CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-302

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number:	21-302
Review number:	3
Sequence number/date/type of submission:	N-000-BP/9-14-01/Response to request for information
Information to sponsor: Yes ( ) No (X)	
Sponsor and/or agent:	Novartis Pharmaceuticals Corporation 59 Route 10 East Hanover, New Jersey 07936 (973) 781-7548
Manufacturer for drug substance :	Novartis Pharma AG Lichtstrasse 35 CH-4056 Basle, Switzerland

Reviewer name:	Barbara Hill
Division name:	Dermatologic and Dental Drug Products
HFD #:	HFD-540
Review completion date:	11-8-01

Drug:

Trade name:	Elidel® cream 1%
Generic name (list alphabetically):	Pimecrolimus
Code name:	ASM 981 Cream, 1%
Chemical name:	(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
CAS registry number:	137071-32-0
Mole file number:	N/A
Molecular formula/molecular weight:	810.47 / $C_{43}H_{68}ClNO_{11}$

UV Absorption: λ_{max} (~ 200 µg/ml in methanol or ethanol): — nm (ϵ = —).
Note: Only an absorption spectra for the active, ASM 981, has been provided for ASM 981 cream. The sponsor has provided no information on UVA/B or visible absorption for the inactive ingredients in the drug product.

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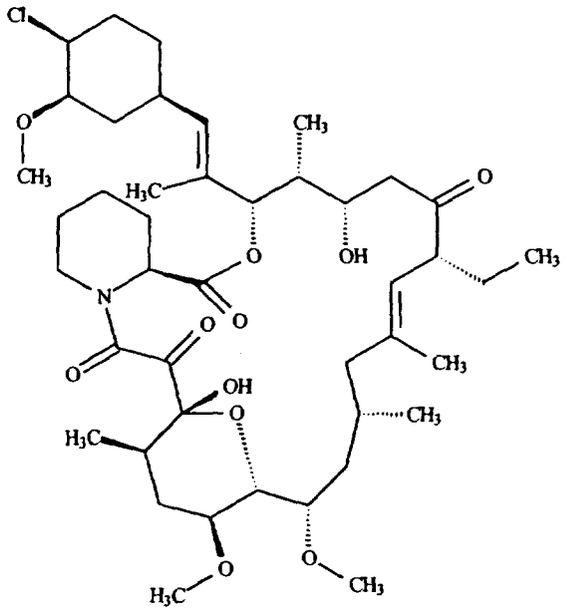
Structure:



Relevant INDs/NDAs/DMFs:

1) IND —— 1% ASM 981 cream, Atopic Dermatitis; HFD-540)
2) IND [redacted]
3) IND
4) IND

Drug class: Anti-inflammatory, immunosuppresant

Indication: Atopic Dermatitis

Clinical formulation:

The composition of the 1% ASM 981 cream (the final clinical formulation) is provided in the following table:

Ingredient	Amount per gram of Drug Product (mg)	Function
ASM 981	10.0	Drug Substance
Sodium Hydroxide		
Citric acid		
Benzyl alcohol		
Sodium cetostearyl sulphate		
Cetyl alcohol		
Stearyl alcohol		
Propylene glycol		
Oleyl alcohol		
Triglycerides,		
Water		

Route of administration: Topical dermal

Proposed use: Elidel® cream 1% is indicated [redacted] Elidel® cream 1% is to be applied to the affected area twice daily.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Introduction and drug history:

An Executive Carcinogenicity Assessment Committee (Exec CAC) meeting was conducted for Elidel on 6/19/01. The Exec CAC had three additional requests for information concerning the results of the dermal mouse and dermal rat carcinogenicity studies. These informational requests were relayed to the sponsor on 7-10-01 via fax. The current submission is a response to the informational requests. The informational requests are reproduced below.

1) It is requested that the sponsor clarify the source of the metastatic carcinoma noted in the thymus of one high dose male in the mouse dermal carcinogenicity study.

2) It is requested that the sponsor 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) It is requested that the sponsor 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.

A discussion of the adequacy of the response to each informational request is provided in the "Carcinogenicity" section of this review.

Executive Summary

I. Recommendations

A. Recommendation on Approvability

It is recommended that NDA 21-302 be approvable from a pharmacology/toxicology perspective provided that the recommended changes in the label discussed in the "Detailed Conclusions and Recommendations" section of this review are incorporated into the label.

B. Recommendation for Nonclinical Studies – None at this time

C. Recommendations on Labeling

It is recommended that the neoplastic finding noted in the dermal rat carcinogenicity study be included in the labeling for Elidel cream. Details concerning the exact wording for recommendation in the label are located in the "Detailed Conclusions and Recommendations" section of this review.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings

A significant increase in the incidence of follicular cell adenoma of the thyroid gland was noted in all treated male rat groups compared to control rats in the dermal rat carcinogenicity study.

B. Pharmacologic Activity

Elidel is an immunosuppressive agent.

C. Nonclinical Safety Issues Relevant to Clinical Use

In addition to the previous findings of lymphoma in the oral mouse carcinogenicity study and thymoma in the oral rat carcinogenicity study conducted for Elidel (details provided in the pharmacology/toxicology review of the original NDA), the following nonclinical finding is relevant to clinical use.

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].

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:

NDA: 21-302 (000)
HFD-340
HFD-540/DIV FILES
HFD-540/TOX/JACOBS
HFD-540/PHARM/HILL
HFD-540/MO/COOK
HFD-540/CHEM/PAPPAS
HFD-540/PM/WRIGHT

Concurrence Only:
HFD-540/DivDir/JWILKIN

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TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

No nonclinical pharmacology studies were included in this submission.

II. SAFETY PHARMACOLOGY:

No nonclinical safety pharmacology studies were included in this submission.

III. PHARMACOKINETICS/TOXICOKINETICS:

No nonclinical pharmacokinetics/toxicokinetics studies were included in this submission.

IV. GENERAL TOXICOLOGY:

No nonclinical general toxicology studies were included in this submission.

V. GENETIC TOXICOLOGY:

No nonclinical genetic toxicology studies were included in this submission.

VI. CARCINOGENICITY:

No nonclinical carcinogenicity studies were included in this submission. However, the sponsor did include responses to the Exec CAC informational requests. Each informational request will be reproduced below, followed by the sponsor's response and then the reviewer's comments.

Informational Request #1

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

Sponsor's Response to Informational Request #1

The primary focus was lungs and bronchi.

Reviewer's Comments

This is an adequate response. It is probable that the metastatic carcinoma noted in the thymus of one high dose male in the mouse dermal carcinogenicity study was not a signal for carcinogenicity in this study.

Informational Request #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.

Sponsor's Response to Informational Request #2

Complete SAS data for all dose groups in the dermal carcinogenicity study are provided. The data files are in compliance with the guidelines for submitting electronic data.

Two amendments to the original study report are provided. Amendment 1 (5 pages) documents the sponsor's request to the contract laboratory to examine the thymus and thyroid/parathyroid glands from animals of the low- and mid-dose groups. Amendment 2 is the fully amended study report.

This incidence of follicular adenomas and follicular cell carcinomas is within the historical control range.

Reviewer's Comments

Detailed reviewer comments for this informational request are contained in the Reviewer's comments for informational request #3. This allows for a combined discussion of the comparison of noted incidence rates for various tumor types in ASM 981 treated rats versus historical control incidence rates in Wistar rats.

No agency statistical re-analysis was performed of the data for the information included in this submission. [ ] the sponsor conducted a statistical evaluation of the new data. Even though the sponsor's analysis may not follow exactly the agency's method for analysis of carcinogenicity study data, it appears that the sponsor performed an adequate statistical assessment of the data. In addition, the data included in this submission lends itself to evaluation by visual examination and comparison to historical control incidence rate data. Therefore, no formal agency statistical evaluation of the new carcinogenicity incidence rates in the thyroid and thymus for the low and mid dose groups was performed for this review.

Informational Request #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.

