FDA Fax

Date: October 24, 2001

To: Novartis Pharmaceuticals Corporation
Sheryl LeRoy
Chemistry, Manufacturing and Controls
Phone: (973) 781-2735
Fax: (973) 781-6325
CC: James DeMartino, Ph.D.
Associate Director, Drug Regulatory Affairs
Phone: (973) 781-2645
Fax: (973) 781-3966

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 4 pages (including this page)

Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

FDA Fax Memo

Date: October 24, 2001

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

CMC Information Request

Hi Sheryl and Jim,

The chemistry reviewer has the following comments and information requests:

If you have questions, please call.

Thanks,
Millie

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Mildred Wright
10/24/01 11:45:42 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

FDA Fax

Date: October 23, 2001

To: Novartis Pharmaceuticals Corporation
James DeMartino, Ph.D.
Associate Director, Drug Regulatory Affairs
Phone: (973) 781-2645
Fax: (973) 781-3966

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 3 pages (including this page)

Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

FDA Fax Memo

Date: October 23, 2001

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

PK Information Request

Hi Jim,

Please explain:

In study 204, as tracer [H3]-FK-506 (batch — 801-7, exp date 13-1-1998) was used.

In subsequent studies (205, 202, and 206), as tracer [H3]-FK-506 (batch – 801-7, exp date 13-1-2001) was used.

How tracer having same batch numbers can have different expiry dates?

If you have questions, please call.

Thanks,

Millie

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Mildred Wright
10/23/01 06:04:30 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

FDA Fax

Date: September 24, 2001

To: Novartis Pharmaceuticals Corporation
James DeMartino, Ph.D.
Associate Director, Drug Regulatory Affairs
Phone: (973) 781-2645
Fax: (973) 781-3966

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 3 pages (including this page)

Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

FDA Fax Memo

Date: September 24, 2001

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

Clinical Information Request

Hi Jim,

As Dr. Cook indicated during the t-con earlier today, we need the following information:

1. Please indicate where in the NDA submission the line listings for the results of the anergy testing (all 112 patients) can be located. If they were not submitted, they need to be submitted now.
2. Please explain how the patients were selected to have anergy testing and explain any differences between the vehicle and ASM cream selections, if applicable. Also, please explain why some patients in the ASM cream arm who had minimal treatment in the last 5 months (0 days, 5 days, 16 days, 20 days, 42 days, etc), which would not be considered long term treatment, were selected for anergy testing.
3. Please provide a listing of all patients with <5% TBSA involvement at baseline in the following studies: B305, B307 and B316.

Please note that we need to have #3 as soon as possible. Please contact us tomorrow and let us know when you can provide the requested information.

If you have questions, please call.

Millie

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Mildred Wright
9/24/01 06:28:07 PM
CSO

APPEARS THIS WAY ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 09-20-01

To: James DeMartino, Ph.D.	**From:** Victoria Lutwak
Company: Novatris	Division of Dermatological and Dental Drug Products
Fax number: 973-781-3966	**Fax number:** 301-827-2075/ 827-2091
Phone number: 973-781-2645	**Phone number:** 301-827-2073

Subject: NDA 21-302 Information Request

Total no. of pages including cover: 2

Comments: See attached request from the statistician.

While Millie is out, I am covering for her. If you have any questions, please call. Thank you. Vickey Lutwak

Document to be mailed: ☐ YES X NO

APPEARS THIS WAY
ON ORIGINAL

September 20, 2001
Request for additional information:

Information Request

Needed by opening of business (9:30am) on Monday, September 24, 2001

1. Please provide the following analysis concerning skin anergy testing:

    a. Two tables, one of the 82 patients on ASM 1% cream who received skin anergy testing (table A) and one table of the remainder of the ASM 1% cream patients (242 subjects according to the submission) who completed the twelve month study (table B).
    b. The following information should be contained in each table:
        1. The age of the patient
        2. The date the patient first applied study medication
        3. The actual number of "treatment days" in the last 5 months of the study
        4. The interval in days between the last day of treatment and the placement of the skin anergy test or end of study (if did not receive the anergy testing).
        5. The date of the skin anergy test (for table A)
    c. Please provide a comparison between these 2 groups of subjects regarding items b3 and b4 via statistical methods ("p" values and 95% confidence intervals).

    Needed as soon as possible:

2. Please provide a table of incidence rates (according to organ class) of treatment emergent AEs that occurred in ≥ 1% of any population (safety population) for the double-blind phase of studies B305 and B307 combined.
3. Please provide the same table for the open-label phase of studies B305 and B307 combined.
4. Please provide a table of incidence rates of <u>local</u> treatment emergent AEs that occurred in ≥ 1% of the safety population for both the double-blind phase and the open-label phases of studies B305 and B307 combined.
5. Please provide a table with a comparative analysis of the incidence rates of treatment emergent AEs that occurred in ≥ 1% of all the patients on ASM 1% cream in studies B305 and B307 (both phases and both studies combined) to the patients on ASM 1% cream in study B313 who received at least one dose of topical corticosteroid. Please include treatment difference and 95% confidence intervals in the analysis.
6. Please provide all data on disc in MSWord.

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

/s/

Victoria Lutwak
9/24/01 11:36:39 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 09-18-01

To: James DeMartino, Ph.D.	**From:** Victoria Lutwak
Company: Novatris	Division of Dermatological and Dental Drug Products
Fax number: 973-781-3590	**Fax number:** 301-827-2075/ 827-2091
Phone number: 973-781-2645	**Phone number:** 301-827-2073

Subject: NDA 21-302

Total no. of pages including cover: 2

Comments: See attached request from the statistician.

While Millie is out, I am covering for her. If you have any questions, please call. Thank you. Vickey Lutwak

Document to be mailed: ☐ YES X NO

APPEARS THIS WAY
ON ORIGINAL

September 19, 2001
Request for additional information:

In Volume 1.291, of the original submission dated December 15, integrated subgroup efficacy analysis includes results of the interim analysis of Study 316. I need an integrated efficacy subgroup analysis based on the completed Study 316.

Would you please fax us tables similar to the following tables in Volume 1.291:
Table 6.3, page 8-76
Table 6.7, page 8-80
Table 6.11, page 8-83
Table 6.15, page 8-86
Table 6.19, page 8-89.
We need these new tables to be based on the completed Study 316 instead of the interim analysis.

FYI

The reviewer will not be in today; therefore, the message that I left earlier this morning is not correct for today but for tomorrow when she returns. We will get this resolved.

If you seek additional clarification on the above, please call me at (301) 827-2073, and we will arrange a teleconference.

Thank you,

Vickey Lutwak

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Victoria Lutwak
9/19/01 09:47:35 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

FDA Fax

Date: September 15, 2001

SEP 15 2001

To: Novartis Pharmaceuticals Corporation
James DeMartino, Ph.D.
Associate Director, Drug Regulatory Affairs
Phone: (973) 781-2645
Fax: (973) 781-3966

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 3 pages (including this page)

Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

FDA Fax Memo

Date: September 15, 2001

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

Request for SAS Data Sets

Hi Jim,

I received your phone message Thursday and your fax Friday related to the SAS data sets we requested. I also received the fax Friday containing the missing pages. Thanks for your follow-up. We can not locate SAS data sets for Study 316. In the June 6, 2001 submission, the CD, included with the submission, contained SAS programs only--no SAS data sets. We need SAS data sets for the completed Study 316. If you believe otherwise, please indicate where we can locate the SAS data sets for the completed Study 316 in you NDA submission.

I will be out of the office next week. Please contact Vickey Lutwak, (301) 827-2020, if you need assistance, or to tell her when we can expect the missing data sets.

I have also noted that your fax number was changed to (973) 781-3966.

If you have questions, please call.

Thanks,

Millie

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Mildred Wright
9/15/01 11:00:42 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

FDA Fax

AUG 8 2001

Date: August 8, 2001

To: Novartis Pharmaceuticals Corporation
James DeMartino, Ph.D.
Associate Director, Drug Regulatory Affairs
Phone: (973) 781-2645
Fax: (973) 781-3590

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 4 pages (including this page)

Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

FDA Fax Memo

Date: August 8, 2001

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

Clinical Information Request

Hi Jim,

The medical reviewer has the following information request:

1. Please provide an analysis or discussion regarding the effect of Elidel cream on the developmental immunology of pediatric patients, especially in children < 2 years of age.

