CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-302

CORRESPONDENCE

NOVARTIS

James L.DeMartino, PhD
Associate Director
Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936
Tel 973 781 2645
Fax 973 781 3550

April 30, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852

NDA No. 21-302
Elidel™ (pimecrolimus cream) Cream 1%

120-Day Safety Update

N-000/S4

NDA ORIG AMENDMI

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000.

In accordance with 21 CFR 314.50(d)(5)(vi)(b), Novartis Pharmaceuticals Corporation herewith submits the 120-day safety update report (Item 9 of the NDA). The update follows the same format as that of the original Integrated Summary of Safety in the original NDA.

This update contains data from 324 new pediatric patients aged 3 months to 23 months who were treated with Elidel cream for up to 6 months. There are no new safety data to report in adults. The information in this update does not alter the safety conclusions contained in the original NDA.

As requested in the original NDA, we also provide paper copies of CRFs for patients who died (no deaths were reported), discontinued for any reason, or had a serious adverse event. We also provide, as requested, for the applicable study (0316), CRFs for those patients who were excluded from per protocol analyses.

For questions or comments on this update, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments: Form FDA 356h
Volumes 1-81

ORIGINAL

NOVARTIS

James L.DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3966

December 10, 2001

Food & Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

NDA No. 21-302
Elidel™ (pimecrolimus) Cream 1%

Labeling

Dear Sir or Madam:

Please refer to NDA 21-302 submitted December 15, 2001. Refer also to a labeling amendment dated November 28, 2001 in which the sponsor proposed revisions to the labeling to the Division of Dermatologic and Dental Drug Products. In that amendment, the sponsor noted that a table (at line 405 of the label) would be provided at a later date. A hard copy of that table, which was sent by email to M. Wright on December 4 is provided herewith.

If there are any questions, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

JLD/tln
21-302 12101 label.doc
Attachments: Form FDA 356h
AE table

APPEARS THIS WAY
ON ORIGINAL

James L.DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3966

December 13, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products (HFD-540)
9201 Corporate Blvd.
Rockville, Maryland 20852-3202

NDA No. 21-302
Elidel® (pimecrolimus cream) Cream 1%

Phase 4 Commitments

Dear Sir or Madam:

Please refer to NDA 21-302 submitted December 15, 2001. Attached is the a of the Phase 4 agreements made between Novartis Pharmaceutical Corporation and the Division of Dermatologic and Dental Drug Products at a teleconference on December 10, 2001. In addition to the description of the commitments, target dates for submission of proposals and reporting of information are included in the list.

If there are any questions, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments: Form FDA 356h
Phase 4 commitments

APPEARS THIS WAY
ON ORIGINAL

James L.DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3966

December 13, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products (HFD-540)
9201 Corporate Blvd.
Rockville, Maryland 20852-3202

NDA No. 21-302
Elidel® (pimecrolimus cream) Cream 1%

Final Labeling

Dear Sir or Madam:

Please refer to NDA 21-302 submitted December 15, 2001. Attached is the final agreed upon labeling (package insert and patient information sheet) for the above mentioned product.

If there are any questions, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments: Form FDA 356h
Elidel® package insert
Elidel® patient information sheet

APPEARS THIS WAY
ON ORIGINAL

James L. DeMartino, Ph.D.
Associate Director
Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936-1080
One Health Plaza
East Hanover, NJ 07936

Tel (973) 781-2645
Fax (973) 781-3966

NOVARTIS

N-000 (BL)
ORIG AMENDMENT

November 28, 2001

Jonathan Wilkin, MD
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, MD 20852

NDA 21-302, Elidel
(pimecrolimus) Cream 1%

RE: Labeling Negotiation

Dear Dr. Wilkin:

Thank you for communicating your revised Elidel Cream labeling with us. We look forward to the opportunity to discuss the details with you further.

To begin, we have accepted much of the text you propose and understand your position concerning the use of Elidel Cream in children under two years of age, based on the selected safety profile provided to us in your revised draft.

As you will notice by our revisions, Novartis' position is based on the language and spirit of the Final Pediatric Rule. Physicians should be made aware through labeling, of the complete profile of Elidel in infants. Our studies have proven that Elidel is highly effective in infants at the 6-week endpoint.

In addition to the safety information currently presented in the label, prescribers should have the opportunity to understand the pharmacokinetic and efficacy data in order to be able to make an informed decision on the use of Elidel in infants. It is our understanding that under the 1999 Pediatric Guidance, FDA requests sponsors to conduct studies that will provide information that may produce health benefits in the pediatric population. We are concerned that by not providing adequate efficacy and pharmacokinetic information for practitioners, a precaution simply to not recommend use of Elidel leaves physicians in exactly the position the Pediatric Rule was meant to avoid.

In keeping with the spirit of FDA's efforts to encourage clinical studies in children we submit that the Elidel labeling should include an accurate and balanced presentation of all the data that were collected in the pediatric populations we studied.

ORIGINAL

We have attached revised draft labeling which retains your proposed indication in patients two years of age and above, yet balances safety and efficacy information based on studies which were the subject of the Written Request. As a guide to the proposed revisions we have also attached a table referencing the line items we request to revise and/or insert.

We look forward to discussing this with you at your earliest convenience. We will work in cooperation with you to ensure that you meet the December 14 Action Date with the goal of issuing an approval of the NDA.

Sincerely,

James L. DeMartino, Ph.D,
Associate Director
Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 5325

November 1, 2001

NDA 21-302
Elidel™ (pimecrolimus) Cream 1%

Response to FDA Information Request - Chemistry, Manufacturing and Controls

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental
Drug Products/HFD-540
Office of Drug Evaluation V
Attn: Document Control Room
Center for Drug Evaluation and Research
Corporate Building
9201 Corporate Boulevard
Rockville, Maryland 20850

Dear Dr. Wilkin:

Reference is made to our pending NDA 21-302 for Pimecrolimus Cream, 1%, submitted on December 15, 2000. The enclosed information and attached documentation is provided in response to the FDA October 24, 2001 Information Request Fax.

Additional reference is made to a teleconference held between FDA participants, Reviewing Chemist, Dr. E. Pappas and Project Manager, Ms. Millie Wright, and Novartis participants, Dr. Michael Malone and Ms. S. LeRoy, on October 30, 2001.

The enclosed response completely answers the seven comments and information requests outlined in the FDA October 24, 2001 fax. A copy of the fax received from FDA appears before our written response, for your convenience.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-2735.

(139)

NOVARTIS

James L.DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3966

DUPLICATE

October 30, 2001

BB

NDA DRUG AMENDMENT

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products (HFD-540)
9201 Corporate Blvd.
Rockville, Maryland 20852-3202

NDA No. 21-302
Elidel® (pimecrolimus cream) Cream 1%

Response to 23-Oct-01 PK Information Request (Expiry dates)

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000. Please also refer to your fax request dated October 23, 2001. (A copy of the fax is attached for your reference.)

Following this cover letter is a response to your query concerning 2 expiration dates on the same batch of a radiolabeled reagent.

If you have any questions or comments, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments:
Form FDA 356h
Attachment

APPEARS THIS WAY
ON ORIGINAL

NOVARTIS

James L.DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3966

DUPLICATE

RECEIVED
NOV 0 2 2001
MEGA/CDER

October 30, 2001

BB

NDA ORIG AMENDMENT

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products (HFD-540)
9201 Corporate Blvd.
Rockville, Maryland 20852-3202

NDA No. 21-302
Elidel® (pimecrolimus cream) Cream 1%

Response to 25-Oct-01 PK Information Request

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000. Please also refer to your fax request dated October 25, 2001. (A copy of the fax is attached for your reference.)