Sponsor's Response to Informational Request #3

The historical control data from the laboratory that conducted the rat dermal carcinogenicity study [redacted] were submitted to this NDA on March 13, 2001 as part of a request for information (pages 14 and 15). To facilitate the review, this relevant information from that submission is provided.

Reviewer's Comments

This submission contained the historical control data on neoplastic findings in Wistar rats from 2 year bioassays conducted by [redacted] between 1982 – 1996. Thirty-six studies were conducted during that time period. Only one of the studies was a dermal carcinogenicity study. One of the studies was an i.m. study and one of the studies was an s.c. study. The remainder of the studies were feed studies.

The contract lab's historical incidence rate for C-cell adenoma, follicular cell adenoma, C-cell carcinoma and follicular cell carcinoma of the thyroid gland in Wistar rats is provided in the following table.

Historical Thyroid Tumor Incidence Rates in Wistar Rats

Thyroid Tumor Type	Male		Female	
	Mean ± SD (%)	Range (%)	Mean ± SD (%)	Range (%)
C-cell adenoma	10.0 ± 7.3	0.0 – 25.0	11.0 ± 6.3	0.0 – 27.1
Follicular cell adenoma	3.2 ± 3.2	0.0 – 14.3	2.0 ± 1.8	0.0 – 8.5
C-cell carcinoma	1.4 ± 2.2	0.0 – 9.4	0.3 ± 0.7	0.0 – 11.4
Follicular cell carcinoma	0.9 ± 1.4	0.0 – 6.0	0.3 ± 0.7	0.0 – 2.0

The information supplied by the sponsor concerning historical incidence rates for various types of thyroid tumors in the submission adequately addresses the informational request #3.

The study design for the ASM 981 rat dermal carcinogenicity study is provided below for background purposes.

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Study Design

ASM 981 Dose (%)	ASM 981 Dose (mg/kg/day)	Number of Main Study Animals		Number of Toxicokinetic Animals	
		Males	Females	Males	Females
Saline Control	0	50	50	10	10
Vehicle Control	0	50	50	10	10
0.2	2	50	50	10	10
0.6	6	50	50	10	10
1.0	10	50	50	10	10

The back of each rat was shaved ~24 hours prior to the first dosing and then on a weekly basis during the course of the study. An intact skin area of ~20 cm^2 was selected from the shaved area for the administration site. Special jackets (supplier – ———) were used for each rat to fix the cover of the application site. Test article (1 gm/kg/day) was applied to the application site and spread as uniformly as possible. The application sites were covered with an insert, which was fixed to the jacket. Test article was gently washed off with lukewarm tap water after each daily 6 hour exposure period. Animals were treated with test article daily, 6 hours/day, 7 days/week for a duration of 104 weeks.

The incidence rate of C-cell adenoma, follicular cell adenoma, C-cell carcinoma and follicular cell carcinoma of the thyroid gland in the rat (Wistar) dermal carcinogenicity study provided in the submission is summarized in the following table. The sponsor's full neoplastic histopathology summary tables for the rat dermal carcinogenicity study are attached as an addendum to this review.

Thyroid Gland Tumor Type	Male					Female				
	Saline	Vehicle	2 mg/kg	6 mg/kg	10 mg/kg	Saline	Vehicle	2 mg/kg	6 mg/kg	10 mg/kg
C-cell adenoma	3/50 (6%)	5/50 (10%)	2/50 (4%)	2/50 (4%)	0/49 (0%)	2/50 (4%)	2/49 (4.1%)	6/50 (12%)	3/50 (6%)	4/50 (8%)
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%)
C-cell carcinoma	1/50 (2%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/49 (0%)	0/50 (0%)	1/49 (2%)	2/50 (4%)	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%)

In the submission the sponsor states that their statistical analysis showed a positive trend with respect to dose rates, with a one-tailed p-value of 0.007, for follicular cell adenomas of the thyroid gland in male rats. The sponsor argues that because of the variability in the incidence within historical control male rats of this strain (0 – 14.3%) this change is considered to likely represent a random event and not to represent an oncogenic effect of the test article. However, it is not always accurate to compare the observed incidence rate with the historical control incidence rate range for a particular type of tumor. Sometimes it is more accurate to compare the

incidence to the concurrent control in the study or to compare to the mean historical control incidence rate for a particular type of tumor.

The incidence rates for follicular cell adenoma of the thyroid of the concurrent saline and vehicle control groups in male rats in this study were 2% and 0%, respectively. The incidence rates of follicular cell adenoma of the thyroid for the low, mid and high dose males were 8%, 12% and 10.2%, respectively. The incidence rates for follicular cell adenoma of the thyroid in all treated male rats is statistically significantly higher than concurrent control group males. Even though the range of incidence rates for follicular cell adenoma of the thyroid in treated males (8 – 12%) was within the historical control range of 0-14.3% it is well above the reported historical control mean level for this type of tumor (3.2 ± 3.2%). This tends to suggest that the effect is probably related to treatment. 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 combined incidence rates for the saline control, vehicle control, low, mid and high dose groups are 1/50 (2%), 0/50 (0%), 6/50 (12%), 6/50 (12%) and 5/49 (10.2%).

One puzzling aspect of this finding in the dermal rat carcinogenicity study is that the thyroid has not been identified as a target organ of toxicity for ASM 981 based on previously conducted repeat dose oral and dermal toxicity studies and an oral rat carcinogenicity study. However, this finding could be significant because of a difference in metabolism that may occur after dermal versus oral administration. Also, excipients in the topical formulation may play a factor in the finding in the rat dermal carcinogenicity study that were not in the oral formulation used in the oral rat carcinogenicity study. Perhaps the increased duration from 6 months, which was the previously longest duration of exposure in repeat dose dermal toxicity studies in rats, played a factor in allowing the expression of follicular cell adenoma in the thyroid in the dermal rat carcinogenicity study. It is unclear whether one or all of these factors contributed to the finding of follicular cell adenoma of the thyroid in male rats in this study.

In general, male rats are more sensitive to potential thyroid effects of a test article compared to female rats compared to humans. The reason for this is that male rats have significantly lower levels of T4 hormone, which is important in thyroid regulation. Therefore, minor alterations in T4 could have major effects in male rats that would less likely be noted in female rats and even less likely to be noted in humans. However, the sponsor has not provided any data to support such a possible mechanism. Therefore, it is unclear if this is a contributing factor to the formation of follicular cell adenoma of the thyroid in male rats in this study or not.

For comparison purposes the incidence of thyroid tumors in Wistar rats noted in the 2 oral carcinogenicity studies are provided below.

Incidence of Thyroid tumors in Wistar rats in Oral Study #1

Thyroid Tumor Type	Male					Female				
	0 mg/kg	0 mg/kg	1 mg/kg	1.5 mg/kg	2.5 mg/kg	0 mg/kg	0 mg/kg	2 mg/kg	3 mg/kg	2.5 mg/kg
Follicular cell adenoma	3/60 (5%)	0/60 (0%)	0/60 (0%)	2/60 (3.3%)	0/59 (0%)	4/60 (6.7%)	4/60 (6.7%)	4/59 (6.8%)	2/60 (3.3%)	0/60 (0%)
Follicular cell carcinoma	0/60 (0%)	2/60 (3.3%)	3/60 (5%)	0/60 (0%)	0/59 (0%)	0/60 (0%)	0/60 (0%)	0/59 (0%)	0/60 (0%)	0/60 (0%)

Incidence of Thyroid tumors in Wistar rats in Oral Study #2

Thyroid Tumor Type	Male			Female		
	0 mg/kg	0 mg/kg	10 mg/kg	0 mg/kg	0 mg/kg	10 mg/kg
Follicular cell adenoma	2/60 (3.3%)	3/60 (5%)	3/60 (5%)	3/60 (5%)	7/60 (11.7%)	1/59 (1.7%)
Follicular cell carcinoma	0/60 (0%)	1/60 (1.7%)	0/60 (0%)	0/60 (0%)	1/60 (1.7%)	0/60 (0%)

