number: (817) 961-0020	Fax number: (301) 827-2091 or 2075
Phone number: (817) 961-5336	Phone number: (301) 827-2020
Subject: NDA 21-535 Information requests	

Total no. of pages including cover: 3

Comments: Statistical information Request is following

Document to be mailed: YES NO

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other action based on the content of this communication is not authorized. If you have
received this document in error, please notify us immediately by telephone at (301) 827-
2020. Thank you.

ORIGINAL

GALDERMA

USA



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FEB 13 2003
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*Reviewed
attc 6/9/03
attach to NDA*

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FEB 12 2003
CDR/CDER

February 6, 2003

Food and Drug Administration
Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
ATTENTION: Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 21-535
CLOBEX™ (clobetasol propionate lotion) Lotion, 0.05%
Response to Information Request (Telecon 15 Jan 2003)

Bm
ORIG AMENDMENT

Dear Sir or Madam:

Reference is made to the New Drug Application for Clobetasol Propionate Lotion 0.05%. This submission amends the application with information requested by FDA medical reviewer during the teleconference of 15 January 2003.

As requested, the applicant has provided subject data line listings for the individual HPA axis response for study 18061. These line listings may also be found in Item 8, pages 3058 through 3067.

Sincere regards,

Paul M. Clark
Vice President, Regulatory Affairs
Telephone: 817-961-5336
Fax: 817-961-0020

c: Archival
Clinical
Desk Copy
Fax of Cover Letter to Melinda Harris, FDA Project Manager

The information below is requested following reviewing the Sponsor's responses (1/27/03) to the Agency's request dated 12/24/02:

1. For study 18001, study sites 1170 and 2067 had patients assigned with randomization numbers not sequentially over time. Please clarify why this occurred.
2. According to the Sponsor's response for study 2651, randomization numbers 001-280 and 281-308 were generated on 4/20/00 and 11/7/00, respectively. However, the total enrollment according to the NDA submission was 222 patients.
 - a. Please clarify why the 2nd set randomization numbers (i.e. 281-308) were generated.
 - b. Also, please provide details on why numbers 29-35 and 211-252 were skipped.

In addition, please provide your safety update, which was due on January 27, 2003 as per 21 CFR 314.50 (d)(5)(vi).

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Melinda Harris
2/6/03 03:04:43 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 6 February 2003

To: Paul Clark	From: Melinda Harris Project Manager
Company: Galderma Laboratories	Division of Dermatologic & Dental Drug Products
Fax number: (817) 961-0020	Fax number: (301) 827-2091 or 2075
Phone number: (817) 961-5336	Phone number: (301) 827-2020
Subject: NDA 21-535 CMC Information Request	

Total no. of pages including cover: 2

Comments: Please provide the following CMC information as soon as possible

***Please submit copies of the container label and package insert for Dermoval, including translations into English

Document to be mailed: YES NO

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/s/

Melinda Harris
2/6/03 10:31:36 AM
CSO

60-minute interval for testing for this reason. While it is true that the 60-minute values are usually higher than the 30-minute values, the difference may not be significant enough in most cases to outweigh the disadvantage of a longer testing period." It is clear that both the 30- and 60-minute intervals are suggested methods for rapid screening of adrenal suppression. The applicant's response provides a justification for the 60-minute collection interval and the criteria used to define normal HPA-axis function.

The applicant feels that adequate evidence has been presented that the HPA axis suppression studies are valid and support the safety of the drug. Since this issue has been identified as critical to the approval of this application, the applicant requests that the Division review this supplement as soon as possible and provide us with their findings. The applicant welcomes a direct dialog with the medical reviewer to address this or any other open clinical question the agency might have during review of this NDA.

If I can be of assistance with any questions or concerns, please contact me.