2. Please provide an analysis regarding the effect of Elidel on growth velocity in children exposed to the drug, especially in children less than 2 years of age.

3. Please provide information as to where in the NDA submission drug "rebound" phenomena is discussed and data provided.

4. Please provide the CRFs or give the location in the NDA for all 14 cases of lymphadenopathy (received 4 cases) that occurred in the trial. It should be accompanied by a table that indicates the patient's age, whether the subject was on ASM 981 cream 1% or vehicle, for how long the patient had been on the drug at the time of the occurrence, and the date of resolution.

5. Please provide the CRFs for all patients who developed iron deficiency anemia during the trials. Please submit a table for all cases of anemia with the specific lab results, study no., patient ID number and the items requested in the table in question 1.

6. Please submit an integrated summary of efficacy that includes the final study report submitted for study B316 (this study had new pivotal efficacy data).

7. Please define "skin papilloma" found in adverse events section, eg. HPV induced warts, etc? Please also include in the response a table with the ages of the subjects, date of onset, location, and resolution. (Refer to Volume 1 of the 120 day safety update, page 45).

8. Please refer to 120 day safety update, Volume 1, page 72. Give a literature source and quote incidence rate for eczema herpeticum (KVE) in patients with atopic dermatitis. In the submission, it was done for herpes simplex virus (HSV) including KVE, but not specifically for eczema herpeticum alone.

9. Please break out from table 5-3, in the safety update, Volume 1, page 42, the adverse event profile, ASM 1% cream compared to vehicle, for adult subjects alone.

If you have questions, please call.

Millie

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

/s/

Mildred Wright
8/8/01 05:02:56 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

FDA Fax

JUL 10 2001

Date: July 10, 2001

To: Novartis Pharmaceuticals Corporation
James DeMartino, Ph.D.
Associate Director, Drug Regulatory Affairs
Phone: (973) 781-2645
Fax: (973) 781-3590

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 3 pages (including this page)

Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

FDA Fax Memo

Date: July 10, 2001

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

Pharm/Tox Information request

Hi Jim,

As you are aware, the carcinogenicity studies conducted for Elidel Cream (1% ASM 981 cream; NDA 21-302) were presented to the Exec CAC on 6/19/01. Based on the committee's recommendation, the Agency is requesting additional information for the dermal rat and mouse carcinogenicity studies. The information requested is as follows:

1. Please clarify the source of the metastatic carcinoma noted in the thymus of one high dose male in the mouse dermal carcinogenicity study.

2. Please reanalyze the histopathology of the thyroid and thymus in all low and mid dose animals in the rat dermal carcinogenicity study. After this data has been submitted to the Agency, then it can be better determined if the potential signal noted from the incomplete histopathological data obtained for the thyroid and thymus in low and mid dose animals is of potential concern or not.

3. Please provide the contract laboratory historical control background incidence rate in Wistar rats (from the laboratory that conducted the rat dermal carcinogenicity study) for the incidence of follicular cell carcinoma and follicular cell adenoma of the thyroid.

If you have questions, please call.

Respectfully,

Millie

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

/s/

Mildred Wright
7/10/01 04:44:22 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

FDA Fax

Date: June 25, 2001

To: Novartis Pharmaceuticals Corporation
James DeMartino, Ph.D.
Associate Director, Drug Regulatory Affairs
Phone: (973) 781-2645
Fax: (973) 781-3590

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 3 pages (including this page)

Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

FDA Fax Memo

Date: June 25, 2001

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

CMC Microbiology Deficiencies

Hi Jim,

The CMC microbiologist's has identified the following deficiencies in your application:

[ ]

Please address the above deficiencies.

If you have questions, please call.

Respectfully,
Millie

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Mildred Wright
6/25/01 11:24:22 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

NDA 21-302 Elidel

FDA Fax

Date: June 4, 2001

To: Novartis Pharmaceuticals Corporation
James DeMartino, Ph.D.
Associate Director, Drug Regulatory Affairs
Phone: (973) 781-2645
Fax: (973) 781-3590

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 3 pages (including this page)

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 BY APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the 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 ***unauthorized and strictly prohibited.*** If you have received this facsimile in error, **please notify Millie Wright by telephone at 301-827-2020 immediately**, return it to HFD-540, 9201 Corporate Blvd, Room N243, Rockville, MD 20850 by US Mail.

Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

FDA Fax Memo

Date: June 4, 2001

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

Clinical Information Request

Hi Jim,

The medical reviewer has the following information request:

1. Please provide all of the case report forms for any subject who had lymphadenopathy at the end of the double-blind and/or open label phases.
2. Please provide all of the case report forms for any subject who had an outbreak of eczema herpeticum (herpes simplex dermatitis) at any time during the trial.
3. Accompany both of the above should be a table indicating the patient's age, whether the subject was on ASM 981 cream 1% or vehicle, how long the patient had been on the drug at the time of the occurrence and the date of resolution.

If you have questions, please call.

Respectfully,
Millie

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

/s/

Mildred Wright
6/4/01 02:48:30 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 05/07/01

To: James DeMartino, Ph.D.	From: Victoria Lutwak
Company: Novatris	Division of Dermatological and Dental Drug Products
Fax number: 973-781-3590	Fax number: 301-827-2075/ 827-2091
Phone number: 973-781-2645	Phone number: 301-827-2073

Subject: NDA 21-302

Total no. of pages including cover: 2

Comments: See attached request from the medical officer.

While Millie is out, I am covering for her. If you have any questions, please call. Thank you. Vickey Lutwak

Document to be mailed: ☐ YES X NO

APPEARS THIS WAY
ON ORIGINAL

NDA 21-302
Elidel

A Request for information from the medical officer.

Would you please provide us with the following information:

1. Drug days and treatment days do not state in gram amount(s) the average amount of medication used by individual patients. Do you have information regarding the actual amount of drug product used by the patients, ie, did you weigh tubes, etc., to ascertain this information?

2. For study B307, could you please provide p-values for the secondary efficacy variables of the individual components of the EASI for visit days 15 and 22.

If you have any question or comments, please call Vickey Lutwak at (301) 827-2073.

Sincerely,

Vickey Lutwak

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

/s/

Victoria Lutwak
5/7/01 02:27:16 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 05/04/01

To: James DeMartino, Ph.D.	From: Victoria Lutwak
Company: Novatris	Division of Dermatological and Dental Drug Products
Fax number: 973-781-3590	Fax number: 301-827-2075/ 827-2091
Phone number: 973-781-2645	Phone number: 301-827-2073

Subject: NDA 21-302

Total no. of pages including cover: 3

Comments: See attached request from the statistician.

While Millie is out, I am covering for her. If you have any questions, please call. Thank you. Vickey Lutwak

Document to be mailed: ☐ YES x NO

APPEARS THIS WAY
ON ORIGINAL

NDA 21-302
Elidel

Would you please provide us with the following information:

1. SAS programs used to generate Tables 7-1 to 7-7, 8-1 to 8-2, and 9-1 to 9-8 in Volumes 156, 171, 186, and 228. We also want a detailed directory for these programs.

2. Average amount of medication used, by treatment arm (with p-value) for studies B305, B307, B313, and 0316.

3. P-values for the differences between treatment arms relative to individual signs (Table 9-6 on page 8-71, Volume 156, Table 9-6 on page 8-72, Volume 171, Table 9-4 on page 8-45, Volume 228, and Table 9.2-29 (overall) on pages 8-251 to 8-254, Volume 187).

If you seek additional clarification on the above, please call me at (301) 827-2073, and we will arrange a teleconference.

Thank you,

Vickey Lutwak

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

/s/

Victoria Lutwak
5/4/01 01:07:52 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 05/03/01

To: James DeMartino	**From:** Victoria Lutwak
Company: Novatris	Division of Dermatological and Dental Drug Products
Fax number: 973-781-3590	**Fax number:** 301-827-2075/ 827-2091
Phone number: 973-781-2645	**Phone number:** 301-827-2073

Subject: NDA 21-302

Total no. of pages including cover: 3

Comments: See attached letter. The official copy will be mailed from the document room.