C-cell adenoma or C-cell carcinoma of the thyroid were not listed as findings in the oral rat carcinogenicity studies. It appears that there was more variability in the follicular cell adenoma of the thyroid incidence rats in control treated males in the two oral rat carcinogenicity studies. However, the vehicle used in these studies was different than what was used in the dermal rat carcinogenicity study. The vehicle for the oral rat carcinogenicity studies was an aqueous solution containing 0.5% Poloxamer 188 and 3.5% hydroxypropylmethyl cellulose. The vehicle and ASM 981 dosing solutions was administered via gavage in the oral rat carcinogenicity study. The difference in the vehicle and handling necessary for gavage administration could contribute to the greater variability noted in the oral rat carcinogenicity studies compared to the dermal rat carcinogenicity study. Therefore, it may not be appropriate to compare the control groups from the oral rat and dermal rat carcinogenicity studies. It is more accurate to compare the incidence rates of follicular cell adenoma of the thyroid noted in the dermal rat carcinogenicity study with the concurrent dermal controls from that study. Also, the historical control range values for the follicular cell adenoma of the thyroid was obtained from mainly studies that were conducted by feed administration which may have introduced additional variables that could have caused an increase in the incidence of follicular cell adenoma of the thyroid in control animals in these studies.

In conclusion, the increased incidence of follicular cell adenoma of the thyroid noted in male rats in the dermal rat carcinogenicity study is statistically significantly increased versus the concurrent controls and is probably related to treatment. It is recommended that this finding be included in the label for Elidel cream.

The incidence of benign thymoma noted in the dermal rat carcinogenicity study is summarized in the following table.

Incidence of Benign Thymoma in the Dermal Rat Carcinogenicity Studies

Dose (mg/kg/day)	Males	Females
0 (Saline Control)	1/50 (2%)	4/49 (8.1%)
0 (Vehicle Control)	0/47 (0%)	2/50 (4%)
2	2/48 (4.2%)	7/49 (14.2%)
6	3/49 (6.1%)	3/49 (6.1%)
10	2/49 (4.1%)	2/49 (4.1%)

The thymus has been identified as a target organ of toxicity in previous repeat dose toxicity studies conducted in rats. Toxicity noted in the thymus in repeat dose toxicity studies was related to the immunosuppressive properties associated with ASM 981. The sponsor provided historical incidence rate ranges for benign thymoma in Wistar rats in a previous submission. The historical incidence rate range of benign thymoma in male Wistar rats is 0.0% - 8.3% and for female Wistar rats is 0.0 – 18.6%.

Even though the incidence rate for benign thymoma was increased in all treated male rats compared to control rats, the incidence rate for benign thymoma fell within the historical incidence percentage range for benign thymoma in male Wistar rats. It appeared that the incidence rate for benign thymoma was significantly elevated in low dose female rats compared to control treated animals. However, this increase in incidence was not noted for mid and high dose females and all of the incidence rates for the treated female groups lie within the historical control incidence rate range. The sponsor's statistical analysis did not show any statistically significant elevation of the incidence of benign thymoma in treated males or females compared to control animals. Benign thymoma was noted as a treatment related neoplastic lesion in the oral rat carcinogenicity study conducted for ASM 981 (details for this study are provided below) and this information has been recommended for inclusion in the label. However, it does not appear that the benign thymoma that was noted in the rat dermal carcinogenicity study is significant.

Benign thymoma was noted as a treatment related neoplastic lesion in the two oral rat carcinogenicity studies conducted with ASM 981. 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). The incidence of benign thymoma for both rat oral carcinogenicity studies combined is provided in the following table.

Incidence of Benign Thymoma in the Oral Rat Carcinogenicity Studies

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

Carcinogenicity summary:

A significant increase in the incidence of follicular cell adenoma of the thyroid gland was noted in the low, mid and high dose male groups compared to control males. The sponsor states that there is a statistically significant increase in the incidence of follicular cell adenomas of the thyroid gland in treated male rats (one-tailed p-value of 0.007). This is a significant finding and is recommended that this finding be included in the label.

No NOAEL could be identified for follicular cell adenoma of the thyroid gland noted in male rats. The lowest dose used in this study was 2 mg/kg/day (0.2% ASM 981 cream). The $AUC_{(0\text{-}24\ hr)}$ value obtained for male rats at this dose after 104 weeks of topical treatment was 57.0 ng·hr/ml. The highest measured $AUC_{(0\text{-}24\ hr)}$ value measured in humans that applied 1% ASM 981 cream was 38 ng·hr/ml. This was measured in a single pediatric patient that applied 1% ASM 981 cream bid to 43.5% BSA. The multiple of human exposure will be calculated based on this highest $AUC_{(0\text{-}24\ hr)}$ value. The multiple of human exposure is 1.5X based on the $AUC_{(0\text{-}24\ hr)}$ level for low dose males identified in this dermal rat carcinogenicity study.

A slight increase in benign thymoma was noted in male and female rats compared to control animals. It was determined that this increase was not significant.

Carcinogenicity conclusions:

A significant increase in the incidence of follicular cell adenoma of the thyroid gland was noted in all treated male rat groups compared to control male rats in the dermal rat carcinogenicity study.

Recommendations for further analysis: It is recommended that the sponsor provide additional information to the NDA if they wish to argue that the follicular cell adenoma of the thyroid in male rats is not relevant to humans. Perhaps a study determining the effect of ASM 981 on T4 levels in male rats would provide additional information to support such an argument.

Labeling Recommendations:

It is recommended that the finding of a significant increase in the incidence of follicular cell adenoma of the thyroid gland noted in male rats compared to control male rats in the dermal rat carcinogenicity study be included in the label.

Addendum/appendix listing:

CAC report:

An Exec CAC meeting to discuss the rat dermal carcinogenicity study conducted for Elidel cream was held on 11-6-01. The minutes from that meeting are provided below.

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	Male					Female				
	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

cc:

/Division File, HFD 540
/AJacobs/Sup, HFD-540
/BHill/Pharm, HFD-540
/MWright/PM, HFD-540
/ASeifried, HFD-024

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Sponsor's incidence of histopathology findings:

The rat dermal carcinogenicity study neoplastic histopathology summary tables (benign neoplasms followed by malignant neoplasms) reproduced below were scanned directly from the NDA submission (Volume 1).

PATHOLOGY REPORT PAGE : 19/1889
SUMMARY TABLES PROJECT: 682705

TEST ARTICLE : SDZ ASM 981 CREAM *PATHOL. NO.*: 20025 JMA
TEST SYSTEM : RAT, 104 WEEKS, DERMAL *DATE* : 01-SEP-01
SPONSOR : NOVARTIS PHARMA

NUMBER OF ANIMALS WITH BENIGN NEOPLASMS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