Sincere regards,



Paul M. Clark
Vice President, Regulatory Affairs
Telephone: 817-961-5336
Fax: 817-961-0020

c: Archival
 Clinical
 Desk Copy
 Fax of Cover Letter to Melinda Harris, FDA Project Manager

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Galderma Laboratories, L.P.	DATE OF SUBMISSION February 10, 2003
TELEPHONE NO. (Include Area Code) 817-961-5000	FACSIMILE (FAX) Number (Include Area Code) 817-961-0020
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 14501 North Freeway Fort Worth, TX 76177	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-535		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Clobetasol Propionate Lotion	PROPRIETARY NAME (trade name) IF ANY Clobex Lotion	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Clobetasol Propionate	CODE NAME (If any) CP Lotion	
DOSAGE FORM: Lotion	STRENGTHS: 0.05%	ROUTE OF ADMINISTRATION: Topical
(PROPOSED) INDICATION(S) FOR USE: For the treatment of steroid responsive dermatosis.		

APPLICATION INFORMATION

APPLICATION TYPE (check one): <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505 (B)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one): <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> PRIOR APPROVAL (PA)
REASON FOR SUBMISSION Response to Clinical Questions
PROPOSED MARKETING STATUS (check one) <input type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

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FEB 12 2003

FEB 13 2003

MEGA/CDER

PAGE 1



January 27, 2003

Food and Drug Administration
Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
ATTENTION: Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 21-535
CLOBEX™ (clobetasol propionate lotion) Lotion, 0.05%
Response to Information Request (27 November 2002) ✓

Dear Sir or Madam:

Reference is made to the New Drug Application for Clobetasol Propionate Lotion 0.05%. This submission amends the application with information requested by FDA reviewers.

As requested, the PPI has been reformatted according to the Medication Guide Format. The applicant has also provided the requested adverse event tables for clinical studies 9707, 18001, and 2651.

If I can be of assistance with any questions or concerns, please contact me.

Sincere regards,

Paul M. Clark
Vice President, Regulatory Affairs
Telephone: 817-961-5336
Fax: 817-961-0020

c: Archival
Clinical
Desk Copy
Fax of Cover Letter to Melinda Harris, FDA Project Manager



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 29 January 2003

To: Paul Clark	From: Melinda Harris Project Manager
Company: Galderma Laboratories	Division of Dermatologic & Dental Drug Products
Fax number: (817) 961-0020	Fax number: (301) 827-2091 or 2075
Phone number: (817) 961-5336	Phone number: (301) 827-2020
Subject: NDA 21-535 Submission 000	

Total no. of pages including cover: 5

Comments: Minutes from the 15 January 2003 telecon

Document to be mailed: YES NO

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have received this document in error, please notify us immediately by telephone at (301)
827-2020. Thank you.**

MEMORANDUM OF TELECON

DATE: 1/15/03, 2:30 P.M.

APPLICATION NUMBER: NDA 21-535

DRUG PRODUCT: Clobex (Clobetasol Propionate Lotion), 0.05%

BETWEEN:

Name: Paul Clark, Vice President, Regulatory Affairs
Christine Shank, Director, Regulatory Affairs
Phone: (817) 961-5336
Representing: Galderma Laboratories, L.P.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
Jonathan Wilkin, M.D. Division Director
Markham Luke, M.D., Ph.D., Clinical Team Leader, Dermatology
Denise Cook, M.D., Medical Officer
Melinda Harris, M.S., Regulatory Project Manager

SUBJECT: NDA 21-535

The teleconference was requested by FDA to discuss specific areas of concern and request information from the sponsor concerning the submitted NDA.

The following concerns were conveyed to the Sponsor:

1. The Agency referred the Sponsor to the End of Phase 2 meeting minutes on September 20, 1999 contained in Volume 1.1, page 257 of their submission. The minutes state that "Conduct of Cortrosyn stimulation testing is suggested at Baseline and at the End of Study. The potential for masking adrenal suppression by multiple stimulations of the adrenal glands in the same patient whether by small or larger amounts of synthetic ACTH, as proposed by the Sponsor, are of major concern."