While Millie is out, I am covering for her. If you have any questions, please call. Thank you. Vickey Lutwak

Document to be mailed: ☐ YES x NO

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES
Service

Public Health

Food and Drug Administration
Rockville, MD 20857

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

MAY 3 2001

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

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Victoria Lutwak
5/3/01 03:09:35 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

NDA 21-302 Elidel

FDA Fax

Date: February 15, 2001

To: Novartis Pharmaceuticals Corporation
James DeMartino, Ph.D.
Associate Director, Drug Regulatory Affairs
Phone: (973) 781-2645
Fax: (973) 781-3590

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 3 pages (including this page)

Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

FDA Fax Memo

Date: February 15, 2001

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

Pharm Tox Information Request

Hi Jim,

The Pharm Tox reviewer has the following information request:

Please provide the contract laboratory historical control background incidence rates in Wistar rats for the incidence of the following neoplastic lesions:

a) Testes – Benign Leydig cell tumor in male animals
b) Thyroid gland – Follicular cell adenoma in male and female animals
c) Hemolymphoreticular system – Malignant lymphoma in male and female animals
d) Pituitary Gland – Adenoma/pars distalis in male and female animals

Respectfully,
Millie

APPEARS THIS WAY
ON ORIGINAL

/s/

Mildred Wright
2/15/01 05:02:05 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

NDA 21-302 Elidel

FDA Fax

Date: February 1, 2001

To: Novartis Pharmaceuticals Corporation
James DeMartino, Ph.D.
Associate Director, Drug Regulatory Affairs
Phone: (973) 781-2645
Fax: (973) 781-3590

From: Millie Wright, Project Manager
Phone: (301) 827-2020
Fax: (301) 827-2091

This transmission includes 3 pages (including this page)

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 BY APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the 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 ***unauthorized and strictly prohibited.*** If you have received this facsimile in error, **please notify Millie Wright by telephone at 301-827-2020 immediately**, return it to HFD-540, 9201 Corporate Blvd, Room N243, Rockville, MD 20850 by US Mail.

Center for Drug Evaluation and Research
Division of Dermatologic and Dental
Drug Products, HFD-540
9201 Corporate Blvd
Building 2, 2nd Floor
Rockville, MD 20850

301-827-2020, fax 301-827-2091

FDA Fax Memo

Date: February 1, 2001

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

Information Request

Hi Jim,

The following information requests were identified during our fileability meeting.

CMC

1. The Sponsor should submit a section to the NDA titled, ——— *Drug Substance Forms and Their Relationship to Bioavailability.* This is described in the Guidance Document titled, Guideline for the Format and Content of the Chemistry, Manufacturing, and Controls Section of an Application. (This information request was discussed with Jim DeMartino and Cheryl LeRoy during telecons on January 23rd and 24th.)

Pharmacology/Toxicology

1. The Sponsor should submit the statistical data on diskettes for the mouse dermal carcinogenicy study, that was conducted with ASM dissolved in ethanol. (Request made in a telecon with Jim DeMartino January 30, 2001.

Biopharmaceutics

1. The Sponsor was requested to submit MS Word version of the reports of the PK studies # ASMW 204, 205, 202, 206, 0301, 0304, 0317, 106, 121, 122 and 124 during a January 24th telecon with Jim Demartino.

Clinical

1. The Sponsor needs to provide the exact volumes that the appendices are located in for each study.
2. The Sponsor should submit line listings of all the pivotal trials (B305, 307, 316) and of the large safety study (B317). Further, the Sponsor was asked to include in the submission the primary efficacy analysis broken down by investigator (at preNDA meeting).
3. The Sponsor was asked at the preNDA meeting to do the following and is again requested to do the same:
   a. Please include in the submission an index that would enable the reviewer to make the association between investigator's verbatim terminology used to describe an adverse event and the preferred term used for coding the adverse event in the submission's adverse event tables.
   b. Please generate a table showing all lab parameters for patients with SAEs and discontinuations.
   c. Please generate a section that shows other lab parameters for patients with one abnormal lab.
4. The Sponsor is requested to submit CRF's on paper for all patients who are excluded from per protocol analysis, who are lost to follow-up, or who are early discontinuations. Additional CRFs may be requested during the course of the review process.

Biostatistics

1. The Sponsor should submit electronic files for Patients Listings, Select Patient Listings, and US Archival Listings
2. Please provide the carcinogenicity data on diskette/CD, following the FDA guidance, for studies T-127/BS-530 and T-133/BS-733. Also provide a complete description of the statistical methodology and results of Survival and Turmorogenicity data analysis for Study T-127/BS-530 .

If you questions, please call.

Respectfully,
Millie

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, Drug Regulatory Affairs
59 Route 10
East Hanover, New Jersey 07936-1080

Dear Dr. DeMartino:

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

AMENDED 07-FEB-2002

We acknowledge receipt of your submissions dated February 15 and 23, March 8 and 15, April 30, May 21, 23, 24 and 29, June 1, 6, 7, 13 and 19, July 6 and 12, August 7, September 10, 11 and 12, October 8, 9 (2), 10, 11, 22, 29, and 30 (2) and November 1 and 28, December 10 and 13 (2) 2001.

This new drug application provides for the use of Elidel (pimecrolimus) Cream, 1%, for short-term and intermittent long-term therapy in the treatment of *mild to moderate* atopic dermatitis in non-immunocompromised patients 2 years of age and older, in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or intolerant of alternative, conventional therapies.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use in patients ages 2 and above as recommended in the agreed upon enclosed labeling text, submitted December 13, 2001. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 21-301." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your post marketing commitments specified in your submission dated December 13, 2001. These commitments, along with any completion dates agreed upon, are listed below.

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.

AMENDED 07-FEB-2002

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)

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81 (b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study correspondence."

AMENDED 07-FEB-2002

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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). We note that you have fulfilled the pediatric study requirement at this time.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

AMENDED 07-FEB-2002

Sincerely,

Jonca C. Bull, M.D.
Acting Director
Office of Drug Evaluation V, HFD 105
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

Elidel®
(pimecrolimus) Cream 1%

FOR DERMATOLOGIC USE ONLY
NOT FOR OPHTHALMIC USE

Rx only
Prescribing Information

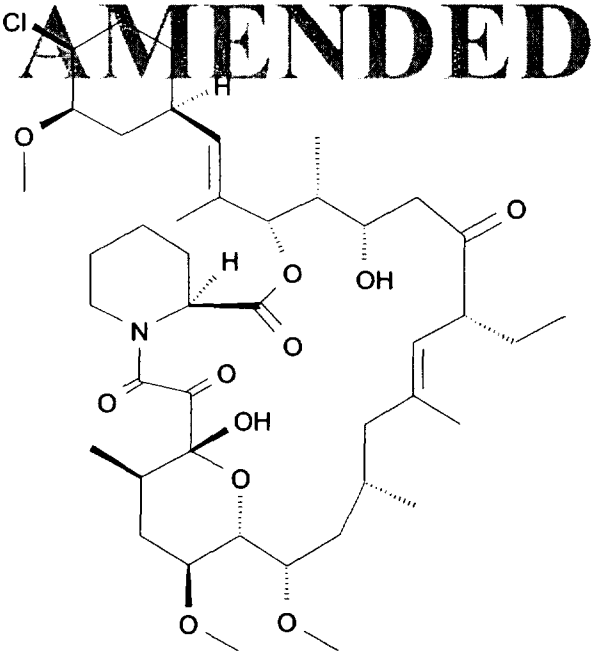
DESCRIPTION

Elidel® (pimecrolimus) Cream 1% contains the compound pimecrolimus, the 33-epi-chloro-derivative of the macrolactam ascomycin.

Chemically, pimecrolimus is (1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-2-{(1R,3R,4S)-4-chloro-3-methoxycyclohexyl}-1-methylvinyl]-17-ethyl-1,14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone.

The compound has the empirical formula $C_{43}H_{68}ClNO_{11}$ and the molecular weight of 810.47. The structural formula is:

AMENDED 07-FEB-2002



Pimecrolimus is a white to off-white fine crystalline powder. It is soluble in methanol and ethanol and insoluble in water.

Each gram of Elidel Cream 1% contains 10 mg of pimecrolimus in a whitish cream base of benzyl alcohol, cetyl alcohol, citric acid, mono- and di-glycerides, oleyl alcohol, propylene glycol, sodium cetostearyl sulphate, sodium hydroxide, stearyl alcohol, triglycerides, and water.