MALE

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	01	02	03	04	05
		50	50	50	50	50
CEREBRUM	No.Examined	50	50	18	23	50
- Granular cell tumor		2	1	-	1	-
LUNG	No.Examined	50	50	29	29	50
- Alveolar/bronchiolar adenoma		-	-	1	1	1
DUODENUM	No.Examined	50	47	16	21	45
- Leiomyoma		-	1	-	-	-
LIVER	No.Examined	50	50	18	23	50
- Hepatocellular adenoma		-	1	-	-	1
BILE DUCT, EXTRAHEP.	No.Examined	3	2	3	3	2
- Leiomyoma		-	-	1	-	-
PANCREAS	No.Examined	50	48	15	21	50
- Islet cell adenoma		2	3	-	1	-
- Mixed acinar-islet cell adenoma		1	-	-	-	-
KIDNEYS	No.Examined	50	50	16	21	50
- Tubular cell adenoma		1	-	-	-	-
TESTES	No.Examined	49	50	23	24	50
- Benign Leydig cell tumor		1	1	1	-	4
- Hemangioma		1	-	-	1	-
PITUITARY GLAND	No.Examined	50	50	19	26	50
- Adenoma/pars distalis		29	17	8	10	11
- Adenoma/pars intermedia		2	-	-	-	-
THYROID GLAND	No.Examined	50	50	50	50	49
- C-cell adenoma		3	5	2	2	-
- Follicular cell adenoma		1	-	4	6	5
PARATHYROID GLANDS	No.Examined	49	50	45	45	46
- Adenoma		2	1	3	3	3
ADRENAL MEDULLAS	No.Examined	49	50	16	21	50
- Benign pheochromocytoma		2	-	-	-	1
- Complex pheochromocytoma		-	-	-	1	-
THYMUS	No.Examined	50	47	48	49	49
- Benign thymoma		1	-	2	3	2
MESENT. LYMPH NODE	No.Examined	50	50	21	22	50
- Hemangioma		3	8	7	3	8
SKIN/SUBCUTIS(ENTRT)	No.Examined	50	49	23	30	50
- Basal cell adenoma		-	-	-	1	-
- Trichoepithelioma		-	-	1	-	-
- Squamous cell papilloma		1	-	1	1	-
- Keratoacanthoma		-	1	1	2	1
- Lipoma		-	-	-	1	-
- Fibroma		-	-	-	1	-
HINDFOOT/HINDFEET	No.Examined	7	21	19	12	13
- Squamous cell papilloma		-	1	-	-	-
APPLICATION SITE 1	No.Examined	50	48	15	21	50
- Basal cell adenoma		-	-	-	1	-

PATHOLOGY REPORT PAGE : 20/1889
SUMMARY TABLES PROJECT: 682705

TEST ARTICLE : SDZ ASM 981 CREAM *PATHOL. NO.*: 20025 JMA
TEST SYSTEM : RAT, 104 WEEKS, DERMAL *DATE* : 01-SEP-01
SPONSOR : NOVARTIS PHARMA

NUMBER OF ANIMALS WITH BENIGN NEOPLASMS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

ORGAN/FINDING	SEX : DOSE GROUP : NO. ANIMALS :	01 50	02 50	03 50	04 50	05 50
		FEMALE				
CEREBRUM	No.Examined :	50	50	23	30	50
- Granular cell tumor	:	1	1	-	1	2
CEREBELLUM	No.Examined :	50	50	22	30	50
- Granular cell tumor	:	3	-	-	-	1
LUNG	No.Examined :	50	50	21	30	50
- Alveolar/bronchiolar adenoma	:	1	-	-	-	-
STOMACH	No.Examined :	50	50	17	19	49
- Adenoma	:	1	-	-	-	-
DUODENUM	No.Examined :	49	49	15	19	45
- Leiomyoma	:	-	1	-	-	-
JEJUNUM	No.Examined :	48	47	12	19	45
- Leiomyoma	:	-	-	-	1	-
LIVER	No.Examined :	50	50	20	20	50
- Hepatocellular adenoma	:	-	1	1	-	1
PANCREAS	No.Examined :	50	50	19	16	49
- Islet cell adenoma	:	-	2	-	-	-
KIDNEYS	No.Examined :	50	50	18	18	50
- Tubular cell adenoma	:	1	-	-	-	-
OVARIES	No.Examined :	50	50	22	26	50
- Benign granulosa cell tumor	:	2	2	2	1	2
- Benign granulosa-theca cell tumor	:	-	-	-	-	1
UTERUS	No.Examined :	50	50	33	32	50
- Polyp/endometrial-stromal	:	4	4	6	7	5
- Leiomyoma	:	-	-	1	-	-
- Hemangioma	:	-	1	-	-	-
- Granular cell tumor	:	1	-	1	1	-
VAGINA	No.Examined :	50	50	33	32	50
- Granular cell tumor	:	1	1	-	-	-
- Hemangioma	:	1	-	-	-	-
PITUITARY GLAND	No.Examined :	50	50	42	39	50
- Adenoma/pars distalis	:	42	41	33	30	34
- Adenoma/pars intermedia	:	-	2	4	1	-
- Pituicytoma	:	-	-	-	-	1
THYROID GLAND	No.Examined :	50	49	50	50	50
- C-cell adenoma	:	2	2	6	3	4
- Follicular cell adenoma	:	-	-	1	-	-
ADRENAL MEDULLAS	No.Examined :	50	50	25	23	50
- Benign pheochromocytoma	:	3	-	2	-	-
SPLEEN	No.Examined :	50	50	17	18	50
- Hemangioma	:	-	-	1	-	-
THYMUS	No.Examined :	49	50	49	49	49
- Benign thymoma	:	4	2	7	3	2
MESENT. LYMPH NODE	No.Examined :	50	49	17	19	50
- Hemangioma	:	2	3	1	2	5

PATHOLOGY REPORT
SUMMARY TABLES

PAGE : 21/1889
PROJECT: 682705

TEST ARTICLE : SDZ ASM 981 CREAM
TEST SYSTEM : RAT, 104 WEEKS, DERMAL
SPONSOR : NOVARTIS PHARMA

PATHOL. NO.: 20025 JMA
DATE : 01-SEP-01

NUMBER OF ANIMALS WITH BENIGN NEOPLASMS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	01	02	03	04	05	FEMALE
MAMMARY GLAND AREA	No.Examined	49	50	25	22	50	
- Fibroadenoma		7	6	4	8	3	
- Adenoma		-	1	-	-	-	
SKIN/SUBCUTIS(UNTRT)	No.Examined	50	50	22	23	49	
- Squamous cell papilloma		-	-	-	-	1	
- Keratoacanthoma		-	-	1	1	1	
- Lipoma		-	-	-	1	1	
- Benign fibrous histiocytoma		1	-	-	-	-	
- Fibroma		-	-	-	1	-	
HINDFOOT/HINDFEET	No.Examined	4	1	2	1	4	
- Hemangioma		1	-	-	-	-	
EYES	No.Examined	50	50	17	19	50	
- Uveal leiomyoma		-	-	-	1	-	
BODY CAVITIES	No.Examined	-	1	-	-	2	
- Hemangioma		-	1	-	-	-	
APPLICATION SITE 1	No.Examined	50	50	18	17	49	
- Basal cell adenoma		-	-	1	-	-	

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PATHOLOGY REPORT PAGE : 22/1889
SUMMARY TABLES PROJECT: 682705

TEST ARTICLE : SDZ ASM 981 CREAM *PATHOL. NO.*: 20025 JMA
TEST SYSTEM : RAT, 104 WEEKS, DERMAL *DATE* : 01-SEP-01
SPONSOR : NOVARTIS PHARMA

NUMBER OF ANIMALS WITH MALIGNANT NEOPLASMS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	01	02	03	04	05
		50	50	50	50	50
MALE						
CEREBRUM	No.Examined	50	50	18	23	50
- Malignant reticulosis		1	-	-	-	-
- Oligodendroglioma		-	-	1	-	1
- Meningeal sarcoma		1	-	-	-	1
CEREBELLUM	No.Examined	50	50	18	23	50
- Meningeal sarcoma		-	-	-	-	1
LUNG	No.Examined	50	50	29	29	50
- Squamous cell carcinoma of bronchus		-	-	-	-	1
STOMACH	No.Examined	50	50	16	24	50
- Leiomyosarcoma		-	-	-	-	1
DUODENUM	No.Examined	50	47	16	21	45
- Leiomyosarcoma		-	-	2	-	-
- Adenocarcinoma		-	-	1	-	-
JEJUNUM	No.Examined	44	43	12	16	42
- Leiomyosarcoma		-	-	-	-	1
COLON	No.Examined	49	49	14	19	47
- Adenocarcinoma		-	1	-	-	-
- Leiomyosarcoma		-	-	1	-	-
LIVER	No.Examined	50	50	18	23	50
- Hepatocellular carcinoma		-	1	2	-	-
PANCREAS	No.Examined	50	48	15	21	50
- Islet cell carcinoma		1	-	-	-	-
KIDNEYS	No.Examined	50	50	16	21	50
- Tubular cell carcinoma		1	1	1	2	1
- Lipomatous tumor		1	-	-	-	-
THYROID GLAND	No.Examined	50	50	50	50	49
- C-cell carcinoma		1	-	-	-	-
- Follicular cell carcinoma		-	-	2	-	-
ADRENAL CORTICES	No.Examined	49	50	17	21	50
- Carcinoma		-	-	1	-	-
ADRENAL MEDULLAS	No.Examined	49	50	16	21	50
- Malignant pheochromocytoma		1	1	-	-	1
HEMOLYMPHORET. SYS.	No.Examined	50	50	15	20	50
- Malignant lymphoma		-	2	-	1	1
- Histiocytic sarcoma		-	-	-	-	1
- Malignant fibrous histiocytoma		-	1	-	-	-
SPLEEN	No.Examined	50	50	16	20	50
- Hemangiosarcoma		1	-	-	1	-
- Leiomyosarcoma		-	-	-	1	-
- Sarcoma (not otherwise specified)		-	-	-	-	1
LYMPH NODES	No.Examined	8	8	8	4	10
- Hemangiosarcoma		1	-	-	-	-
HARDERIAN GLANDS	No.Examined	4	8	8	6	3
- Squamous cell carcinoma		-	-	-	1	-