The results supplied in the adult psoriasis HPA axis study in the NDA submission, list Cortrosyn stimulation at screening, baseline, week 1, week 2, and week 4. It is possible that the stimulation in week 2 will be compromised by week 1 and the stimulation in week 4 will be compromised by week 1 and 2. This could result in lesser levels of stimulation. Multiple time points of stimulation were also done in the atopic dermatitis study in adults, at

screening, baseline, week 1 and week 2. If the Sponsor could provide further information on additional studies, the Agency may be able to accept them during the review clock. Without receiving further information, the application runs the potential of receiving an NA.

The Sponsor is requested to send the subject data line listings for the Individual HPA axis Response for Study 18061 with adolescents which was missing from the application. The criteria for adrenal axis suppression should be the three criteria stated in the Cortrosyn labeling with the post-stimulation blood draw conducted at 30 minutes. In Study 18061, the blood draws were conducted at 60 minutes. This will have to be reviewed in context of the Cortrosyn labeling by the Division.

The Sponsor asked if the study would be adequate if it meets the requirements of 60 minutes per the Cortrosyn labeling or would they need to conduct an additional study. The Sponsor stated that it would be difficult to enroll enough patients, especially adolescents, during the review clock. The Sponsor also stated that they realized that the first two studies would not meet FDA requirements, so they conducted the third study.

The Agency responded that we cannot comment until we receive the individual line listings.

The Sponsor stated that they will send the line-listings in the next few days. They will discuss the 60 minute issue and respond as soon as possible.

The conversation ended amicably.

APPEARS THIS WAY
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/s/

Markham Luke
1/23/03 01:40:40 PM
Acting for Dr. Jonathan Wilkin, Division Director, DDDDP

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/s/

Melinda Harris
1/29/03 02:43:14 PM
CSO



January 27, 2003

356 H
Jan 28

Food and Drug Administration
Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
ATTENTION: Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 21-535
CLOBEX™ (clobetasol propionate lotion) Lotion, 0.05%
Response to Information Request (24 December 2002) ✓

Dear Sir or Madam:

Reference is made to the New Drug Application for Clobetasol Propionate Lotion 0.05%. This submission amends the application with information requested by FDA Statistical reviewers.

If I can be of assistance with any questions or concerns, please contact me.

Sincere regards,

Paul M. Clark
Vice President, Regulatory Affairs
Telephone: 817-961-5336
Fax: 817-961-0020

c: Archival
Statistical
Desk Copy
Fax of Cover Letter to Melinda Harris, FDA Project Manager

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Galderma Laboratories, L.P.	DATE OF SUBMISSION January 28, 2003
TELEPHONE NO. (Include Area Code) 817-961-5000	FACSIMILE (FAX) NUMBER (Include Area Code) 817-961-0020
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 14501 North Freeway Fort Worth, TX 76177	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-535		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Clobetasol Propionate Lotion	PROPRIETARY NAME (trade name) IF ANY Clobex Lotion	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Clobetasol Propionate	CODE NAME (If any) CP Lotion	
DOSAGE FORM: Lotion	STRENGTHS: 0.05%	ROUTE OF ADMINISTRATION: Topical

(PROPOSED) INDICATION(S) FOR USE:
for the treatment of steroid responsive dermatosis.

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505 (B)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> PRIOR APPROVAL (PA)
REASON FOR SUBMISSION Response to information request
PROPOSED MARKETING STATUS (check one) <input type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 24 December 2002

To: Paul Clark	From: Melinda Harris Project Manager
Company: Galderma Laboratories	Division of Dermatologic & Dental Drug Products
Fax number: (817) 961-0020	Fax number: (301) 827-2091 or 2075
Phone number: (817) 961-5336	Phone number: (301) 827-2020
Subject: NDA 21-535 Information Request	

Total no. of pages including cover: 3

Comments: Statistical Information Request, Please provide as soon as possible

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS
ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL,
AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the
addressee, you are hereby notified that any review, disclosure, dissemination, copying, or
other action based on the content of this communication is not authorized. If you have
received this document in error, please notify us immediately by telephone at (301) 827-
2020. Thank you.