CLINICAL PHARMACOLOGY

Mechanism of Action/Pharmacodynamics

The mechanism of action of pimecrolimus in atopic dermatitis is not known. While the following have been observed, the clinical significance of these observations in atopic dermatitis is not known. It has been demonstrated that pimecrolimus binds with high affinity to macrophilin-12 (FKBP-12) and inhibits the calcium-dependent phosphatase, calcineurin. As a consequence, it inhibits T cell activation by blocking the transcription of early cytokines. In particular, pimecrolimus inhibits at nanomolar concentrations Interleukin-2 and interferon gamma (Th1-type) and Interleukin-4 and Interleukin-10 (Th2-type) cytokine synthesis in human T cells. In addition, pimecrolimus prevents the release of inflammatory cytokines and mediators from mast cells in vitro after stimulation by antigen/IgE.

Pharmacokinetics

Absorption

In adult patients being treated for atopic dermatitis (13-62% Body Surface Area (BSA) involvement) for periods up to a year, blood concentrations of pimecrolimus are routinely either at or below the limit of quantification of the assay (<0.5ng/ml). In those subjects with detectable blood levels they are routinely < 2ng/ml and show no sign of drug accumulation with time. Because of the low systemic absorption of pimecrolimus following topical application the calculation of standard pharmacokinetic measures such as AUC, Cmax, $T_{1/2}$, etc. cannot be reliably done.

Distribution

In vitro studies of the protein binding of pimecrolimus indicate that it is 74 – 87% bound to plasma proteins.

Metabolism

Following the administration of a single oral radiolabeled dose of pimecrolimus numerous circulating O-demethylation metabolites were seen. Studies with human liver microsomes indicate that pimecrolimus is metabolized in vitro by the CYP3A sub-family of metabolizing enzymes. No evidence of skin mediated drug metabolism was identified in vivo using the minipig or in vitro using stripped human skin.

Elimination

Based on the results of the aforementioned radiolabeled study, following a single oral dose of pimecrolimus ~81% of the administered radioactivity was recovered, primarily in the feces (78.4%) as metabolites. Less than 1% of the radioactivity found in the feces was due to unchanged pimecrolimus.

Special Populations

Pediatrics

The systemic exposure to pimecrolimus from Elidel 1% Cream was investigated in 26 pediatric patients with

atopic dermatitis (20-69% BSA involvement) between the ages of 2 to 14yrs. Following twice daily application for three weeks, blood concentrations of pimecrolimus were consistently low (< 3ng/ml), with the majority of the blood samples being below the limit of quantification (0.5ng/ml). However, the children (20 children out of total 23 children investigated) had at least one detectable blood level as compared to the adults (13 adults out of total 25 adults investigated) over a 3-week treatment period. Due to the low and erratic nature of the blood levels observed, no correlation could be made between amount of cream, degree of BSA involvement, and blood concentrations. In general, the blood concentrations measured in adult atopic dermatitis patients were comparable to those seen in the pediatric population.

In a second group of 22 pediatric patients aged 3 to 23 months with 10-92% BSA involvement, a higher proportion of detectable blood levels was seen ranging from 0.1 ng/mL to 2.6 ng/mL (limit of quantification 0.1 ng/mL). This increase in the absolute number of positive blood levels may be due to the larger surface area to body mass ratio seen in these younger subjects. In addition, a higher incidence of upper respiratory symptoms/infections was also seen relative to the older age group in the PK studies. At this time a causal relationship between these findings and ELIDEL use cannot be ruled out. Use of ELIDEL in this population is not recommended. (See **Pediatric Use Section**)

Renal Insufficiency

The effect of renal insufficiency on the pharmacokinetics of topically administered pimecrolimus has not been evaluated. Given the very low systemic exposure of pimecrolimus via the topical route, no change in dosing is required.

AMENDED 07-FEB-2002

Hepatic Insufficiency

The effect of hepatic insufficiency on the pharmacokinetics of topically administered pimecrolimus has not been evaluated. Given the very low systemic exposure of pimecrolimus via the topical route, no change in dosing is required.

CLINICAL STUDIES

Three randomized, double-blind, vehicle-controlled, multi-center, phase 3 studies were conducted in 1335 pediatric patients ages 3 months–17 years old to evaluate Elidel Cream for the treatment of mild to moderate atopic dermatitis. Two of the three trials support the use of Elidel Cream in patients 2 years and older with mild to moderate atopic dermatitis (See **Pediatric Use Section**). Three other trials provided additional data regarding the safety of Elidel cream in the treatment of atopic dermatitis. Two of these other trials were vehicle controlled with optional sequential use of a medium potency topical corticosteroid in pediatric patients and one trial was an active comparator trial in adult patients with atopic dermatitis (See **Pediatric Use and Adverse Events Sections**).

Two identical 6-week, randomized, vehicle-controlled, multi-center, phase 3 trials were conducted to evaluate Elidel® (pimecrolimus) Cream 1% for the treatment of mild to moderate atopic dermatitis. A total of 403 pediatric patients 2-17 years old were included in the studies. The male/female ratio was approximately 50% and 29% of the patients were African American. At study entry, 59% of patients had moderate disease and the mean body surface area (BSA) affected was 26%. About 75% of patients had atopic dermatitis affecting the face and/or neck region. In these studies, patients applied either Elidel Cream or vehicle cream twice daily to 5% to 96% of their BSA for up to 6 weeks. At endpoint, based on the physician's global evaluation of clinical response, 35% of patients treated with Elidel Cream were clear or almost clear of signs of atopic dermatitis compared to only 18% of vehicle-treated patients. More Elidel patients (57%) had mild or no pruritus at 6 weeks

compared to vehicle patients (34%). The improvement in pruritus occurred in conjunction with the improvement of the patients' atopic dermatitis.

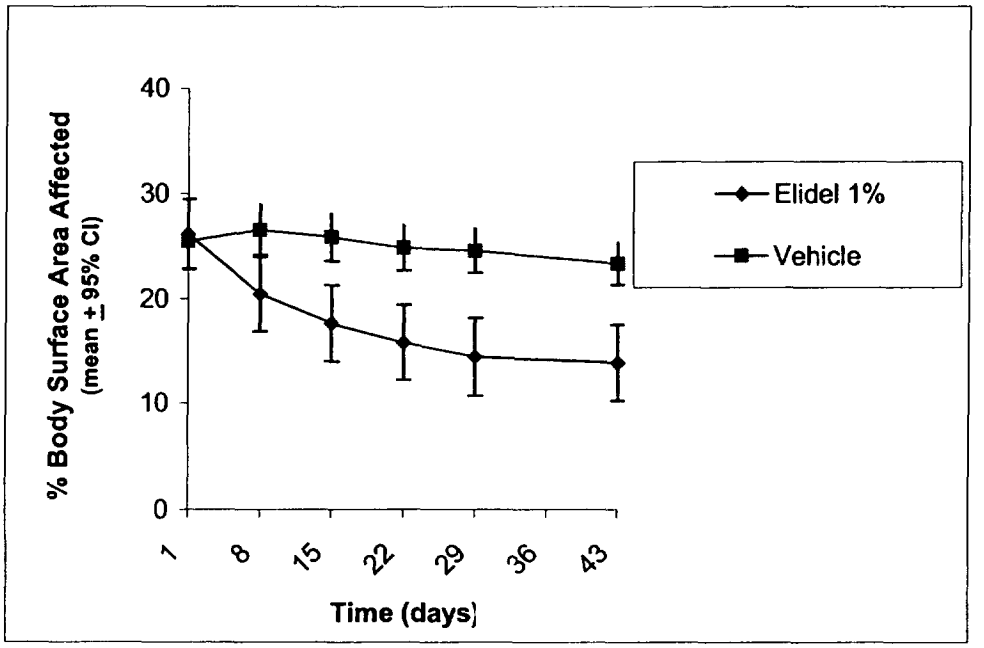
In these two 6-week studies of Elidel, the combined efficacy results at endpoint are as follows:

	% Patients	
	Elidel (N= 267)	Vehicle (N= 136)
Global Assessment		
Clear	28 (10%)	5 (4%)
Clear or Almost Clear	93 (35%)	25 (18%)
Clear to Mild Disease	180 (67%)	55 (40%)

In the two pediatric studies that independently support the use of Elidel Cream in mild to moderate atopic dermatitis, a significant treatment effect was seen by Day 15. Of the key signs of atopic dermatitis, erythema, infiltration/papulation, lichenification, and excoriations, erythema and infiltration/papulation were reduced at day 8 when compared to vehicle.