Following this cover letter is a response to your query. Also attached are the text of Study 301 extension and Appendix 4, which contains the specific PK data requested.

If you have any questions or comments, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments:
Form FDA 356h
Attachment

APPEARS THIS WAY
ON ORIGINAL

(142)

NOVARTIS

James L.DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3966

ORIGINAL

October 29, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products (HFD-540)
9201 Corporate Blvd.
Rockville, Maryland 20852-3202

NDA No. 21-302
Elidel® (pimecrolimus cream) Cream 1%

Response to 24-Oct-01 Request for Information (Validation report)

BB
NDA ORIG AMENDMENT

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000. Please also refer to your fax request dated October 24, 2001. (A copy of the fax is attached for your reference.)

Following this cover letter is an amendment to report no. 303-123. This amendment addresses the question from the biopharmaceutics reviewer. The amendment provides for a typographical correction in the description of how ——— were made

If you have any questions or comments, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments:
Form FDA 356h
Attachments

APPEARS THIS WAY
ON ORIGINAL

1324

NOVARTIS

James L.DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3966

N,000/BM.

NDA ORIG AMENDMENT

RECEIVED
OCT 2 9 2001
MEGA/CDER

October 22, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products (HFD-540)
9201 Corporate Blvd.
Rockville, Maryland 20852-3202

NDA No. 21-302
Elidel™ (pimecrolimus cream) Cream 1%

Response to 01-Oct-01 Telephone Request for Information and 19-Oct-01 Fax Request for Information

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000. Please also refer to your requests conveyed by telephone on October 1 and by fax on October 19, 2001 and to the Novartis fax dated October 12, 2001 in response to the October 1 request.

In a teleconference with Drs. Cook and Luke and Ms. MaryJean Kozma-Fornaro on October 19, we agreed that Novartis did not collect the specified information concerning growth velocity that was requested on October 1.

Following this cover letter is the list of patients from the October 19 fax. (A copy of the fax is attached for your reference.) Within that select group of patients, those who used topical steroid or not at any time during Study 313 are identified.

For questions or comments on this submission, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments:
Form FDA 356h

ORIGINAL

NOVARTIS

James L. DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3966

October 11, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products (HFD-540)
9201 Corporate Blvd.
Rockville, Maryland 20852-3202

NDA No. 21-302
Elidel™ (pimecrolimus cream) Cream 1%

Response to 20-Sep-01 Request for Information

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000. Please also refer to your faxed request for information dated September 20, 2001. We submitted a response to the first item in your request by fax on September 21, 2001. We submitted that information to the NDA in a submission dated October 8, 2001.

We herewith submit the responses to the outstanding items 2-6.

As you requested, a desk copy of a diskette containing electronic copies of the requested tables (responses 1-5) is included with this submission.

For your reference, a copy of your September 20 fax request is provided.

For questions or comments on this submission, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments:
Form FDA 356h

ORIGINAL

119

B2

NOVARTIS

James L.DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3966

October 10, 2001

ood and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products (HFD-540)
9201 Corporate Blvd.
Rockville, Maryland 20852-3202

NDA No. 21-302
Elidel™ (pimecrolimus cream) Cream 1%

Partial response to 01-Oct-01 Telephone Request for Information

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000. Please also refer to your request conveyed by telephone on October 1, 2001.

In part, your request asked for a reanalysis of the growth velocity data using the 90% confidence interval. In a submission to the NDA dated September 10, 2001 in response to requests received on August 8, we submitted these same analyses using the 95% confidence interval.

We herewith submit post-text tables 10.4-2a and b, and listing 10.3-8b with reference to the 90% confidence interval

For questions or comments on this submission, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments:
Form FDA 356h

ORIGINAL

179

OCT 16 2001

NOVARTIS

James L. DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3966

October 9, 2001

ORIGINAL
ORIG AMENDMENT

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products (HFD-540)
9201 Corporate Blvd.
Rockville, Maryland 20852-3202

NDA No. 21-302
Elidel™ (pimecrolimus cream) Cream 1%

Response to 26-Sep-01 Request for Information

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000. Please also refer to your faxed request for information dated September 26, 2001. You requested information concerning study 0316: SAS datasets, and frequency tables by age and body surface area involved.

We herewith submit a complete response to your requests.

For your reference, a copy of your September 26 fax request is provided.

For questions or comments on this submission, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments:
Form FDA 356h

APPEARS THIS WAY
ON ORIGINAL

NEW CORRESP

NOVARTIS

James L.DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3966

October 9, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products (HFD-540)
9201 Corporate Blvd.
Rockville, Maryland 20852-3202

NDA No. 21-302
Elidel™ (pimecrolimus cream) Cream 1%

Responses to Requests for Information

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000. Please also refer to your faxed request for information dated September 24, 2001. You requested information concerning anergy testing and a listing of patients with less than 5% TBSA involvement at baseline in studies 305, 307, and 316.

We herewith submit a complete response to the three itemized requests. Please note that the response to the third item was previously faxed to your division on September 25, 2001. A copy of that exact fax response is provided.

For your reference, a copy of your September 24 fax request is provided.

For questions or comments on this submission, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments:
Form FDA 356h

24

NEW CORRESP.

NOVARTIS

James L.DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3966

RECEIVED
OCT 15 2001
MEGA/CDER

October 8, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products (HFD-540)
9201 Corporate Blvd.
Rockville, Maryland 20852-3202

NDA No. 21-302
Elidel™ (pimecrolimus cream) Cream 1%

Responses to Requests for Information

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000.

The information supplied herewith comprises official copies of faxes previously sent to the Division. The contents of the fax submissions address the requests for information as noted below.

Date of Request	Date of Response (fax)	Contents
9/10/2001 (telephone request)	9/17/2001	Missing post-text table 9.1-15a, page 4 (Study 316) from the May 23, 2001 submission
9/19/2001 (fax)	9/19/2001	Specified tables from the updated ISE, submitted 9/10/2001
9/20/2001 (fax)	9/21/2001	Response to Item 1 only – analysis of skin anergy testing

For your reference, copies of your September 19 and 20 fax requests are provided.

For questions or comments on this submission, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments:
Form FDA 356h

DUPLICATE

(13)

NOVARTIS

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

James DeMartino
Tel: 973-781-2645
Fax: 973-781-3590
email address: james.demartino@pharma..novartis.com

September 12, 2001

Food & Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

NDA No. 21-302
Elidel® (pimecrolimus) cream 1%

Response to request for financial disclosure information

NC

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000. In response to a June 4 telephone request for information from Millie Wright of the DDDDP, we herewith provide a response to specific questions concerning financial disclosure information.

For questions or comments on this submission, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments:
Form FDA 356h
21-302 091201 response to request.doc

(12)

BP

ORIG AMEND

NOVARTIS

James L.DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080
Tel 973 781 2645
Fax 973 781 3590

September 11, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products (HFD-540)
9201 Corporate Blvd.
Rockville, Maryland 20852-3202

NDA No. 21-302
Elidel® (pimecrolimus) cream 1%

Response to request for pharm/tox information

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000. Also refer to your fax dated July 10, 2001 in which the pharmacology reviewer listed 3 items in an information request.

We herewith submit a complete response to that request for information. For the convenience of the reviewer, a copy of the July 10 fax follows this letter.