PATHOLOGY REPORT PAGE : 23/1889
SUMMARY TABLES PROJECT: 682705

TEST ARTICLE : SDZ ASM 981 CREAM *PATHOL. NO.*: 20025 JMA
TEST SYSTEM : RAT, 104 WEEKS, DERMAL *DATE* : 01-SEP-01
SPONSOR : NOVARTIS PHARMA

NUMBER OF ANIMALS WITH MALIGNANT NEOPLASMS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

ORGAN/FINDING	SEX / DOSE GROUP / NO. ANIMALS	01	02	03	04	05	MALE
SKIN/SUBCUTIS(UNTRT)	No.Examined	50	49	23	30	50	
- Sarcoma (not otherwise specified)		-	1	-	-	2	
- Malignant Schwannoma		-	1	-	-	-	
- Fibrosarcoma		-	-	-	1	2	
- Liposarcoma		-	-	-	-	1	
HINDFOOT/HINDFEET	No.Examined	7	21	19	12	13	
- Hemangiosarcoma		-	1	-	-	-	
EYES	No.Examined	50	50	20	24	50	
- Amelanotic melanoma		1	-	-	-	-	
BODY CAVITIES	No.Examined	3	2	2	1	-	
- Malignant Schwannoma		1	-	-	-	-	
- Malignant mesothelioma		2	2	2	-	-	
- Sarcoma (not otherwise specified)		-	-	-	1	-	
ZYMBAL'S GLANDS	No.Examined	-	-	-	1	-	
- Carcinoma		-	-	-	1	-	

PATHOLOGY REPORT
SUMMARY TABLES

PAGE : 24/1889
PROJECT: 682705

TEST ARTICLE : SDZ ASM 981 CREAM
TEST SYSTEM : RAT, 104 WEEKS, DERMAL
SPONSOR : NOVARTIS PHARMA

PATHOL. NO. : 20025 JMA
DATE : 01-SEP-01

NUMBER OF ANIMALS WITH MALIGNANT NEOPLASMS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO, INCL. DEATHS

ORGAN/FINDING	SEX : FEMALE DOSE GROUP : NO. ANIMALS :	01 50	02 50	03 50	04 50	05 50
CEREBRUM	No.Examined :	50	50	23	30	50
- Astrocytoma	:	-	-	-	-	2
HEART	No.Examined :	50	50	17	18	50
- Malignant endocardial schwannoma	:	-	1	-	-	-
PANCREAS	No.Examined :	50	50	19	16	49
- Islet cell carcinoma	:	-	1	-	-	-
KIDNEYS	No.Examined :	50	50	18	18	50
- Tubular cell carcinoma	:	1	2	-	2	-
OVARIES	No.Examined :	50	50	22	26	50
- Malignant granulosa cell tumor	:	2	-	-	2	-
- Yolk sac carcinoma	:	-	-	-	-	1
OVIDUCTS	No.Examined :	-	-	-	-	1
- Cystadenocarcinoma	:	-	-	-	-	1
UTERUS	No.Examined :	50	50	33	32	50
- Adenocarcinoma	:	3	3	2	4	2
- Leiomyosarcoma	:	-	-	1	-	-
- Malignant Schwannoma	:	1	-	-	1	2
- Stromal sarcoma	:	-	-	1	-	-
- Hemangiosarcoma	:	-	1	-	-	1
THYROID GLAND	No.Examined :	50	49	50	50	50
- C-cell carcinoma	:	-	1	2	-	-
- Follicular cell carcinoma	:	1	-	1	-	1
HEMOLYMPHORET. SYS.	No.Examined :	50	50	17	18	50
- Malignant lymphoma	:	1	2	-	-	3
SPLEEN	No.Examined :	50	50	17	18	50
- Hemangiosarcoma	:	1	-	-	1	-
- Sarcoma (not otherwise specified)	:	-	-	-	-	1
PAROTID GLAND, LEFT	No.Examined :	-	-	1	-	-
- Adenocarcinoma	:	-	-	1	-	-
MAMMARY GLAND AREA	No.Examined :	49	50	25	22	50
- Adenocarcinoma	:	1	6	1	-	-
SKIN/SUBCUTIS(UNIRT)	No.Examined :	50	50	22	23	49
- Malignant Schwannoma	:	1	-	-	-	-
- Fibrosarcoma	:	1	-	-	-	-
BODY CAVITIES	No.Examined :	-	1	-	-	2
- Malignant Schwannoma	:	-	-	-	-	1
ZYMBAL'S GLANDS	No.Examined :	-	-	1	-	-
- Carcinoma	:	-	-	1	-	-

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

No nonclinical reproductive and developmental toxicology studies were included in this submission.

VIII. SPECIAL TOXICOLOGY STUDIES:

No nonclinical special toxicology studies were included in this submission.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions:

A significant increase in the incidence of follicular cell adenoma of the thyroid gland was noted in all treated male rat groups compared to control male rats in the dermal rat carcinogenicity study.

Recommendations:

It is recommended that this finding be included in the labeling for Elidel cream.

Labeling with basis for findings:

The basis for the labeling recommendation in this review is the recent results of the rat dermal carcinogenicity study submitted to the NDA.

The following label recommendation was made for the Elidel label in the Pharmacology/Toxicology review of the original NDA submission. This sentence is located as the first sentence in the "Carcinogenesis, Mutagenesis, Impairment of Fertility" section of the label. Sections that were recommended for deletion are marked by ~~strikeout.~~ Sections that were recommended for addition are marked by highlight.

In a 2-year rat dermal carcinogenicity study — using Elidel cream, ——————

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It is recommended that this entire portion of the label concerning the results of the rat dermal carcinogenicity study be deleted from the label and replaced with the following statement.

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].