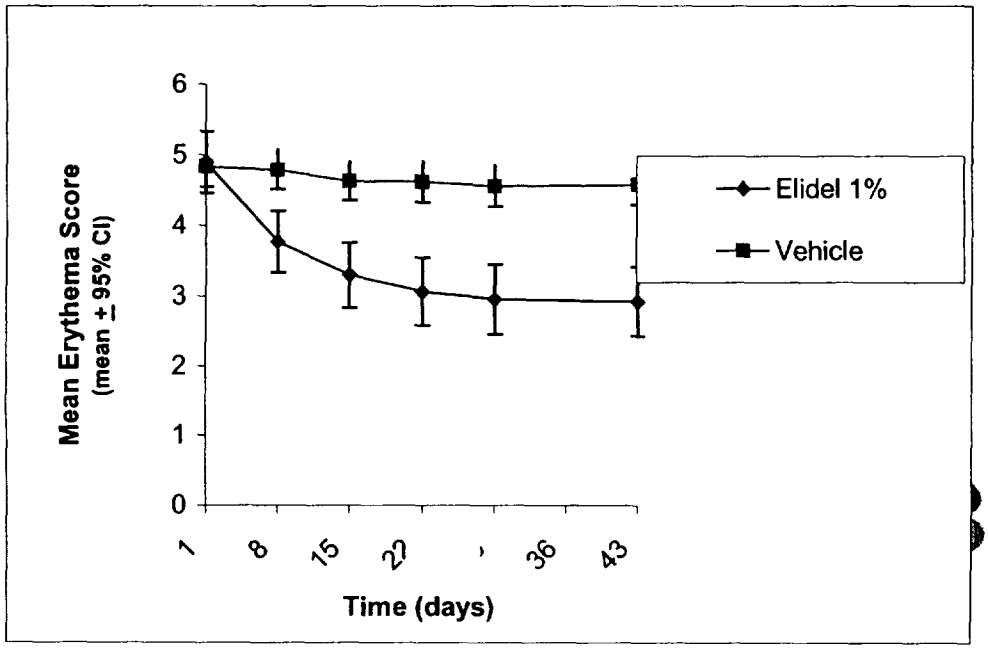
The following graph depicts the time course of improvement in the percent body surface area affected as a result of treatment with Elidel in 2 – 17 year olds.

Figure 1 Body Surface Area Over Time



The following graph shows the time course of improvement in erythema as a result of treatment with Elidel Cream in 2 – 17 year olds.

Figure 2 Mean Erythema Over Time



-2002

INDICATIONS AND USAGE

Elidel® (pimecrolimus) Cream 1% is indicated for short-term and intermittent long-term therapy in the treatment of *mild to moderate* atopic dermatitis in non-immunocompromised patients 2 years of age and older, in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or intolerant of alternative, conventional therapies. (See **DOSAGE AND ADMINISTRATION Section)**

CONTRAINDICATIONS

Elidel® (pimecrolimus) Cream 1% is contraindicated in individuals with a history of hypersensitivity to pimecrolimus or any of the components of the cream.

PRECAUTIONS

General

Elidel® (pimecrolimus) cream 1% should not be applied to areas of active cutaneous viral infections.

Studies have not evaluated the safety and efficacy of Elidel Cream in the treatment of clinically infected atopic dermatitis. Before commencing treatment with Elidel Cream, clinical infections at treatment sites should be cleared.

While patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi's varicelliform eruption), treatment with Elidel Cream may be associated with an increased risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum. In the presence of these skin infections, the balance of risks and benefits associated with Elidel cream use should be evaluated.

In clinical studies, 14 cases of lymphadenopathy (0.9%) were reported while using Elidel Cream. These cases of lymphadenopathy were usually related to infections and noted to resolve upon appropriate antibiotic therapy. Of these 14 cases, the majority had either a clear etiology or were known to resolve. Patients who receive Elidel Cream and who develop lymphadenopathy should have the etiology of their lymphadenopathy investigated. In the absence of a clear etiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, discontinuation of Elidel Cream should be considered. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.

In clinical studies, 15 cases of skin papilloma or warts (1%) were observed in patients using Elidel Cream. The youngest patient was age 2 and the oldest was age 12. In cases where there is worsening of skin papillomas or they do not respond to conventional therapy, discontinuation of Elidel Cream should be considered until complete resolution of the warts is achieved.

The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Despite the absence of observed phototoxicity in humans (See **ADVERSE REACTIONS Section**), Elidel Cream shortened the time to skin tumor formation in an animal photo-carcinogenicity study (see Carcinogenesis, Mutagenesis, Impairment of Fertility). Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure.

AMENDED 07-FEB-2002

The use of Elidel Cream in patients with Netherton's Syndrome is not recommended due to the potential for increased systemic absorption of pimecrolimus.

There are no data to support use of Elidel in immunocompromised patients.

The use of Elidel Cream may cause local symptoms such as skin burning. Localized symptoms are most common during the first few days of Elidel cream application and typically improve as the lesions of atopic dermatitis resolve. Most application site reactions lasted no more than 5 days, were mild to moderate in severity, and started within 1-5 days of treatment. (See **ADVERSE REACTIONS Section).**

Information for Patients

Patients using Elidel should receive the following information and instructions:

Patients should use Elidel Cream as directed by the physician. Elidel Cream is for external use on the skin only. As with any topical medication, patients or caregivers should wash hands after application if hands are not an area for treatment.

Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using Elidel Cream.

Patients should not use this medication for any disorder other than that for which it was prescribed.

Patients should report any signs or symptoms of adverse reactions to their physician.

Therapy should be discontinued after signs and symptoms of atopic dermatitis have resolved. Treatment with Elidel should be resumed at the first signs or symptoms of recurrence.

Use of Elidel may cause reactions at the site of application such as a mild to moderate feeling of warmth and/or sensation of burning. Patients should see a physician if an application site reaction is severe or persists for more than 1 week.

The patient should contact the physician if no improvement in the atopic dermatitis is seen following 6 weeks of treatment, or if at any time the condition worsens.

Drug Interactions
Potential interactions between Elidel and other drugs, including immunizations, have not been systematically evaluated. Due to the very low blood levels of pimecrolimus detected in some patients after topical application, systemic drug interactions are not expected, but cannot be ruled out. The concomitant administration of known CYP3A family of inhibitors in patients with widespread and/or erythrodermic disease should be done with caution. Some examples of such drugs are erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers and cimetidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 2-year rat dermal carcinogenicity study using Elidel Cream, a statistically significant increase in the incidence of follicular cell adenoma of the thyroid was noted in low, mid and high dose male animals compared to vehicle and saline control male animals. Follicular cell adenoma of the thyroid was noted in the dermal rat carcinogenicity study at the lowest dose of 2 mg/kg/day [0.2% pimecrolimus cream; 1.5X the Maximum Recommended Human Dose (MRHD) based on AUC comparisons]. No increase in the incidence of follicular cell adenoma of the thyroid was noted in the oral carcinogenicity study in male rats up to 10 mg/kg/day (66X MRHD based on AUC comparisons). However, oral studies may not reflect continuous exposure or the same metabolic profile as by the dermal route. In a mouse dermal carcinogenicity study using pimecrolimus in an ethanolic solution, no increase in incidence of neoplasms was observed in the skin or other organs up to the highest dose of 4 mg/kg/day (0.32% pimecrolimus in ethanol) 27X MRHD based on AUC comparisons. However, lymphoproliferative changes (including lymphoma) were noted in a 13 week repeat dose dermal toxicity study conducted in mice using pimecrolimus in an ethanolic solution at a dose of 25 mg/kg/day (47X MRHD based on AUC comparisons). No lymphoproliferative changes were noted in this study at a dose of 10 mg/kg/day (17X MRHD based on AUC comparison). However, the latency time to lymphoma formation was shortened to 8 weeks after dermal administration of pimecrolimus dissolved in ethanol at a dose of 100 mg/kg/day (179-217X MRHD based on AUC comparisons).

In a mouse oral (gavage) carcinogenicity study, a statistically significant increase in the incidence of lymphoma was noted in high dose male and female animals compared to vehicle control male and female animals. Lymphomas were noted in the oral mouse carcinogenicity at a dose of 45 mg/kg/day (258-340X MRHD based on AUC comparisons). No drug-related tumors were noted in the mouse oral carcinogenicity study at a dose of 15 mg/kg/day (60-133X MRHD based on AUC comparisons). In an oral (gavage) rat carcinogenicity study, a statistically significant increase in the incidence of benign thymoma was noted in 10 mg/kg/day pimecrolimus treated male and female animals compared to vehicle control treated male and female animals. In addition, a significant increase in the incidence of benign thymoma was noted in another oral (gavage) rat carcinogenicity study in 5 mg/kg/day pimecrolimus treated male animals compared to vehicle control treated male animals. No drug-related tumors were noted in the rat oral carcinogenicity study at a dose of 1 mg/kg/day male animals (1.1X MRHD based on AUC comparisons) and at a dose of 5 mg/kg/day for female animals (21X MRHD based on AUC comparisons).