Information Request for NDA 21-535 Statistical Review

- Please clarify whether treatment allocation (computer-generated list) was carried out prior to study enrollment. Further, please explain any deviations occurred during the course of the trials on whether the treatment allocation was done sequentially over time for each of the two pivotal trials (studies 9707 and 18001).
- Please clarify whether same investigators and/or patients, if any, participated in the two pivotal studies (studies 9707 and 18001) along with the rationale on why this occurred in case it happened.
- For study 2651, please clarify whether the generation of treatment allocation list was done prior to study enrollment and whether treatment assignment was carried out sequentially over time. Please explain any deviations from the sequential treatment allocation.
- For study 18001, please further discuss the investigational site under . Were there sub-investigators at this site? Can distinction be made as to who followed the patients at this site? If so, please provide details.

Please provide this information as soon as possible.

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/s/

Melinda Harris

12/24/02 09:42:44 AM

CSO



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 27 November 2002

To: Paul Clark	From: Melinda Harris Project Manager
Company: Galderma Laboratories	Division of Dermatologic & Dental Drug Products
Fax number: (817) 961-0020	Fax number: (301) 827-2091 or 2075
Phone number: (817) 961-5336	Phone number: (301) 827-2020
Subject: NDA 21-535 Submission date 25 September 2002	

Total no. of pages including cover: 3

Comments: Regulatory and Clinical request for information are following

Document to be mailed: YES NO

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10/20/07
NDA 21-535

Regulatory Request for Information

1. Please reformat the PPI into the Medication Guide Format.

Clinical Request for Information

1. The sponsor needs to provide separate line listings for cutaneous adverse events. The sponsor should also provide adverse events in a tabular form for all adverse events that occurred $\geq 1\%$ and a separate listing in tabular form for cutaneous adverse events that occurred $\geq 1\%$. This should be done for each study and also combined in the integrated summary of safety.
2. The sponsor should provide any information regarding the marketing or pending applications of this product in other countries.
3. One filing review issue noted at this time is that clobetasol propionate lotion, 0.05% appears to cause more HPA axis suppression than the reference listed drug product, Temovate E Cream, 0.05%. This may have an impact on the final recommendation for use of clobetasol propionate lotion, 0.05%.

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/s/

Melinda Harris
11/27/02 09:57:16 AM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: 19 November 2002

To: Paul Clark	From: Melinda Harris Project Manager
Company: Galderma Laboratories	Division of Dermatologic & Dental Drug Products
Fax number: (817) 961-0020	Fax number: (301) 827-2091 or 2075
Phone number: (817) 961-5336	Phone number: (301) 827-2020
Subject: NDA 21-535 Statistical request for information	

Total no. of pages including cover: 2

Comments:

We request that you provide the Agency with randomization lists with dates of generation for studies 9707, 18001 and 2651 as soon as possible to facilitate the statistical review.

Document to be mailed: YES NO

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/s/

Melinda Harris
11/19/02 02:01:07 PM
CSO



January 10, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products (HFD-540)
Attention: Document Control Room
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 21-535
Clobetasol Propionate Topical Lotion 0.05%
Response to FDA's Request for Information

Dear Sir or Madam:

Reference is made to the New Drug Application for Clobetasol Propionate Lotion 0.05%. This submission amends the application with information requested by FDA reviewers.

The randomization lists for studies 9797, 18001, and 2651 are enclosed.

If I can be of assistance with any questions or concerns, please contact me.

Sincere regards,

Paul Clark
Vice President, Regulatory Affairs
Tel. 817-961-5336
FAX 817-961-0020

c: Archival
Clinical
Statistical
Desk Copy
FAX of Cover Letter to Melinda Harris, FDA Project Manager



RECEIVED

SEP 30 2002

MEGA/CDER



September 25, 2002

Food and Drug Administration
Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
ATTENTION: Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852

RE: NDA 21-535 (User Fee I.D. #4379)
CLOBEX™ (clobetasol propionate lotion) Lotion, 0.05%
Original New Drug Application Submission

Dear Sir or Madam:

The applicant, Galderma Laboratories, LP, is pleased to submit herewith a New Drug Application for CLOBEX™ (clobetasol propionate lotion) Lotion, 0.05%. This application is submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and in accordance with the applicable procedures and requirements established in Part 314 of Title 21 of the *Code of Federal Regulations*.