For questions or comments on this submission, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments:
Form FDA 356h

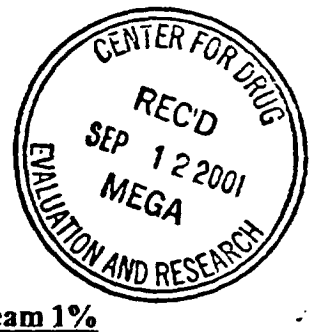
APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

James DeMartino
Tel: 973-781-2645
Fax: 973-781-3590
email address: james.demartino@pharma.novartis.com

NOVARTIS



September 10, 2001

Food & Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

NDA No. 21-302
Elidel® (pimecrolimus) Cream 1%

Response to request for clinical information

N-000/BZA

NDA ORIG AMENDMENT

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000. Also refer to your fax dated August 8, 2001 in which the medical reviewer listed 9 items in an information request.

We herewith submit a complete response to that request for information. For the convenience of the reviewer, a copy of the August 8 fax follows this letter.

For questions or comments on this submission, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

JLD/tln
Attachments:
Form FDA 356h
Submitted in duplicate
21-302 091001 response to request.doc

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

(46)

NOVARTIS

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

N-000/Be
NDA ORIG AMENDMENT

July 12, 2001

NDA 21-302
Elidel (pimecrolimus) Cream 1%

Amendment to Pending NDA - Chemistry, Manufacturing and Controls

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental
Drug Products/HFD-540
Office of Drug Evaluation V
Attn Document Control Room
Center for Drug Evaluation and Research
9201 Corporate Boulevard
Rockville, Maryland 20850

Dear Dr. Wilkin:

Reference is made to our pending NDA 21-302 for Elidel Cream, 1%. The following enclosed stability reports contain 18 month data on Elidel Cream, 1% in support of our proposed 24-month expiration period.

- ASM 981 1% Cream, Registration Stability Report, RSR 1765B, dated 10-Jul-01
- ASM 981 1% Cream, Registration Stability Report, RSR 1765 Annex-1B, dated 10-Jul-01

The 18 month stability results support our proposed 24-month expiration period.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-2735. If there are any general or Clinical related issues please contact James DeMartino, DRA Therapeutic Area representative at (973) 781-2645.

Sincerely,

Per S. LeRoy

Sheryl LeRoy
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

Attachments
Submitted in Duplicate

cc: Ms. Regina Brown, - New Jersey District Office, (cover letter only)

ORIGINAL

(64)

NOVARTIS

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

N-000/BC

NDA ORIG AMENDME

July 6, 2001

NDA 21-302
ASM 981 (pimecrolimus) Cream 1%

Response to FDA Deficiency Fax - Chemistry, Manufacturing and Controls

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental
Drug Products/HFD-540
Office of Drug Evaluation V
Attn Document Control Room
Center for Drug Evaluation and Research
Corporate Building
9201 Corporate Boulevard
Rockville, Maryland 20850

Dear Dr. Wilkin:

Reference is made to our pending NDA 21-302 for Pimecrolimus Cream, 1%, submitted on December 15, 2000. The enclosed information and attached documentation is provided in response to the FDA June 25, 2001 fax outlining microbiology deficiencies.

The enclosed response completely answers the two deficiencies stated in the FDA June 25, 2001 fax. A copy of the fax received from FDA appears before our written response, for your convenience.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-2735. If there are any general or Clinical related issues please contact James DeMartino, DRA Therapeutic Area representative at (973) 781-2645.

Sincerely,

Sheryl LeRoy
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

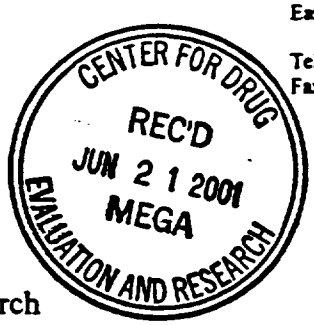
ORIGINAL

James L. DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3590

NOVARTIS



N-000/B2

June 19, 2001

NDA ORIG AMENDMENT

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products (HFD-540)
9201 Corporate Blvd.
Rockville, Maryland 20852-3202

NDA No. 21-302
Elidel™ (pimecrolimus) cream 1%

Labeling amendment

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000. Also refer to our safety update (April 30, 2001) and our clincal and preclinical amendments (May 24 and June 7, 2001, respectively).

We herewith submit revised draft labeling (package insert) that takes into consideration the new and updated information submitted in the safety update and amendments mentioned above. To complete the annotation of the revised label, one new preclinical report and clinical output of data previously submitted to the NDA are appended to this submission. The new information is tabbed to correspond to the referenced annotation in the revised label.

This submission also provides for the latest carton and container labeling.

One of the desk copies includes a diskette that holds Word files of the annotated PI and the final draft PI.

For questions or comments on this submission, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments:
Form FDA 356h
7 desk copies

ORIGINAL

(76)

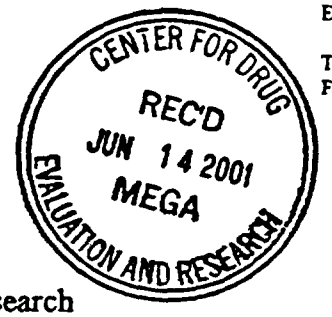
ORIG AMENDMENT BM

NOVARTIS

James L. DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3590



June 13, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products (HFD-540)
9201 Corporate Blvd.
Rockville, Maryland 20852-3202

NDA No. 21-302
Elidel™ (pimecrolimus cream) Cream 1%

Response to request for information

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000. Also refer to your faxed request for information received on June 4, 2001.

We herewith submit a response to your request for specified CRFs and include a table listing the information you requested. For your reference a copy of your fax also is provided.

For questions or comments on this submission, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments:
Form FDA 356h

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

(78)

BP

NOVARTIS

James L.DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3590

June 7, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products (HFD-540)
9201 Corporate Blvd.
Rockville, Maryland 20852-3202

NDA No. 21-302
Elidel™ (pimecrolimus cream) Cream 1%

PreClinical Amendment

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000.

We herewith submit 3 new preclinical reports that support statements in revised labeling to be submitted to the NDA within the next 2 weeks.

For questions or comments on this submission, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments:
Form FDA 356h
Preclinical reports

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

74

NOVARTIS

James L. DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3590

N-000/82

NDA ORIG AMENDMENT

June 6, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products (HFD-540)
9201 Corporate Blvd.
Rockville, Maryland 20852-3202

NDA No. 21-302
Elidel™ (pimecrolimus cream) Cream 1%

Response to Request for Information

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000. Please also refer to a faxed request for information dated May 4 from you statistician. This submission addresses the final outstanding item of that May 4 request.

The information supplied herewith provides for SAS programs for specified tables in the clincal reports of 4 studies (305, 307, 313, and 316). The accompanying CD contains the SAS programs and, as you requested, a detailed directory of the programs (in an MS Excel document).

The second item of the May 4 request was answered on May 8, 2001 in an email to Vickey Lutwak of the Division of Dermatologic and Dental Drug Products. The p-values requested in the third and final item were provided in a submission dated May 23, 2001.

For your reference, a copy of the May 4 request is attached.

For questions or comments on this submission, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments:
Form FDA 356h
CD containing SAS programs

ORIGINAL

71

James L.DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3590

N-000/BM.

NDA ORIG AMENDMENT

June 1, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

NDA No. 21-302
Elidel™ (pimecrolimus cream) Cream 1%

Clinical Amendment

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000. Also, refer to our clinical amendment dated May 24, 2001.

We herewith submit a clinical amendment providing for the electronic case report tabulations (CRTs) that correspond to the updated (313 and 316) or new (315) clinical study reports that we submitted in May. In addition, we submit financial disclosure information related to Study 315. We included the financial disclosure information for Studies 313 and 316 in the original NDA.