In a 52 week dermal photo-carcinogenicity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing with concurrent exposure to UV radiation (40 weeks of treatment followed by 12 weeks of observation) with the Elidel Cream vehicle alone. No additional effect on tumor development beyond the vehicle effect was noted with the addition of the active ingredient, pimecrolimus, to the vehicle cream.

A battery of in vitro genotoxicity texts, including Ames assay, mouse lymphoma L5178Y assay, and chromosome aberration test in V79 Chinese hamster cells and an in vivo mouse micronucleus test revealed no evidence for a mutagenic or clastogenic potential for the drug.

An oral fertility and embryofetal developmental study in rats revealed estrus cycle disturbances, post-implantation loss and reduction in litter size at the 45 mg/kg/day dose (38X MRHD based on AUC comparisons). No effect on fertility in female rats was noted at 10 mg/kg/day (12X MRHD based on AUC comparisons). No effect on fertility in male rats was noted at 45 mg/kg/day (23X MRHD based on AUC comparisons), which was the highest dose tested in this study.

Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies of topically administered pimecrolimus in pregnant women. The experience with Elidel cream when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy.

In dermal embryofetal developmental studies, no maternal or fetal toxicity was observed up to the highest practicable doses tested, 10 mg/kg/day (1% pimecrolimus cream) in rats (0.14X MRHD based on body surface area) and 10 mg/kg/day (1% pimecrolimus cream) in rabbits (0.65X MRHD based on AUC comparisons). The 1% pimecrolimus cream was administered topically for 6 hours/day during the period of organogenesis in rats and rabbits (gestational days 6-21 in rats and gestational days 6-20 in rabbits).

A combined oral fertility and embryofetal developmental study was conducted in rats and an oral embryofetal developmental study was conducted in rabbits. Pimecrolimus was administered during the period of organogenesis (2 weeks prior to mating until gestational day 16 in rats, gestational days 6-18 in rabbits) up to dose levels of 45 mg/kg/day in rats and 20 mg/kg/day in rabbits. In the absence of maternal toxicity, indicators of embryofetal toxicity (post-implantation loss and reduction in litter size) were noted at 45 mg/kg/day (38X MRHD based on AUC comparisons) in the oral fertility and embryofetal developmental study conducted in rats. No malformations in the fetuses were noted at 45 mg/kg/day (38X MRHD based on AUC comparisons) in this study. No maternal toxicity, embryotoxicity or teratogenicity were noted in the oral rabbit embryofetal developmental toxicity study at 20 mg/kg/day (3.9X MRHD based on AUC comparisons), which was the highest dose tested in this study.

An oral peri- and post-natal developmental study was conducted in rats. Pimecrolimus was administered from gestational day 6 through lactational day 21 up to a dose level of 40 mg/kg/day. Only 2 of 22 females delivered live pups at the highest dose of 40 mg/kg. Postnatal survival, development of the F1 generation, their subsequent maturation and fertility were not affected at 10 mg/kg/day (12X MRHD based on AUC comparisons), the highest dose evaluated in this study.

Pimecrolimus was transferred across the placenta in oral rat and rabbit embryofetal developmental studies.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed during pregnancy.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from pimecrolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Elidel Cream may be used in pediatric patients 2 years of age and older. Three phase 3 pediatric studies were conducted involving 1114 patients 2-17 years of age. Two studies were 6-week randomized vehicle-controlled studies with a 20 week open-label phase and one was a vehicle- controlled long-term (up to 1 year) safety study with the option for sequential topical corticosteroid use. Of these patients 542 (49%) were 2 to 6 years of age. In the short-term studies, 11% of Elidel patients did not complete these studies and 1.5% of Elidel patients discontinued due to adverse events. In the one-year study, 32% of Elidel patients did not complete this study and 3% of Elidel patients discontinued due to adverse events. Most discontinuations were due to unsatisfactory therapeutic effect.

The most common local adverse event in the short-term studies of Elidel Cream in pediatric patients ages 2-17 was application site burning (10% vs. 13% vehicle); the incidence in the long-term study was 9% Elidel vs. 7% vehicle (see ADVERSE REACTIONS). Adverse events that were more frequent (>5%) in patients treated with Elidel cream compared to vehicle were headache (14% vs. 9%) in the short-term trial. Nasopharyngitis (26% vs. 21%), influenza (13% vs. 4%), pharyngitis (8% vs. 3%), viral infection (7% vs. 1%), pyrexia (13% vs. 5%), cough (16% vs. 11%), and headache (25% vs. 16%) were increased over vehicle in the 1-year safety study. (see ADVERSE REACTIONS). In 843 patients ages 2-17 years treated with Elidel Cream, 9 (0.8%) developed eczema herpeticum (5 on Elidel Cream alone and 4 on Elidel Cream used in sequence with corticosteroids). In 211 patients on vehicle alone, there were no cases of eczema herpeticum. The majority of adverse events were mild to moderate in severity.

Elidel Cream is not recommended for use in pediatric patients below the age of 2 years. Two phase 3 studies were conducted involving 436 infants age 3 months – 23 months. One 6-week randomized vehicle-controlled study with a 20-week open-label phase and one long term safety study were conducted. In the 6-week study, 11% of Elidel and 48% of vehicle patients did not complete this study; no patient in either group discontinued due to adverse events. Infants on Elidel Cream had an increased incidence of some adverse events compared to vehicle. In the 6-week vehicle-controlled study these adverse events included pyrexia (32% vs. 13% vehicle), URI (24% vs. 14%), nasopharyngitis (15% vs. 8%), gastroenteritis (7% vs. 3%), otitis media (4% vs. 0%), and diarrhea (8% vs. 0%). In the open-label phase of the study, for infants who switched to Elidel Cream from vehicle, the incidence of the above-cited adverse events approached or equaled the incidence of those patients who remained on Elidel Cream. In the 6 month safety data, 16% of Elidel and 35% of vehicle patients discontinued early and 1.5% of Elidel and 0% of vehicle patients discontinued due to adverse events. Infants on Elidel Cream had a greater incidence of some adverse events as compared to vehicle. These included pyrexia (30% vs. 20%), URI (21% vs. 17%), cough (15% vs. 9%), hypersensitivity (8% vs. 2%), teething (27% vs. 22%), vomiting (9% vs. 4%), rhinitis (13% vs. 9%), viral rash (4% vs. 0%), rhinorrhea (4% vs. 0%), and wheezing (4% vs. 0%).

The effects of Elidel Cream on the developing immune system in infants are unknown.

Geriatric Use

Nine (9) patients ≥ 65 years old received Elidel cream in phase 3 studies. Clinical studies of Elidel did not include sufficient numbers of patients aged 65 and over to assess efficacy and safety.

ADVERSE REACTIONS

In human dermal safety studies, Elidel did not induce contact sensitization, phototoxicity, or photoallergy, nor did it show any cumulative irritation.

In a one year safety study in pediatric patients age 2-17 years old involving sequential use of Elidel Cream and a topical corticosteroid, 43% of Elidel patients and 68% of vehicle patients used corticosteroids during the study.

Corticosteroids were used for more than 7 days by 34% of Elidel patients and 54% of vehicle patients. An increased incidence of impetigo, skin infection, superinfection (infected atopic dermatitis), rhinitis, and urticaria were found in the patients that had used Elidel Cream and topical corticosteroid sequentially as compared to Elidel Cream alone

In 3 randomized, double-blind vehicle-controlled pediatric studies and one active controlled adult study, 843 and 328 patients respectively, were treated with Elidel® (pimecrolimus) Cream 1%. In these clinical trials, 48 (4%) of the 1171 Elidel patients and 13 (3%) of 408 vehicle-treated patients discontinued therapy due to adverse events. Discontinuations for AEs were primarily due to application site reactions, and cutaneous infections. The most common application site reaction was application site burning, which occurred in 8 - 26% of patients treated with Elidel Cream.