The proposed new drug product is a topical lotion dosage form of clobetasol propionate indicated for the treatment of corticosteroid responsive dermatoses. The drug product has been the subject of clinical investigations in the United States under IND 54,230. The approved commercial product will be made available to patients only by prescription from a licensed health care provider.

Drug Development Overview

CLOBEX Lotion 0.05% is a new dosage form of clobetasol propionate, 0.05%. There are other approved prescription dosage forms of clobetasol propionate 0.05%, creams, ointments, gels, and scalp applications currently on the market. All dosage forms are indicated for twice-daily application limited to 2 consecutive weeks for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses and 4 consecutive weeks in the treatment of moderate to severe plaque-type psoriasis. The total dosage should not exceed 50 g per week.

The U.S. clinical trials with CLOBEX Lotion were initiated in 1998 under IND ———. The clinical development program followed the guidance and recommendations of the Division of Dermatologic and Dental Drug Products.

Development of a lotion formulation follows a typical progression of marketing initiatives in recognition of the needs and preferences of physicians and patients. The CLOBEX Lotion formulation incorporates dosage form that will appeal to patients with dry skin. The CLOBEX Lotion formulation offers an alternative therapeutic dosage form to the prescribing dermatologist or physician for patients who could benefit from an easily spreadable topical super-potent corticosteroid.

FDA Meetings and Correspondence

There have been meetings with the division at appropriate stages of development to ensure that the development plans were consistent with FDA's expectations, and to ensure that there was adequate information presented to support a 505(b)(2) application. Meetings with the division's representatives that influenced the development of this application are included in this section on pages *al* through *cl*.

Contact Person

It is requested that any questions or comments regarding this application be directed to the person named as follows:

Mr. Paul Clark
Vice President, Regulatory Affairs
Galderma Laboratories, Inc.
14501 North Freeway
Fort Worth, Texas 76177

Telephone (817) 961-5336
Fax (817) 961-0020

Reviewers Guide to the Application and Content and Format of the Application

In the administrative part of the application following the Form FDA 356h in Volume 1.1, page *ah*, reviewers are directed to the Reviewers Guide to the Application. This brief presentation describes the organizational and structural features of the application in order to orient the reviewer and assist in location of data and information. It is hoped that this will facilitate understanding of the features of the application and ease location of information; however, if we can be of assistance, please contact us directly.

The Application Index in Volume 1.1 contains a brief two-page introductory **FORMAT AND CONTENT OF THE APPLICATION** index that provides a quick reference to the Archive Volumes of the application and the pages of the ITEM 1. Application Index by section.

Electronic Versions of the Application

Except for SAS data sets that are provided in electronic format for statistical evaluation of the Phase 3 clinical studies, this application is not available in a CANDa format. The applicant can, however, provide the **narrative text** only in electronic format to any reviewer upon request. Please direct a request to the contact person identified above and specify the format desired. All narrative text within the application was created in MICROSOFT WORD0 but may be converted to other software for use by reviewers.

Field Copy Certification

A signed certification of submission of a Field Copy of the Summary Section and the Chemistry, Manufacturing, and Controls Section of the application is provided in Volume 1.1. See application index for location.

The applicant extends its sincere appreciation to the agency staff and reviewers for their time spent in review and consideration of this application. We welcome any requests for assistance and any questions regarding this application.

Sincere regards,



Paul M. Clark
Vice President, Regulatory Affairs

Desk Copy of Volume 1.1 - Ms. Mary Jean Kosma-Fornaro
(4 copies) Division of Dermatological and Dental Drug Products
HFD-540

c: Mr. Humberto Antunes
General Manager, Galderma Laboratories, L.P.

Oliver Watts, Ph.D.
Vice-president, Corporate Regulatory Affairs
Galderma S.A.