If you have any questions or comments concerning this submission, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

(64)

NOVARTIS

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

May 29, 2001

NDA 21-302
ASM 981 (pimecrolimus) Cream 1%

Amendment to Original NDA - Chemistry, Manufacturing and Controls

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental
Drug Products/HFD-540
Office of Drug Evaluation V
Attn Document Control Room
Center for Drug Evaluation and Research
Corporate Building
9201 Corporate Boulevard
Rockville, Maryland 20850

Dear Dr. Wilkin:

Reference is made to our pending NDA 21-302 for Pimecrolimus Cream, 1%, submitted on December 15, 2000. Additional reference is made to our drug substance submissions to this NDA: a CMC amendment dated March 8, 2001, and a response to FDA dated May 21, 2001.

The enclosed information and attached documentation is provided as replacement documentation for inclusion in the drug substance section. This documentation more accurately represents the manufacturing process that is being used to make pimecrolimus drug substance. Details of the changes in this amendment are provided in the attached documentation.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-2735. If there are any general or Clinical related issues please contact James DeMartino, DRA Therapeutic Area representative at (973) 781-2645.

Sincerely,

Sheryl LeRoy
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

ORIG AMENDMENT
PM

NOVARTIS

James L. DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3590

May 24, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

NDA No. 21-302
Elidel™ (pimecrolimus cream) Cream 1%

Clinical Amendment

SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000. In accordance with 21 CFR 314.60, Novartis Pharmaceuticals Corporation herewith submits a clinical amendment to the pending NDA to provide for additional safety and effectiveness data in pediatric patients aged 3 mo. to 17 yr.

The clinical report for study 313 satisfies the last outstanding requirement for qualifying for pediatric exclusivity. For your reference and per the guidance for qualifying for pediatric exclusivity, we provide the following documents with this submission:

- Written Request (September 27, 1999)
- Amendment to the Written Request (December 13, 2000)
- Annotated Written Request (indicating where, by volume and page number, in the reports of studies in the NDA and clinical amendment we have responded to each part of the Written Request)

A short description of the rationale and contents of this submission is also included.

For questions or comments on this submission, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

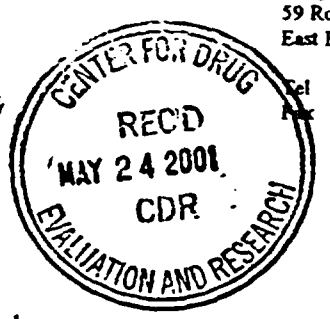
Attachments: Form FDA 356h
Volumes 1-74

Fax copy of cover letter to:
Director, Office of Generic Drugs (HFD-600)
(301) 594-0183 (fax)

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 2 5 2001
MEGA

ORIGINAL

AMENDMENT B2



NOVARTIS

James L.DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3590

May 23, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852

NDA No. 21-302
Elidel™ (pimecrolimus cream) Cream 1%

Response to Request for Information

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000. Please also refer to faxed requests for information dated May 4 (statistical) and May 7, 2001 (clinical).

The information supplied herewith provides for the p-values requested in item 3 of the request dated May 4 and item 2 of the request dated May 7. For your reference, copies of the 2 requests are attached. Please note that only item 1 of the May 7 request is outstanding. Response to that request is expected before the end of May.

For questions or comments on this submission, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments:
Form FDA 356h
Statistical output
Desk copy directly to Millie Wright (HFD-540)

APPEARS THIS WAY
ON ORIGINAL

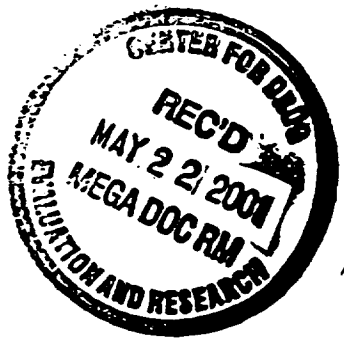
ORIGINAL

(61)

NOVARTIS

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325



N-000/BC
NDA ORIG AMENDMEN

May 21, 2001

NDA 21-302
ASM 981 (pimecrolimus) Cream 1%

Response to FDA Information Request Letter - Chemistry, Manufacturing and Controls

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental
Drug Products/HFD-540
Office of Drug Evaluation V
Attn Document Control Room
Center for Drug Evaluation and Research
Corporate Building
9201 Corporate Boulevard
Rockville, Maryland 20850

Dear Dr. Wilkin:

Reference is made to our pending NDA 21-302 for Pimecrolimus Cream, 1%, submitted on December 15, 2000. Additional reference is made to our CMC amendment, dated March 8, 2001, which provided information on the ——— forms of pimecrolimus drug substance.

The enclosed information and attached documentation is provided in response to FDA's Information Request Letter, dated May 3, 2001. This response provides additional information on the pimecrolimus ——— forms and drug substance batch analyses.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-2735. If there are any general or Clinical related issues please contact James DeMartino, DRA Therapeutic Area representative at (973) 781-2645.

Sincerely,

Sheryl LeRoy
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

ORIGINAL

NOVARTIS

James L. DeMartino, PhD
Associate Director
Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936
Tel 973 781 2645
Fax 973 781 3550

April 30, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852

NDA No. 21-302
Elidel™ (pimecrolimus cream) Cream 1%

120-Day Safety Update

N-000154

NDA ORIG AMENDMENT

Dear Sir or Madam:

Please refer to our pending NDA 21-302 for Elidel® (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000.

In accordance with 21 CFR 314.50(d)(5)(vi)(b), Novartis Pharmaceuticals Corporation herewith submits the 120-day safety update report (Item 9 of the NDA). The update follows the same format as that of the original Integrated Summary of Safety in the original NDA.

This update contains data from 324 new pediatric patients aged 3 months to 23 months who were treated with Elidel cream for up to 6 months. There are no new safety data to report in adults. The information in this update does not alter the safety conclusions contained in the original NDA.

As requested in the original NDA, we also provide paper copies of CRFs for patients who died (no deaths were reported), discontinued for any reason, or had a serious adverse event. We also provide, as requested, for the applicable study (0316), CRFs for those patients who were excluded from per protocol analyses.

For questions or comments on this update, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments: Form FDA 356h
Volumes 1-81

ORIGINAL

(25)

NOVARTIS

March 13, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

NDA 21-302
ASM 981 Cream, 1%

RESPONSE TO REQUEST FOR INFORMATION

NDA ORIG AMENDMENT

BP

Dear Dr. Wilkin:

On February 15, 2001, Ms. Millie Wright faxed to me a request for information from your pharm/tox reviewer of the above mentioned NDA. The request was for contract laboratory historical control background incidence rates in Wistar rats for 4 types of neoplastic tumors. On February 21, Ms. Wright informed me by voice mail that this request was in reference to the NDA rat dermal carcinogenicity study, 972025 (T-133/BS-733).

The attachment to this letter provides the requested historical control data.

If you have any questions concerning this submission, please contact me at (973) 781-2645.

Sincerely,

James L. DeMartino

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

/
Submitted in duplicate

l010313 hist tumor data.doc

APPEARS THIS WAY ON ORIGINAL

ORIGINAL

(24)

ORIG AMENDMENT DC

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

March 8, 2001

NDA 21-302
ASM 981 (pimecrolimus) Cream 1%

Amendment - Chemistry, Manufacturing and Controls

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental
Drug Products/HFD-540
Office of Drug Evaluation V
Attn Document Control Room
Center for Drug Evaluation and Research
Corporate Building
9201 Corporate Boulevard
Rockville, Maryland 20850

Dear Dr. Wilkin:

Reference is made to our pending NDA for Pimecrolimus Cream. This amendment provides additional information on ——— forms of pimecrolimus drug substance.