The table below depicts the incidence of adverse events pooled across the 2 identically designed 6 week studies with their open label extensions and the 1 year safety study for pediatric patients ages 2-17. Data from the adult active control study is also included in this table. Adverse events are listed regardless of relationship to study drug.

Treatment Emergent Adverse Events (≥ 1%) in Elidel Treatment Groups

	Pediatric Patients* Vehicle-Controlled (6 weeks)		Pediatric Patients* Open-Label (20 weeks)	Pediatric Patients* Vehicle-Controlled (1 year)		Adult Active Comparator (1 year)
	Elidel Cream (N=267) N (%)	Vehicle (N=136) N (%)	Elidel Cream (N=333) N (%)	Elidel Cream (N=272) N (%)	Vehicle (N=75) N (%)	Elidel Cream (N=328) N (%)
At least 1 AE	182 (68.2%)	97 (71.3%)	240 (72.0%)	230 (84.6%)	56 (74.7%)	256 (78.0%)
Infections and infestations						
Upper Respiratory Tract Infection NOS	38 (14.2%)	18 (13.2%)	65 (19.4%)	13 (4.8%)	6 (8.0%)	14 (4.3%)
Nasopharyngitis	27 (10.1%)	10 (7.4%)	32 (19.6%)	72 (26.5%)	16 (21.3%)	25 (7.6%)
Skin Infection NOS	8 (3.0%)	9 (5.1%)	18 (5.4%)	6 (2.2%)	3 (4.0%)	21 (6.4%)
Influenza	8 (3.0%)	1 (0.7%)	22 (6.6%)	36 (13.2%)	3 (4.0%)	32 (9.8%)
Ear Infection NOS	6 (2.2%)	2 (1.5%)	19 (5.7%)	9 (3.3%)	1 (1.3%)	2 (0.6%)
Otitis Media	6 (2.2%)	1 (0.7%)	10 (3.0%)	8 (2.9%)	4 (5.3%)	2 (0.6%)
Impetigo	5 (1.9%)	3 (2.2%)	12 (3.6%)	11 (4.0%)	4 (5.3%)	8 (2.4%)
Bacterial Infection	4 (1.5%)	3 (2.2%)	4 (1.2%)	3 (1.1%)	0	6 (1.8%)
Folliculitis	3 (1.1%)	1 (0.7%)	3 (0.9%)	6 (2.2%)	3 (4.0%)	20 (6.1%)
Sinusitis	3 (1.1%)	1 (0.7%)	11 (3.3%)	6 (2.2%)	1 (1.3%)	2 (0.6%)
Pneumonia NOS	3 (1.1%)	1 (0.7%)	5 (1.5%)	0	1 (1.3%)	1 (0.3%)
Pharyngitis NOS	2 (0.7%)	2 (1.5%)	3 (0.9%)	22 (8.1%)	2 (2.7%)	3 (0.9%)
Pharyngitis Streptococcal	2 (0.7%)	2 (1.5%)	10 (3.0%)	0	<1%	0
Molluscum Contagiosum	2 (0.7%)	0	4 (1.2%)	5 (1.8%)	0	0
Staphylococcal Infection	1 (0.4%)	5 (3.7%)	7 (2.1%)	0	<1%	3 (0.9%)
Bronchitis NOS	1 (0.4%)	3 (2.2%)	4 (1.2%)	29 (10.7%)	6 (8.0%)	8 (2.4%)
Herpes Simplex	1 (0.4%)	0	4 (1.2%)	9 (3.3%)	2 (2.7%)	13 (4.0%)
Tonsillitis NOS	1 (0.4%)	0	3 (0.9%)	17 (6.3%)	0	2 (0.6%)
Viral Infection NOS	2 (0.7%)	1 (0.7%)	1 (0.3%)	18 (6.6%)	1 (1.3%)	0
Gastroenteritis NOS	0	3 (2.2%)	2 (0.6%)	20 (7.4%)	2 (2.7%)	6 (1.8%)
Chickenpox	2 (0.7%)	0	3 (0.9%)	8 (2.9%)	3 (4.0%)	1 (0.3%)
Skin Papilloma	1 (0.4%)	0	2 (0.6%)	9 (3.3%)	< 1%	0
Tonsillitis Acute NOS	0	0	0	7 (2.6%)	0	0
Upper Respiratory Tract Infection Viral NOS	1 (0.4%)	0	3 (0.9%)	4 (1.5%)	0	1 (0.3%)
Herpes Simplex Dermatitis	0	0	1 (0.3%)	4 (1.5%)	0	2 (0.6%)
Bronchitis Acute NOS	0	0	0	4 (1.5%)	0	0
Eye Infection NOS	0	0	0	3 (1.1%)	<1%	1 (0.3%)
General disorders and administration site conditions						
Application Site Burning	28 (10.4%)	17 (12.5%)	5 (1.5%)	23 (8.5%)	5 (6.7%)	85 (25.9%)

	Pediatric Patients* Vehicle-Controlled (6 weeks)		Pediatric Patients* Open-Label (20 weeks)	Pediatric Patients* Vehicle-Controlled (1-year)		Adult Active Comparator (1 year)
	Elidel Cream (N=267) N (%)	Vehicle (N=136) N (%)	Elidel Cream (N=335) N (%)	Elidel Cream (N=272) N (%)	Vehicle (N=75) N (%)	Elidel Cream (N=328) N (%)
Pyrexia	20 (7.5%)	12 (8.8%)	41 (12.2%)	34 (12.5%)	4 (5.3%)	4 (1.2%)
Application Site Reaction NOS	8 (3.0%)	7 (5.1%)	7 (2.1%)	9 (3.3%)	2 (2.7%)	48 (14.6%)
Application Site Irritation	8 (3.0%)	8 (5.9%)	3 (0.9%)	5 (1.1%)	3 (4.0%)	21 (6.4%)
Influenza Like Illness	1 (0.4%)	0	2 (0.6%)	5 (1.8%)	2 (2.7%)	6 (1.8%)
Application Site Erythema	1 (0.4%)	0	0	6 (2.2%)	0	7 (2.1%)
Application Site Pruritus	3 (1.1%)	2 (1.5%)	2 (0.6%)	5 (1.8%)	0	18 (5.5%)
Respiratory, thoracic and mediastinal disorders						
Cough	31 (11.6%)	11 (8.1%)	31 (9.3%)	43 (15.8%)	8 (10.7%)	8 (2.4%)
Nasal Congestion	7 (2.6%)	2 (1.5%)	6 (1.8%)	4 (1.5%)	1 (1.3%)	2 (0.6%)
Rhinorrhea	5 (1.9%)	1 (0.7%)	3 (0.9%)	1 (0.4%)	1 (1.3%)	0
Asthma Aggravated	4 (1.5%)	3 (2.2%)	13 (3.9%)	3 (1.1%)	1 (1.3%)	0
Sinus Congestion	3 (1.1%)	1 (0.7%)	2 (0.6%)	< 1%	< 1%	3 (0.9%)
Rhinitis	1 (0.4%)	0	5 (1.5%)	12 (4.4%)	5 (6.7%)	7 (2.1%)
Wheezing	1 (0.4%)	1 (0.7%)	4 (1.2%)	2 (0.7%)	< 1%	0
Asthma NOS	2 (0.7%)	1 (0.7%)	11 (3.3%)	10 (3.7%)	2 (2.7%)	8 (2.4%)
Epistaxis	0	1 (0.7%)	0	9 (3.3%)	1 (1.3%)	1 (0.3%)
Dyspnea NOS	0	0	0	5 (1.8%)	1 (1.3%)	2 (0.6%)
Gastrointestinal disorders						
Abdominal Pain Upper	11 (4.1%)	6 (4.4%)	10 (3.0%)	15 (5.5%)	5 (6.7%)	1 (0.3%)
Sore Throat	9 (3.4%)	5 (3.7%)	15 (5.4%)	22 (8.1%)	4 (5.3%)	12 (3.7%)
Vomiting NOS	8 (3.0%)	6 (4.4%)	14 (4.2%)	18 (6.6%)	6 (8.0%)	2 (0.6%)
Diarrhea NOS	3 (1.1%)	1 (0.7%)	2 (0.6%)	18 (6.6%)	4 (5.3%)	7 (2.1%)
Nausea	1 (0.4%)	3 (2.2%)	4 (1.2%)	11 (4.0%)	5 (6.7%)	6 (1.8%)
Abdominal Pain NOS	1 (0.4%)	1 (0.7%)	5 (1.5%)	12 (4.4%)	3 (4.0%)	1 (0.3%)
Toothache	1 (0.4%)	1 (0.7%)	2 (0.6%)	7 (2.6%)	1 (1.3%)	2 (0.6%)
Constipation	1 (0.4%)	0	2 (0.6%)	10 (3.7%)	< 1%	0
Loose Stools	0	1 (0.7%)	4 (1.2%)	< 1%	< 1%	0
Reproductive System and Breast Disorders						
Dysmenorrhea	3 (1.1%)	0	5 (1.5%)	3 (1.1%)	1 (1.3%)	4 (1.2%)
Eye Disorders						
Conjunctivitis NEC	2 (0.7%)	1 (0.7%)	7 (2.1%)	6 (2.2%)	3 (4.0%)	10 (3.0%)
Skin & Subcutaneous Tissue Disorders						
Urticaria	3 (1.1%)	0	1 (0.3%)	1 (1.5%)	< 1%	3 (0.9%)
Acne NOS	0	1 (0.7%)	1 (0.3%)	4 (1.5%)	<1%	6 (1.8%)
Immune System Disorders						
Hypersensitivity NOS	11 (4.1%)	6 (4.4%)	16 (4.8%)	14 (5.1%)	1 (1.3%)	11 (3.4%)
Injury and poisoning						
Accident NOS	3 (1.1%)	1 (0.7%)	1 (0.3%)	<1 %	1 (1.3%)	0
Laceration	2 (0.9%)	1 (0.7%)	5 (1.5%)	< 1%	< 1%	0
Musculoskeletal, Connective Tissue and Bone Disorders						
Back Pain	1 (0.4%)	2 (1.5%)	1 (0.3%)	< 1%	0	6 (1.8%)
Arthralgias	0	0	1 (0.3%)	3 (1.1%)	1 (1.3%)	5 (1.5%)
Ear and Labyrinth Disorders						
Earache	2 (0.7%)	1 (0.7%)	0	8 (2.7%)	2 (2.7%)	0
Nervous system disorders						
Headache	37 (13.9%)	12 (8.8%)	38 (11.3%)	69 (25.4%)	12 (16.0%)	23 (7.0%)