X. APPENDIX/ATTACHMENTS:

Addendum to review: None

Other relevant materials (Studies not reviewed, appended consults, etc.): None

Any compliance issues: None

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

/s/

Barbara Hill
11/8/01 01:17:51 PM
PHARMACOLOGIST

Abby Jacobs
11/8/01 01:33:59 PM
PHARMACOLOGIST

Jonathan Wilkin
11/28/01 05:45:15 PM
MEDICAL OFFICER

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

NDA number: 21-302
Review number: 1
Sequence number/date/type of submission:

1) 000 / 12-19-00 / Original NDA Submission
2) BP / 3-14-01 / Minor amendment – Pharmacology (Historical control background incidence rates for neoplastic lesions in Wistar rats)
3) BP / 6-8-01 / Minor amendment – Pharmacology (Additional nonclinical pharmacology study reports to support revised labeling)
4) BL / 6-19-01 / Labeling amendment

Information to sponsor: Yes () No (X)

Sponsor: Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, New Jersey 07936
(973) 781-7548

Manufacturer for drug substance: Novartis Pharma AG
Lichtstrasse 35
CH-4056 Basle, Switzerland

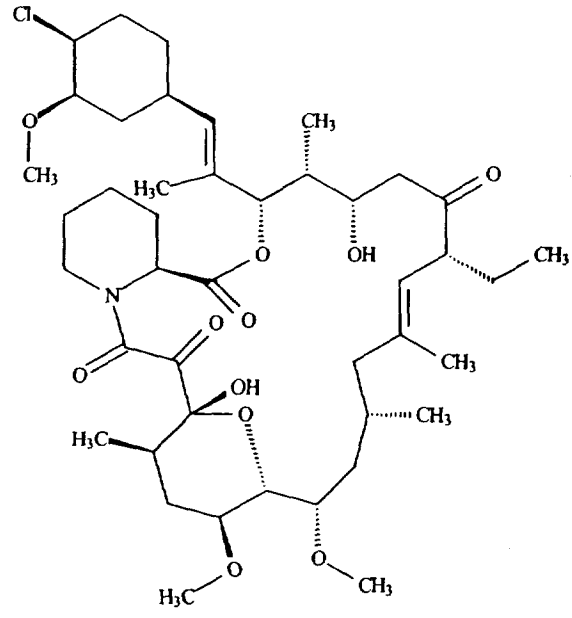
Reviewer Name: Barbara Hill
Division Name: Dermatologic and Dental Drug Products
HFD#: HFD-540
Review Completion Date: 9-12-01

Drug:

Trade Name: Elidel™
Generic Name: Pimecrolimus
Code Name: ASM 981 Cream, 1%
Chemical Name: (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
CAS Registry Number: 137071-32-0
Molecular Formula/ Molecular Weight: 810.47 / $C_{43}H_{68}ClNO_{11}$

UV Absorption: λ_{max} (~ 200 µg/ml in methanol or ethanol): ——nm (ϵ = ——.
Note: Only an absorption spectra for the active, ASM 981, has been provided for ASM 981 cream. ASM 981 absorbs in the UVB range. The sponsor provided no information on UVA/UVB/VIS absorption for the inactive ingredients in the drug product.

Structure:



Relevant INDs/NDAs/DMFs:

1) IND — (1% ASM 981 cream, Atopic Dermatitis; HFD-540)
2) IND [redacted]
3) IND
4) IND

Drug Class: Anti-inflammatory, immunosuppresant

Indication: Atopic Dermatitis

Clinical formulation:

The composition of the 1% ASM 981 cream (the final clinical formulation) is provided in the following table:

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Ingredient	Amount per gram of Drug Product (mg)	Function
ASM 981	10.0	Drug Substance
Sodium Hydroxide		
Citric acid		
Benzyl alcohol		
Sodium cetostearyl sulphate		
Cetyl alcohol		
Stearyl alcohol		
Propylene glycol		
Oleyl alcohol		
Triglycerides		
Water		

Dose:

The sponsor provided the following information for a request of anticipated maximum dose for 1% ASM 981 cream.

- Up to 60-75% total body surface area will be treated in both adult and pediatric patients
- The maximum amount of ASM 981 cream, 1% to be applied per application is approximately 15-20 grams.
- Frequency of application is BID (twice daily)

Based on this information the maximum daily dose of 1% ASM 981 cream would deliver 0.4 gm of active ingredient (20 gms x .01 x 2/day = 0.4 gm/day). For a 50 kg person, this dose would be 8 mg/kg/day (296 mg/m^2/day).

Note: It is estimated that up to 80% of the body could be treated in a severe case of atopic dermatitis. Approximately 30 g of 1% ASM 981 cream could be applied per treatment to cover 80% of the body. Therefore, the maximum daily dose of the 1% ASM 981 cream would be 12 mg/kg/day (444 mg/m^2/day) for a 50 kg person (30,000 mg x .01 x 2/day ÷ 50 kg = 12 mg/kg/day). This estimate is 1.5 fold greater than the estimate based on the data provided by the sponsor. It is recommended that this estimate be used for calculation of fold human exposure levels based on nonclinical toxicity studies when AUC data is not available for the nonclinical toxicity study.

The highest $AUC_{(0\text{-}24\ hr)}$ value measured in humans was 38 ng·hr/ml and was measured in a single pediatric patient that applied 1% ASM 981 cream bid to 43.5% BSA. It is recommended that the multiple of human exposure levels based on nonclinical toxicity studies be calculated based on this $AUC_{(0\text{-}24\ hr)}$ value where nonclinical AUC data is available.

Route of administration: Topical dermal

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

OVERALL SUMMARY AND EVALUATION:

Introduction:

Pimecrolimus (ASM 981) is an ascomycin macrolactam derivative. Pimecrolimus inhibits activation of T-cells and mast cells. It has been demonstrated that pimecrolimus is an inhibitor of inflammatory cytokine release. In addition, pimecrolimus possess immunosuppressant activity. The topical formulation developed for this NDA (Elidel™ {pimecrolimus} cream) has been developed for the treatment of moderate ——— Atopic Dermatitis. Atopic Dermatitis is primarily a pediatric indication and the duration of treatment is chronic. The sponsor has performed a full set of nonclinical toxicology studies to support the topical formulation of pimecrolimus (Elidel™ cream). A brief summary of the significant toxicities and corresponding safety evaluation based on these studies is provided in the following section.

Safety evaluation:

Nonclinical special toxicology studies were conducted with the 1% ASM 981 cream. The 1% ASM 981 cream was a minimal irritant in the rabbit eye. The photoirritation study conducted in guinea pigs under UVA exposure conditions did not demonstrate photoirritation. This result is not surprising since the drug product does not absorb in the VIS/UVA range. It would have been preferable if this study utilized UVB exposure.

Oral and dermal repeat dose toxicity studies were conducted in mice (duration up to 13 weeks), rats (duration up to 26 weeks) and minipigs (duration up to 26 weeks). Results from the longest duration studies and studies designed to address a particular question will be described in this summary.

The immune suppressive and toxicity related effects of ASM 981 were delineated in the 13 week oral toxicity study in mice. Reduced lymphocyte counts and atrophy of thymus cortex was noted at doses ≥ 50 mg/kg. Lymphomas were seen in the spleen and mesenteric lymph nodes at doses ≥ 100 mg/kg and in the thymus at 312.5 mg/kg. These findings were considered to be related to an overt systemic immunosuppression. Toxicity to the endocrine pancreas was evident as islet cell vaculation and slight increases in serum glucose in females at 312.5 mg/kg. Effects on reproductive organs were noted as an alteration of cycle-related histomorphological changes in the vagina associated with uterine atrophy at 312.5 mg/kg. Treatment related reductions in serum magnesium were observed at dose ≥ 100 mg/kg. The NOAEL identified in this study was 10 mg/kg/day ($AUC_{0.5\text{-}4hr}$ = 1029 and 2949 ng·hg/ml in males and females, respectively) for mice after 13 weeks of oral administration of ASM 981.

The dermal toxicity studies conducted in mice used ethanol as a vehicle. These studies were conducted prior to submission of the IND to the division. The rationale for ethanol was that the dermal carcinogenicity performed for ASM 981 was conducted with ethanol as a vehicle as

well. The sponsor was informed when the IND was submitted for the ASM 981 cream that it was recommended that nonclinical dermal toxicity studies be conducted with the final to be marketed cream formulation of ASM 981. Therefore, the dermal studies conducted in rats and minipigs were conducted with the final to be marketed ASM 981 cream formulation. It is important to note that the maximum feasible concentration of ASM 981 in the cream formulation is 1% and this concentration was used as the high dose in the rat and minipig dermal toxicity studies.

Dermal administration of ASM 981 in ethanol to mice for 13 weeks established the lymphoproliferative potential of ASM 981. Pleomorphic lymphoma was noted at the 60 mg/kg/day dose level. Potential target organs of toxicity identified in this study included the hemopoietic tissue, mandibular and mesenteric lymph nodes, spleen, thymus, ovaries, uterus or cervix, kidneys and salivary glands. The effects noted in the hemopoietic tissue, mandibular and mesenteric lymph nodes, spleen and thymus are probably related to the pharmacological (immunosuppressive) activity of ASM 981. The effects noted in the pancreas, ovaries, uterus or cervix, kidneys and salivary glands are probably related to the overt toxicological properties of ASM 981. The NOAEL identified in this study was 6 mg/kg/day for mice after 13 weeks of topical administration of ASM 981 dissolved in ethanol.