On January 23 and 24, 2001, Dr. E. Pappas, Dr. W. DeCamp and Ms. M. Wright of the FDA reviewing division and I discussed issues surrounding ——— forms of pimecrolimus drug substance and their effect on bioavailability of the drug product. As a result of these discussions Novartis committed to provide a section on ——— forms and their effects on bioavailability to the FDA by March 9, 2001. This amendment fulfills this commitment.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-2735. If there are any general or Clinical related issues please contact James DeMartino, DRA Therapeutic Area representative at (973) 781-2645.

Sincerely,

Sheryl LeRoy
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

ORIGINAL

Attachments
Submitted in Duplicate

cc: Ms. Regina Brown, - New Jersey District Office,
North Brunswick Resident Post - Certified Field Copy (cover letter only)

APPEARS THIS WAY
ON ORIGINAL

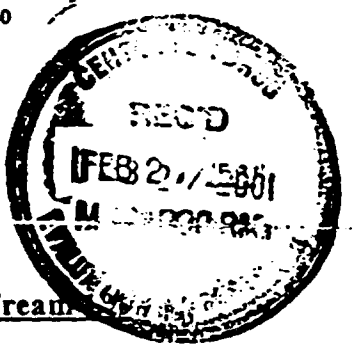
(B)

NOVARTIS

James L. DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3590



February 23, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd.
Rockville, MD 20850-3202

NDA No. 21-302
Elidel™ (pimecrolimus cream) Cream

Response to request for information

Dear Dr. Wilkin:

Please refer to our February 15, 2001 response to your request for information. We herewith submit 3 additional responses that were incomplete in the February 15 submission.

This submission includes:

- A 3-page document describing the responses to the outstanding Pharmacology/ Toxicology, Clinical, and Biostatistics requests.
- One CD which contains the electronic tumor data for study 15142 (T-127/BS-530) requested by your pharmacology and biostatistics reviewers.
- A 52-page output of the primary efficacy analysis by investigator (center) for the long-term safety study, 313, as requested by your clinical reviewer.

If you have any questions concerning the information in this submission, please contact me at (973) 781-2645.

Sincerely,

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

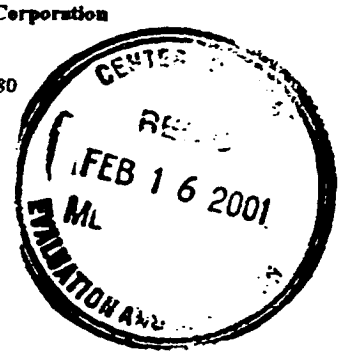
(6)

NOVARTIS

James L. DeMartino, PhD
Associate Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 2645
Fax 973 781 3590



February 15, 2001

NDA [illegible] AMENDM

BZ

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd.
Rockville, MD 20850-3202

NDA No. 21-302
Elidel™ (pimecrolimus cream) Cream 1%

Response to request for information

Dear Dr. Wilkin:

In response to your request for additional information dated February 2, 2001, please find attached a four-page document that addresses each item. Appended to the response are 3 attachments that include:

1. A CD containing patient data listings for pivotal trials 305, 307, and 313.
2. Primary efficacy analyses by investigator (center) for the pivotal studies 305, 307, and 316
3. A diskette containing a Word file of an index associating reported AE terms with preferred terms.

Additional information about these attachments is included in the text of the response.

If you have any questions, please contact me at (973) 781-2645.

Sincerely,

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

James L. DeMartino, PhD
Associate Director
Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080
Tel 973 781 2645
Fax 973 781 3590

December 15, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852

NDA No. 21-302
Elidel™ (pimecrolimus cream) Cream 1%
ORIGINAL NEW DRUG APPLICATION

Dear Sir or Madam:

In accordance with 21 CFR 314.50, Novartis Pharmaceuticals Corporation herewith submits an original New Drug Application for Elidel™ (pimecrolimus cream) Cream, 1% for the treatment of atopic dermatitis in patients ———————

Elidel was studied under INDs —— (atopic dermatitis) and ———————— —— filed in the Division of Dermatologic and Dental Drug Products (HFD-540). We seek only the atopic dermatitis indication in this application.

Elidel was evaluated in 12 controlled trials involving a total of 2,225 patients with atopic dermatitis. Evidence from the key controlled trials (Studies B305, B307, 0316, and B313) as well as evidence from other controlled trials included in this application, demonstrate that Elidel is safe and effective in the short-term treatment and long-term management of atopic dermatitis in patients ———————

In compliance with 21 CFR 314.55, we have submitted at the beginning of the Clinical Data section of this application a request for a waiver for pediatric use information in patients under the age ————

Additionally, we refer to the pediatric Written Request issued by the Division of Dermatologic and Dental Drug Products on September 27, 1999 and to the amended Written Request dated December 13, 2000. A copy of the Written Request and the amendment is provided for your reference. This application provides some of the data asked for in the Written Request. The outstanding data will be provided in a subsequent submission. At that time, as per the revised September 1999 Guidance entitled "Qualifying for Pediatric Exclusivity" (p. 12), we will clearly state that the requirements of the Written Request are complete.

As agreed during the pre-NDA meeting on May 8, 2000, this submission includes paper copies of CRFs for patients who had a serious adverse event, who discontinued for any reason, and (for studies B305, B307, 0316, and B202) who were excluded from the per protocol analyses. Per the Division's request, complete laboratory data profiles are provided for patients who had at least one abnormal laboratory value. That information is provided as part of Appendix 3.2 to the Integrated Safety Summary.

Item 11 (Case Report Tabulations) is being submitted electronically on CD-ROM in accordance with the January 1999 Guidance: "Providing Regulatory Submissions in Electronic Format – NDAs". For the studies B202, B305, B307, B308, B313, and 0316, data are provided as SAS transport files, along with the associated data definition. Data listings are provided electronically as PDF files for studies 0301, 0316, 0317, B202, B203, B205, B307, B308, B313. The overall size of these electronic files is approximately 2.5 gigabytes. The files are being submitted on five CD-ROMs. Word files of the draft labeling, the annotated label, and the patient package insert are provided on diskette. All other sections of the NDA are provided in paper format for both the archival and review copies.

Per the Division's request in a teleconference to Novartis on September 21, 1999, preclinical carcinogenicity data in electronic format (xpt files) from oral and dermal studies (excepting the photocarcinogenicity study) are also provided in this NDA. The rat dermal carcinogenicity data in electronic format is submitted here for the first time. The carcinogenicity xpt data files from the oral rat and mice studies were previously submitted to ——— on November 20, 2000 (Ser. No. 140).

A certified copy of Item 4 of this New Drug Application is being provided to the New Jersey district office in compliance with the pre-approval inspection (PAI) requirements.

The FDA User Fee for this application (user fee ID — was submitted on November 2, 2000.

For questions or comments on this application, please contact the undersigned at (973) 781-2645.

Sincerely,

James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs

Attachments: Form FDA 356h
Volumes 1-519

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: May 9, 2001

APPLICATION NUMBER: NDA 21-302 Elidel Cream

BETWEEN:

Name: James DeMartino, Kate Marshall, and Primo Patel
Phone: 973-781-2645
Representing: Novartis

AND

Name: Denise Cook, M.D. and Vickey Lutwak. Project Manager
HFD-540

SUBJECT: Request for additional information following submission of ISS.