ages 2-17 years

OVERDOSAGE

There has been no experience of overdose with Elidel® (pimecrolimus) cream 1%. No incidents of accidental ingestion have been reported. If oral ingestion occurs, medical advice should be sought.

DOSAGE AND ADMINISTRATION

Apply a thin layer of Elidel® (pimecrolimus) Cream 1% to the affected skin twice daily and rub in gently and completely. Elidel may be used on all skin surfaces, including the head, neck, and intertriginous areas.

Elidel should be used twice daily for as long as signs and symptoms persist. Treatment should be discontinued if resolution of disease occurs. If symptoms persist beyond 6 weeks, the patient should be re-evaluated.

The safety of Elidel Cream under occlusion, which may promote systemic exposure, has not been evaluated. **Elidel Cream should not be used with occlusive dressings.**

HOW SUPPLIED

Elidel Cream is available in tubes of 15 grams, 30 grams, and 100 grams.

15 gram tube	NDC 0078-0375-40
30 gram tube	NDC 0078-0375-46
100 gram tube	NDC 0078-0375-63

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). Do not freeze.

AMENDED 07-FEB-2002

Rx Only

Manufactured by

Novartis Pharma GmbH

Wehr/Baden, Germany

Distributed by

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

Date (month/year)

Code #

APPEARS THIS WAY
ON ORIGINAL

Patient Information

Elidel™ Cream, 1%
(pimecrolimus cream)

Read this important information before you start using ELIDEL [EL'-ee-del] Cream and each time you refill your prescription. There may be new information. This summary is not meant to take the place of your doctor's advice.

What is ELIDEL?
ELIDEL is a prescription medicine you put on your skin (topical) to treat atopic dermatitis, also known as eczema. Elidel is for use on the skin *only*. ELIDEL is for adults and children age 2 years and older. You can use ELIDEL for short or intermittent long periods of treatment. Intermittent means starting and stopping repeatedly, as directed by your doctor. You can use it on all affected areas of your skin, including your face and neck.

AMENDED 07-FEB-2002

Who should not use ELIDEL?

- If you are pregnant or a nursing mother, you should use ELIDEL only if your doctor determines that it is clearly necessary. It is not known if the medicine in ELIDEL will pass through your milk to the baby.
- If you have a skin condition called Netherton's syndrome, ask your doctor before you start using ELIDEL.
- If you are allergic to ELIDEL or any of its ingredients. The active ingredient is pimecrolimus. If you need to know the inactive ingredients, ask your doctor or pharmacist.
- If you think you have a viral infection of your skin, like chicken pox or herpes, do not apply ELIDEL on these areas. Check with your doctor about what to do.

Before you start using ELIDEL, tell your doctor if you are:

- using **any** other prescription medicines, non-prescription (over-the-counter) medicines, supplements or herbal medicines. Some medicines should be used carefully if you use ELIDEL.
- receiving any form of light therapy (phototherapy, UVA or UVB) on your skin
- using any other type of skin product.
- pregnant or planning to become pregnant. ELIDEL may not be right for you.

How should I use ELIDEL?

Use ELIDEL only to treat eczema that has been diagnosed by a doctor.

Wash your hands before using ELIDEL.

Use ELIDEL *only* on your skin. Apply a thin layer of ELIDEL to the affected skin twice daily as directed by your doctor. You can apply ELIDEL cream on affected areas on all skin surfaces, including your face, head, and neck. Avoid contact with your eyes.

You can use moisturizers with Elidel. Because the skin of patients with eczema can be very dry, you should discuss good skin care practices with your doctor to keep your skin healthy and moisturized. If you use moisturizers, apply them after ELIDEL.

If you are a caregiver applying ELIDEL Cream to a patient, or if you are a patient who is **not** treating your hands, wash your hands with soap and water after applying ELIDEL. This should remove any cream left on the hands.

Do **not** cover the skin being treated with bandages, dressings or wraps. However, you can wear normal clothing.

Do **not** bathe, shower or swim right after applying ELIDEL. This could wash off the cream.

Do **not** use this medication for any disorder other than that for which it was prescribed. Do **not** use ELIDEL in the eyes. Do **not** swallow ELIDEL.

If your condition gets worse at any time or you see no improvement after 6 weeks of treatment, contact your doctor.

Stop using ELIDEL after the signs and symptoms of eczema disappear.

What should I avoid while using ELIDEL?

Avoid sunlight and sun lamps, tanning beds, and treatment with UVA or UVB light. If you need to be outdoors after applying ELIDEL, wear loose fitting clothing that protects the treated area from the sun. In addition, ask your doctor what other type of protection from the sun you should use.
Check with your doctor or pharmacist before you

- start taking any new medicines while using ELIDEL.
- start using any other ointment, lotions, or creams on your skin

What are the possible side effects of Elidel?

The most common side effect at the site of application is burning or a feeling of warmth. The burning feeling is usually mild or moderate, occurring in the first 5 days of treatment, and the burning usually clears up in a few days. See your doctor if an application site reaction is severe or persists for more than 1 week.

Other common side effects include headache, and with long-term intermittent use, nasopharyngitis (common cold/stuffy nose), influenza, pharyngitis (sore throat), fever, viral infection, and cough. Some people may get herpes skin infections (like cold sores, chicken pox, or shingles), warts, or swollen lymph nodes (glands).

See your doctor if side effects continue or become a problem.

How Should I Store ELIDEL?

Store ELIDEL at room temperature (59° to 86°F). Do not freeze. For instance, never leave ELIDEL in your car in cold or hot weather. Make sure the cap on the tube is tightly closed. Keep ELIDEL out of the reach of children.

General Advice about ELIDEL
Do not use ELIDEL for a condition for which it was not prescribed. If you have any concerns about ELIDEL, ask your doctor. Your doctor or pharmacist can give you information about ELIDEL that was written for health care professionals. For more information, you can also visit the Novartis Internet site at www.elidel.com or call the ELIDEL Help Line at877-4 ELIDEL (877-435-4335).

Manufactured by

Novartis Pharma GmbH

Wehr/Baden, Germany

Distributed by

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

AMENDED 07-FEB-2002

Date (month/year)

Code #

APPEARS THIS WAY
ON ORIGINAL

AMENDED 07-FEB-2002