A series of dermal toxicity studies were conducted in mice to better clarify the timing of the development of lymphoproliferative lesions after topical ASM 981 administration. The focus of one 13 week dermal toxicity study in mice was to assess the dose response relationship of immunousuppression and lymphoproliferative disorders following dermal administration of ASM 981. Doses of 25 and 50 mg/kg/day by dermal administration for 13 weeks were associated with lymphoproliferative changes, including malignancies. These findings were generally dose related in incidence and severity. No lymphoproliferative changes were noted at the 10 mg/kg/day dose level. Therefore, the NOAEL for lymphoproliferative changes was identified in this study as 10 mg/kg/day ($AUC_{0\text{-}24hr}$ = 643 and 675 ng·hg/ml for males and females, respectively) for mice after 13 weeks of topical administration of ASM 981 dissolved in ethanol.

Another 13 week dermal toxicity study in mice was conducted to assess the severity of immunosuppression and the rate of onset of lymphoproliferative disorders following dermal administration of ASM 981 to CD-1 mice. Doses of 25 mg/kg/day and above by dermal administration for 13 weeks were associated with lymphoproliferative changes indicative of immunosuppression, including malignancies. These findings were generally dose related in incidence and severity. No NOAEL was established in this study. Pleomorphic lymphoma was noted in the mid-high (100 mg/kg/day) and high dose (200 mg/kg/day) groups after 8 weeks of treatment. No pleomorphic lymphoma was noted in the low dose group (25 mg/kg/day) after 13 weeks of treatment. The results of this study indicate that at the appropriate dose level (100 mg/kg/day or greater) pleomorphic lymphoma can be noted as early as after 8 weeks of treatment.

A 52 week dermal carcinogenicity study in mice was conducted with a high dose group that was less than the NOAEL dose in the 13 week oral toxicity study in CD-1 mice and less than the dose that demonstrated lymphoproliferative changes in the 13 week dermal toxicity study in

CD-1 mice. The highest dose tested in this 52 week dermal toxicity study was 5.0 mg/kg/day for males (AUC = 424 ng·hr/ml after 52 weeks) and 6.6 mg/kg/day in females (AUC = 833 ng·hr/ml after 52 weeks). It is not terribly surprising that no significant toxicity effects were noted in the 52 week study. If this study had continued, the review of this study would have determined that an adequate dose selection was not used for this study. The sponsor did repeat the mouse dermal carcinogenicity study with an ethanolic ASM 981 solution. Typically the dermal carcinogenicity study for a particular drug product is conducted with the final to be marketed formulation. Therefore, the sponsor was informed that a dermal carcinogenicity study with the final marketed formulation for the ASM 981 cream formulation is recommended. The sponsor conducted a dermal carcinogenicity study in the rat with the final marketed formulation of the ASM 981 cream. The results from both of these studies will be discussed later in this section.

It is important to note that the mouse had significant systemic exposure to ASM 981 after dermal application of ASM 981 dissolved in ethanol. The toxic effects noted in the dermal mouse toxicity studies were similar to those noted in the oral mouse toxicity studies. This may over represent the systemic toxicity associated with dermal administration of 1% ASM 981 cream in humans due to the limited systemic exposure achieved after topical application of 1% ASM 981 cream. Systemic exposure to ASM 981 after dermal application of the 1% ASM 981 cream to rats and minipigs was very low as will be discussed later in this section. No systemic toxicity was associated with dermal application of 1% ASM 981 cream in the long term dermal rat and minipig toxicity studies. Therefore, the rat and minipig maybe a better model for systemic toxicity associated with topical application of the 1% ASM 981 cream in humans.

Lymphoreticular effects were noted in oral toxicity studies conducted in rats. Reduced lymphocyte counts and medullary atrophy in the thymus were indicative of immunosuppressive activity associated with ASM 981. Low serum magnesium concentrations usually accompanied thymus medullary atrophy. The occurrence of inflammatory cell infiltration and edema noted in the glandular stomach may also be associated with immune suppression.

Direct toxicological effects associated with oral administration of ASM 981 were noted in the rat. Functional and/or morphological changes were noted in the kidney and pancreas at high doses of ASM 981. The functional kidney changes were expressed by low urine specific gravity, loss of electrolytes, decreased creatinine clearance and increased serum urea and creatinine concentrations. Morphological changes in the kidney were characterized by an increased incidence of basophilic tubuli and increased incidence and severity of corticomedullary mineralization. Morphological changes in the pancreas were described as vacuolation and reduction in number of islet cells. An increased incidence of lens cataracts was noted after chronic oral treatment with high doses of ASM 981. ASM 981 also showed effects on reproductive organs at high doses. Specifically noted were reduced prostate gland weight, epithelial atrophy of seminal vesicles, suppression of estrus cycle, vaginal and uterine atrophy. These findings may have been related to altered sex hormone function in male and female rats. To investigate this possibility further, two 4 week investigational oral toxicity studies were conducted in male and female rats. Results from these studies demonstrated a moderate suppression of testosterone secretion in male rats that was not dose related and decreased estrogen levels in high dose females during diestrus and proestrus. The sponsor proposes that the effects on testosterone and estrogen levels in rats plays in role in the benign thymoma noted in

the oral rat carcinogenicity study. Another possible explanation for the noted benign thymoma could be related to the immunosuppressive effects associated with ASM 981 since the thymus has been characterized as a target organ in repeat dose oral toxicity studies conducted in Wistar rats. The NOAEL identified in the 26 week repeat dose oral toxicity study in rats was 1 mg/kg/day ($AUC_{0\text{-}24\ hr}$ = 17.5 and 23.7 ng·hr/ml for males and females, respectively).

No systemic toxicity was noted in the 26 week dermal toxicity study in rats. The only treatment related effect noted in this study was a slight thickening of the epithelium noted in vehicle control and high dose animals. No difference in the extent of the epidermal thickening was noted between the two groups. This may have been due to the cream formulation and not attributed to ASM 981. Therefore, the NOAEL identified in this study was 10 mg/kg/day (1% ASM 981 cream; $AUC_{0\text{-}24\ hr}$ = 4.9 ng·hr/ml for males and females) for rats after 26 weeks of topical administration of ASM 981 cream.

It is not surprising that no systemic toxicity was noted in the 26 week dermal toxicity study in rats due to the low levels of systemic exposure achieved in this study. The high dose group in the 26 week rat dermal toxicity study did not yield $AUC_{0\text{-}24\ hr}$ values that were greater than the 26 week oral rat NOAEL. Therefore, no systemic toxicity would be anticipated in this study. However, the design of the study was adequate because the 1% ASM 981 cream is the maximum feasible concentration in the to be marketed cream formulation and an adequate amount of the cream was applied daily for 20 hours/day.

Potential target organs of toxicity identified in the 26 week oral toxicity study in minipigs included the arteries, adrenals and lungs in minipigs. Arteries were considered the major target organ for toxicity in minipigs. Damage to the arteries in the adrenals was noted in all high dose animals and in various other organs in some of the high dose animals. Effects in adrenals and lungs were noted in mid and high dose animals. The effects noted in the adrenals and lungs were probably related to the exaggerated pharmacology of ASM 981. One potential explanation proposed for the noted arteritis was that it was caused by a bacterial infection spread in the vascular system as a sequela due to immunosuppression. However, additional data would need to be provided to support this theory. It would appear that arteritis became more prominent in minipigs after treatment with ASM 981 for a longer duration of treatment. The NOAEL identified in this study was 2 mg/kg/day ($AUC_{0\text{-}24\ hr}$ = 316 and 305 ng·hr/ml for males and females, respectively) for minipigs after 26 weeks of oral administration of ASM 981. Oral toxicity studies conducted in juvenile minipigs (up to 4 weeks in duration) demonstrated a similar toxicity profile as that noted in adult minipigs. The NOAEL identified in juvenile minipigs was 5 mg/kg/day ($AUC_{0\text{-}24\ hr}$ = 545 and 444 ng·hr/ml for males and females, respectively) after 4 weeks of oral administration of ASM 981.