We requested information from the sponsor regarding the submission status for Study B 316, the pivotal trial in infants. Jim DeMartino stated that the full report, including the efficacy data from the infant trial will be submitted within the next two weeks. In fact, during this period, we will be receiving the final reports for B 313, the 1-year safety study in pediatric patients ages 2-17 years. He commented that although at the start of the study, 474 patients were in the ASM 1% cream arm, 270 subjects completed the 1-year duration. Skin antigen testing was performed on patients that completed the study. For protocol 315, it is still ongoing but the 6 month data has been submitted in the 120 day safety update. The sponsor stated that with this study all the points of the pediatric request should be covered. It was clarified that study 315 had not been submitted with the original NDA but is the 1-year safety study in infants, ages 3 – 23 months. We requested that, besides the hard copy, we would like electronic versions in MS Word and appropriate SAS data sets.

Victoria Lutwak, Project Manager for
Mildred Wright, Project Manager

cc:
Archival IND/NDA 21-302
HFD-540/Division Files
HFD-540/Reviewers and Team Leaders

Drafted by: vl

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/s/

Victoria Lutwak
5/9/01 03:07:23 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

APR 19 2001

NDA 21-302 Elidel

MEMORANDUM OF TELECON

DATE: February 1, 2001

APPLICATION NUMBER: NDA 21-302/Elidel (pimecrolimus) Cream, 1%

BETWEEN:

Name: James DeMartino, Ph.D., Associate Director, Drug Regulatory Affairs
Stephanie Barber, Ph.D., Director, Drug Regulatory Affairs
Robert Cherill, MS, Clinical Development
Chris Bush, Biostatistics

Phone: (973) 781-2344

Representing: Novartis Pharmaceuticals

AND

Name: Millie Wright, Project Manager
Susan Walker, M.D., Clinical Team Leader
Denise Cook, M.D., Clinical Reviewer

SUBJECT: Fileability of NDA 21-302/Elidel (pimecrolimus) Cream, 1%

BACKGROUND: NDA 21-302 was submitted December 15th. An internal 45 fileability meeting was held January 31, 2001 to determine if the application was fileable and if reviewers needed additional information. This t-con was scheduled to convey the conclusions of the meeting.

DISCUSSION:

FDA's Comments:

1. The Sponsor should be aware that the NDA is minimally fileable and because of the incomplete nature of the submission(clinical trial data still outstanding), the label that may result may be more restrictive than envisioned. Development of the drug product during the review cycle is not the best approach.

2. The submission has been reviewed for fileability, and there are concerns about the lack of information available for review to support the submitted labeling. Specifically, there is:
   a. incomplete safety and efficacy data to review for ages less than two years (open trials)
   b. incomplete long term safety data (open trials)

3. It is noted that these trials are ongoing at the time of NDA submission.
   a. Should the Sponsor plan to complete the trials during the review period (i.e. on the review clock), the Division cannot guarantee that they would be reviewed prior to taking an action. Studies should be finalized prior to original submission of the NDA.
   b. The Sponsor should understand that the adequacy for filing the NDA is based upon the

completed trials submitted in the NDA.

Sponsor's Comments:

1. Sponsor stated that this point (ongoing studies) was discussed during the pre-NDA meeting.

Agency's Response:
The Division did not agree in the preNDA meeting to accept ongoing studies as part of the NDA submission.
(Addendum: Please note page 4 of the May 8, 2000, pre-NDA meeting minutes:
"Sponsor's Question:

1) **Does the Division accept the proposal for submitting the specified reports and data in the original NDA and the supplemental data in the Safety Update? See Tables 1.1 (p. 21) and 1.2 (p. 22).**

FDA's Answer:

1) Double-blind studies that will have a pivotal role in the approval process for a particular age group should be submitted with the original NDA. The agency would prefer to have *all* of the double-blind studies that support the indication for children [redacted] to be submitted at the time the original NDA is filed. Ongoing open-label studies that are analyzing long-term safety can be submitted as safety updates. Phototoxicity and photoallergy are usually done as separate studies with approximately 30 patients in each study."

Agency's Question:
When will you submit the remaining data for the ongoing studies?

Sponsor's Response:
We hope to have the Safety Update in to the Division by May 1, 2000.

Agency's Comment:
A fax detailing information requests from each discipline will be sent to you. The information requested will assist the reviewers' in completing their reviews.

Minutes drafted by M.Wright

APPEARS THIS WAY ON ORIGINAL

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/s/

Mildred Wright
4/18/01 04:43:02 PM
CSO

Susan Walker
4/19/01 02:06:46 PM
MEDICAL OFFICER

APPEARS THIS WAY ON ORIGINAL

Phase 4s
for NDA 21-302 Elidel

1. a. The preclinical rodent studies found an increased risk for lymphoma and follicular cell thyroid adenoma in the studies evaluating an oral formulation of pimecrolimus. We agree to conduct a registry study of pediatric patients (aged 2-17, with emphasis on the younger ages) with atopic dermatitis followed through adulthood for those who have long-term intermittent treatment with Elidel (pimecrolimus) 1% Cream to assess the risk of developing systemic malignancies.

   Study proposal for review: April 30, 2002
   Report: Every 5 years after the division reviews and accepts the proposal and the study is initiated. Data will be submitted with NDA annual report.

   b. A preclinical mouse photocarcinogenicity study showed an accelerated rate of development of cutaneous malignancies. We agree to conduct a registry or case-controlled study of sun-exposed adult patients, aged 40 and above, with atopic dermatitis, who have long-term intermittent treatment with Elidel (pimecrolimus) 1 % Cream to assess the risk of developing cutaneous malignancies.

   Study proposal for review: June 30, 2002
   Report: Every 5 years after the division reviews and accepts the proposal and the study is initiated. Data will be submitted with NDA annual report.

2. We agree to establish a pregnancy registry to assess the relationship of pimecrolimus cream to spontaneous abortions to determine if the signal in the clinical studies is a valid one. This could be waived by FDA if an acceptable preclinical dermal embryofetal study is performed with continuous dermal drug exposure and found to be negative.

   Draft preclinical protocol: April 30, 2002
   Study Report: 1 year after the Division reviews and agrees to the protocol (est. June 30, 2003)

   Proposal for pregnancy registry: September 30, 2002
   Initiation of registry: June 30, 2003 (unless waived by FDA
   Report: Yearly, in NDA annual report

3. We agree to study pimecrolimus cream in immunocompromised patients, who have atopic dermatitis, both for efficacy and safety.

   Protocol for review: April 30, 2002
   Study report: 2 years after the Division reviews and agrees to the protocol (est.June 30, 2004)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-302

Novartis Pharmaceuticals Corporation
Attention: James L. DeMartino, Ph.D.
Associate Director, PPD Regulatory Affairs
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Dr. DeMartino:

Reference is made to your new drug application (NDA) for Elidel (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000.

We also refer to your September 11, 2001 submission which contained the study report for the rat dermal carcinogenicity study

Your study report was reviewed by our Executive Carcinogenicity Assessment Committee (ECAC) on November 6, 2001. A copy of the final report of the ECAC regarding Elidel is enclosed. Please note that the recommendations made by the ECAC are advisory in nature and should not be interpreted as a measure of the approvability of any application for this drug.

If you have any questions, call Millie Wright, Project Manager, at 301-827-2020.

Sincerely,

{See appended electronic signature page}

Mary Jean Kozma-Fornaro.
Chief, Project Management Staff
Division of Dermatologic and
Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

**APPEARS THIS WAY
ON ORIGINAL**

Executive CAC
November 6, 2001

Committee: David Morse, Ph.D., HFD-150, Acting Chair
James Farrelly, Ph.D., HFD-530, Alternate Member
Jeri El Hage, Ph.D., HFD-510, Alternate Member
Barbara Hill, Ph.D., HFD-540, Presenting Reviewer

Author of Draft: Barbara Hill

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA # 21-302
Drug Name: Elidel (pimecrolimus) cream; 1% ASM 981 cream
Sponsor: Novartis Pharmaceuticals Corporation

Background:

ASM 981 is an anti-inflammatory/immunosuppressive ascomycin macrolactam derivative that is being developed for the topical treatment of Atopic Dermatitis. Atopic Dermatitis is primarily a pediatric indication and the duration of treatment is chronic. The results from the final report for the rat dermal carcinogenicity study conducted with ASM 981 cream were presented to the Exec CAC on 6/19/01. The Exec CAC commented that the histopathological analysis for this study was incomplete since all the animals in the low and mid dose groups were not examined in this study. The committee did note that there may be a possible signal in the thyroid and/or thymus based on the incomplete histopathological data available for the low and mid dose groups. The Exec CAC requested that the sponsor reanalyze the histopathology for the thyroid and thymus in all low and mid dose animals in the rat dermal carcinogenicity study. An informational request was relayed to the sponsor on 7/10/01 via fax. The sponsor submitted the requested information along with the contract laboratory historical control background incidence rates for the appropriate tumors on 9/14/01. A summary of the submitted results is provided in the following section.

Rat Dermal Carcinogenicity Study:

Doses tested in this study were 0 (saline control), 0 (vehicle control), 2 (0.2%), 6 (0.6%) and 10 (1.0%) mg/kg/day ASM 981 cream. The final to be marketed ASM 981 cream formulation was used in this rat dermal carcinogenicity study. A statistically significant increase in follicular cell adenoma of the thyroid was noted in all ASM 981 cream treated male dose groups compared to control animals. This effect is biologically relevant even though the incidence rates in the male treated animals fell within the contract laboratory's historical control incidence range for follicular cell adenoma of the thyroid gland in Wistar rats (0 – 14.3%). The majority of carcinogenicity studies included in the historical control incidence range evaluation were oral feed carcinogenicity studies (33/36). This may not be an appropriate control value for comparison for the current rat dermal carcinogenicity study. Therefore, comparison to concurrent controls is more appropriate for the results from this rat dermal carcinogenicity study. In addition, if the incidence rates for follicular cell adenoma and follicular cell carcinoma of the thyroid in male rats are combined, then the potential carcinogenicity signal is slightly stronger. The incidence rates for follicular cell adenoma and carcinoma of the thyroid for male and female rats are provided in the following table.

Thyroid Tumor Type	Males					Females				
	Saline	Vehicle	2 mg/kg	6 mg/kg	10 mg/kg	Saline	Vehicle	2 mg/kg	6 mg/kg	10 mg/kg
Follicular cell adenoma	1/50 (2%)	0/50 (0%)	4/50 (8%)	6/50 (12%)	5/49 (10.2%)	0/50 (0%)	0/49 (0%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
Follicular cell carcinoma	0/50 (0%)	0/50 (0%)	2/50 (4%)	0/50 (0%)	0/49 (0%)	1/50 (2%)	0/50 (0%)	1/50 (2%)	0/50 (0%)	1/50 (2%)

The incidence of benign thymoma noted in all ASM 981 male and female dose groups was not significantly increased compared to control animals.

Executive CAC Recommendations and Conclusions:

1. The committee agreed that there is an affect on follicular cell adenomas of the thyroid gland in male rats and that this finding should be included in the product labeling for Elidel cream.

David Morse, Ph.D.
Acting Chair, Executive CAC

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/s/

David Morse
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Mary Jean Kozma Fornaro
11/8/01 12:14:41 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-302
IND [redacted]

JUL 10 2001

Novartis Pharmaceuticals Corporation
Attention: James L. DeMartino, Ph.D.
Associate Director, PPD Regulatory Affairs
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Dr. DeMartino:

Reference is made to your new drug application (NDA) for Elidel (pimecrolimus) Cream, 1%, which was submitted on December 15, 2000.

We also refer to your carcinogenicity study results submitted to IND [redacted] dated July 28, 1999 and January 28, 2000, respectively.

Your study report was reviewed by our Executive Carcinogenicity Assessment Committee (ECAC) on June 19, 2001. A copy of the final report of the ECAC regarding Elidel is enclosed. Please note that the recommendations made by the ECAC are advisory in nature and should not be interpreted as a measure of the approvability of any application for this drug.

If you have any questions, call Millie Wright, Project Manager, at 301-827-2020.

Sincerely,

{See appended electronic signature page}

Mary Jean Kozma-Fornaro.
Chief, Project Management Staff
Division of Dermatologic and
Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

Executive CAC

June 19, 2001

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Jasti Choudary, B.V.Sc,. Ph.D., HFD-180, Alternate Member
Abby Jacobs, Ph.D., HFD-540, Supervisor
Barbara Hill, Ph.D., HFD-540, Presenting Reviewer

Author of Draft: Barbara Hill

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA # 21-302
Drug Name: Elidel (pimecrolimus) cream; 1% ASM 981 cream
Sponsor: Novartis Pharmaceuticals Corporation

Background:

ASM 981 is an anti-inflammatory/immunosuppressive ascomycin macrolactam derivative that is being developed for the topical treatment of moderate —— Atopic Dermatitis. Atopic Dermatitis is primarily a pediatric indication and the duration of treatment is chronic. ASM 981 has undergone testing in a full battery of genotoxicity tests and showed no genotoxic potential. The sponsor has conducted an oral mouse carcinogenicity study, two oral rat carcinogenicity studies, a dermal mouse carcinogenicity study and a dermal rat carcinogenicity study. Exec CAC concurrence for the dose range selected in each of these studies was not obtained prior to the conduct of each study.

Mouse Oral Carcinogenicity Study:

A statistically significant increase in malignant lymphoma was noted in high dose male and female mice in the mouse oral (gavage) carcinogenicity study (refer to following table).

Incidence of Malignant Lymphoma in mice treated with ASM 981

Dose (mg/kg/day)	Males	Females
Vehicle Control 1	3/60	19/60
Vehicle Control 2	8/60	10/60
1	3/60	9/60
5	6/60	14/60
15	8/60	18/60
45	17/60	27/60

Rat Oral Carcinogenicity Studies:

Two rat oral (gavage) carcinogenicity studies were conducted for ASM 981. The doses used in the first study were 0 (Vehicle Control 1), 0 (Vehicle Control 2), 1, 5 and 25 mg/kg/day ASM 981. The doses used in the second study were 0 (Vehicle Control 1), 0 (Vehicle Control 2) and 10 mg/kg/day ASM 981. High mortality due to overt toxicity (males and females terminated after 58 weeks) was noted in high dose male and female rats in the first study. Therefore, the sponsor decided to conduct the second rat oral carcinogenicity study with a dose between the 5 and 25 mg/kg/day dose levels.

A statistically significant increase in benign thymoma was noted in 10 mg/kg/day treated male and female rats in the second rat oral carcinogenicity study. An increase in benign thymoma was noted in 5 mg/kg/day treated male rats in the first rat oral carcinogenicity study but did not reach statistical significance (the two rat oral carcinogenicity studies were not combined for statistical analysis). Therefore, the NOAEL for benign thymoma in male rats is 1 mg/kg/day and in female rats is 5 mg/kg/day. The incidence of benign thymoma for both rat oral carcinogenicity studies combined is provided in the following table.

Incidence of Benign Thymoma in rats treated with ASM 981

Study #	Dose (mg/kg/day)	Males	Females
1	Vehicle Control 1	4/60	5/58
1	Vehicle Control 2	3/60	7/60
2	Vehicle Control 1	1/60	9/60
2	Vehicle Control 2	2/60	6/60
1	1	4/60	4/59
1	5	9/60[a]	6/60
2	10	7/60[b]	17/60
1	25	1/59[c]	6/60

a – treated for 104 weeks; b – treated for 88 weeks; c – treated for 58 weeks

Mouse Dermal Carcinogenicity Study:

Doses tested in this study were 0 (untreated control), 0 (vehicle control), 0.04 (0.0032%), 0.40 (0.032%) and 4.0 (0.32%) mg/kg/day. ASM 981 was dissolved in ethanol for this mouse dermal carcinogenicity study. The highest concentration tested was 0.32% ASM 981 which is ~1/3 the concentration that will be used clinically (1% ASM 981 cream). It would have been preferable to have the highest dose be at least the 1% concentration and in the final to be marketed formulation. No signal for potential systemic or dermal carcinogenicity was noted in this study. However, the dose selection for this study was not adequate. The results of a 13 week dermal repeat dose toxicity study (ASM 981 dissolved in ethanol) demonstrated malignant lymphoma in the 50 mg/kg/day dose group. Therefore, the high dose selected for the mouse dermal carcinogenicity study was too low to have detected a possible malignant lymphoma signal.

Rat Dermal Carcinogenicity Study:

Doses tested in this study were 0 (saline control), 0 (vehicle control), 2 (0.2%), 6 (0.6%) and 10 (1.0%) mg/kg/day. The final to be marketed ASM 981 cream formulation was used in this rat dermal carcinogenicity study. The maximum feasible concentration of ASM 981 in the cream formulation (1%) was used as the high dose in this study. No apparent signal for potential systemic or dermal carcinogenicity was noted in this study. However, it is important to note that incomplete histopathological evaluation was performed for the low and mid dose groups in this study.

Executive CAC Recommendations and Conclusions:

Oral Mouse Carcinogencity Study:

1. The committee determined that a MTD was not achieved in this study.
2. The committee concurred that there was a strong signal for malignant lymphoma in this study.
3. The committee noted that hyperplastic changes were seen in the thymus at higher doses (≥ 50 mg/kg/day) in the 13 week repeat dose oral toxicity study in mice. The committee expressed concern that thymomas might have been seen at a true MTD dose in the mouse oral carcinogenicity study.
4. The committee recommended that the malignant lymphoma findings noted in this study be included in the label if the drug product is approved.
5. The committee recommended that information concerning the short latency of malignant lymphoma formation in mice after repeat oral dosing be included in the label if the drug product is approved.

Oral Rat Carcinogenicity Studies:

1. The committee determined that a MTD had been reached in this study.
2. The committee felt that this was an adequate study.
3. The committee concurred that there was a signal for benign thymoma in this study.
4. The committee commented that the finding of benign thymoma in this study does not seem irrelevant in conjunction with the hyperplastic changes noted in the thymus in the 13 week repeat dose oral toxicity study in mice.
5. The committee recommended that the benign thymoma findings noted in this study be included in the label if the drug product is approved.

Dermal Mouse Carcinogenicity Study:

1. The committee felt that this study was negative. However, the committee commented that the test article had obvious effects after dermal administration in mice (malignant lymphoma noted in the 13 week repeat dermal toxicity study in mice at doses $\geq$ 50 mg/kg/day). The committee recommended that this information be included in the label if the drug product is approved.
2. The committee asked about the source of the metastatic carcinoma noted in the thymus of one high dose male. A request will be sent to the sponsor to clarify the source of this metastatic tumor.

Dermal Rat Carcinogenicity Study:

1. The committee commented that the histopathological analysis for this study was incomplete since all the animals in the low and mid dose groups were not examined in this study. The committee did note that there may be a possible signal in the thyroid and/or thymus based on the incomplete histopathological data available for the low and mid dose groups.
2. The committee requested that the sponsor reanalyze the histopathology of the thyroid and thymus in all low and mid dose animals. In addition, the committee requested that another statistical analysis be performed after the data for the complete histopathological analysis of the thyroid and thymus in all low and mid dose animals has been submitted to the agency. A request for this histopathological re-analysis will be sent to the sponsor.
3. The committee recommended that a statistical reanalysis be performed for the combined incidence for the follicular cell adenoma and follicular cell carcinoma of the thyroid. The request for statistical reanalysis will be submitted to the biostatistical division in the agency after the complete histopathological reanalysis data has been submitted to the agency.

4. The committee requested the historical background incidence rate for follicular cell carcinoma of the thyroid for the strain of rat used in the dermal rat carcinogenicity study. This request will be sent to the sponsor.

General Comments:

[ ]

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

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/s/

Joseph DeGeorge
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Mary Jean Kozma Fornaro
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

MAY 3 2001

NDA 21-302

INFORMATION REQUEST LETTER

Novartis Pharmaceuticals Corporation
Attention: James L. DeMartino, PhD
Associate Director
Drug Regulatory Affairs
59 Route 10
East Hanover, New Jersey 07936-1080

Dear Mr. DeMartino:

Please refer to your December 15, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Elidel (pimecrolimus) Cream, 1%.

We also refer to your submission dated March 8, 2001.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

[ ]

If you have any questions, call Millie Wright, Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader for the
Division of Dermatologic & Dental Drug Products,
HFD-540
DNDC 3, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Wilson H. DeCamp
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concur with review

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-302

JAN 16 2001

Novartis Pharmaceuticals Corporation
Attention: James L. DeMartino, Ph.D.
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Dr. DeMartino:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Elidel (pimecrolimus) Cream 1%

Review Priority Classification: Standard (S)

Date of Application: December 15, 2000

Date of Receipt: December 15, 2000

Our Reference Number: NDA 21-302

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 13, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 15, 2001 and the secondary user fee goal date will be December 15, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Millie Wright, Consumer Safety Officer, at (301) 443-4250.

Sincerely,

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Mary Jean Kozma Fornaro
1/16/01 03:17:20 PM

APPEARS THIS WAY
ON ORIGINAL

FDA Fax Memo

Date: November 8, 2001

Subject: NDA 21-302/Elide (pimecrolimus) Cream, 1%
Meeting Minutes

Hi Jim,
Attached you will find a copy of the letter containing the meeting minutes from the Executive CAC meeting held November 6, 2001. A hard copy will also be mailed.

If you have questions, please call.

Respectfully,
Millie

APPEARS THIS WAY
ON ORIGINAL

FDA Fax Memo

Date: October 25, 2001

Subject: NDA 21-302 Elidel (pimecrolimus) Cream 1%

PK Information Request

Hi Jim,

In the label, lines 96 and 105 read as follows:

96 ⌜

105 ⌟

Please provide detailed information of the % total body surface area affected of each patient participated in studies 204, 205, 202, 206, 301 and 304 and an analysis to substantiate their claim at line 96 above.

It appears that the second sentence above (Line 105) is included from the result of the extension study CASM981 0301E1. The reviewer does not have a copy of that result. If it has been submitted previously, please indicate the submission date. If it has not, please submit it.

In addition, are the result of another extension study ——— is ready yet or not. If it is ready, please submit.

If you have questions, please call.
Thanks,

Millie

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/s/

Mildred Wright
10/25/01 05:33:31 PM
CSO

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