No systemic or local dermal toxicity was noted in a 26 week dermal toxicity study in adult minipigs and a 13 week dermal toxicity study in juvenile minipigs. The NOAEL identified in the adult minipig study was 20 mg/kg/day (1% ASM 981 cream; $AUC_{0\text{-}24\ hr}$ = 7.2 and 2.8 ng·hr/ml for males and females, respectively) after 26 weeks of topical administration of ASM 981 cream. The NOAEL identified in juvenile minipigs was 20 mg/kg/day (1% ASM 981 cream) for juvenile minipigs after 13 weeks of topical administration of ASM 981 cream. No consistent systemic absorption was noted in the juvenile minipigs study.

It is not surprising that no systemic toxicity was noted in either the adult or juvenile minipig studies due to the low systemic exposure noted in these studies. The design of the both studies was adequate because the 1% ASM 981 cream is the maximum feasible concentration in the to be marketed cream formulation and an adequate amount of the cream was applied daily for 20 hours/day.

ASM 981 was negative in two *in vitro* bacterial mutagenesis assays (Ames test), an *in vitro* mammalian cell mutagenesis assay (L5178Y/TK+/- mouse lymphoma assay), an *in vitro* chromosomal aberration test in Chinese hamster cells and an *in vivo* mouse bone marrow micronucleus test. ASM 981 did not demonstrate a positive genotoxicity signal based on the results of the *in vitro* and *in vivo* genotoxicity studies conducted for ASM 981.

A dramatic vehicle effect was observed on the median tumor onset (decreased time to tumor onset) in the photocarcinogenicity study. The vehicle induced enhancement tended to be greater in male mice as compared to female mice. No additional effect of ASM 981 cream treatment on tumor development beyond the vehicle effect was noted in this study. For female animals, there was actually a protective effect observed at all three dose levels of ASM 981 cream. The reason for this is unclear. The vehicle enhancement of photocarcinogenesis has been noted in other photocarcinogenicity studies conducted in the literature and submitted to the agency. One potential explanation for this could be the modification of the optical quality of the skin with resulting enhancement of UVR penetration, which could lead to an increase in UVR induced skin tumors.

Five carcinogenicity studies were conducted for ASM 981. The carcinogenicity studies included an oral mouse carcinogenicity study, two oral rat carcinogenicity studies, a dermal mouse carcinogenicity study and a dermal rat carcinogenicity study.

Malignant lymphoma was noted as a treatment related neoplastic lesion in the oral mouse carcinogenicity study. The NOAEL for lymphoma formation was identified as the 15 mg/kg/day dose group ($AUC_{(0\text{-}24\ hr)}$ for males = 2260 ng·hr/ml after week 70 of treatment; $AUC_{(0\text{-}24\ hr)}$ for females = 5059 ng·hr/ml after week 70 of treatment) in this study.

Benign thymoma was noted as a treatment related neoplastic lesion in the oral rat carcinogenicity studies. Combining the results of the two oral rat carcinogenicity studies, the NOAEL for benign thymoma formation is 1 mg/kg/day in male rats ($AUC_{(0\text{-}24\ hr)}$ for males = 42 ng·hr/ml after week 72 of treatment) and 5 mg/kg/day in female rats ($AUC_{(0\text{-}24\ hr)}$ for females = 805 ng·hr/ml after week 72 of treatment). It is important to note a comment made by the Exec CAC members during a meeting conducted on 6-19-01 to discuss the results from all of the carcinogenicity studies conducted for ASM 981. 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.

No signal for dermal or systemic carcinogenicity was noted in the dermal mouse carcinogenicity study. However, the doses selected for this study were not adequate according to agency criteria. In addition, the vehicle for this study was ethanol instead of the to be marketed

topical formulation vehicle. This also makes the design of this dermal mouse carcinogenicity study not adequate according to agency criteria. The sponsor selected a high dose group (4 mg/kg/day; average $AUC_{(0\text{-}24\ hr)}$ = 1080 ng·hr/ml after 52 weeks of treatment) in the dermal mouse carcinogenicity study that would not cause lymphoma formation. The results of a study to investigate the dosage response of immunosuppression and lymphoproliferative disorders following dermal administration to CD-1 mice for 13 weeks was able to determine a NOAEL for lymphoproliferative changes. The NOAEL for lymphoproliferative changes was identified in this study as 10 mg/kg/day ($AUC_{0\text{-}24hr}$ = 643 and 675 ng·hg/ml for males and females, respectively) for mice after 13 weeks of topical administration of ASM 981 dissolved in ethanol. The lowest dose that a low incidence of lymphoproliferative changes was identified in this study was 25 mg/kg/day ($AUC_{0\text{-}24hr}$ = 1845 and 1745 ng·hg/ml for males and females, respectively) for mice after 13 weeks of topical administration of ASM 981 dissolved in ethanol. It is important to note that during the 6-19-01 Exec CAC meeting, the committee asked about the source of the metastatic carcinoma noted in the thymus of one high dose male. A request was sent to the sponsor on 7-10-01 to clarify the source of this metastatic tumor.

No signal for dermal or systemic carcinogenicity was noted in the dermal rat carcinogenicity study. The rat dermal carcinogenicity study was conducted with the final to be marketed 1% ASM 981 cream. No rare or uncommon tumors were noted in this study. In addition, no statistically significant increase in any common tumors was detected in this study. All of the potential common neoplastic microscopic findings were within the historical control background incidence rate ranges for Wistar rats from the conducting laboratory. Therefore, it can be concluded that no significant treatment related effects on neoplastic microscopic findings were noted in this study. No significant toxicity was noted in this rat dermal carcinogenicity study. Therefore, the NOAEL is considered to be 10 mg/kg/day (average $AUC_{(0\text{-}24\ hr)}$ = 125 ng·hr/ml after 104 weeks of treatment).

It is important to note that incomplete histopathological analysis was performed in the low and mid dose groups in the dermal rat carcinogenicity study. During the 6-19-01 Exec CAC meeting, the committee determined that a histopathological reanalysis of the thymus and thyroid from all low and mid dose animals is necessary to determine if the potential signal noted in these two dose groups is of potential concern or not. In addition, the committee requested a statistical reanalysis for the combined incidence for the follicular cell adenoma and follicular cell carcinoma of the thyroid. The committee inquired about the historical background incidence rate for follicular cell carcinoma of the thyroid for the strain of rat used in this study. A request was sent to the sponsor on 7-10-01 for the additional information needs. A statistical reanalysis will be performed after the requested information is submitted to the agency.

The reproductive toxicity of ASM 981 was evaluated in fertility (rats), embryofetal developmental (rats and rabbits) and peri- and post-natal developmental (rats) oral studies. In addition, dermal teratogenicity (embryofetal developmental) studies were conducted in rats and rabbits.

Dermal administration of ASM 981 cream to rats and rabbits during the time of organogenesis was well tolerated and did not show any indication of embryotoxic or teratogenic potential. The NOAEL for embryotoxic and teratogenic effects in both studies was the highest

dose tested (10 mg/kg/day; 1% ASM 981 cream; no AUC values in rat; $AUC_{0\text{-}24\ hr}$ = 24.8 ng·hr/ml in rabbits). One possible reason for no effects being demonstrated in the dermal studies was the low levels of systemic exposure noted in both studies. The level of systemic exposure after topical administration of the ASM 981 cream was greater in rabbits compared to rats. However, overall the level of systemic exposure in the dermal rabbit teratogenicity study was significantly less (12.5X lower) than noted in the oral teratogenicity study conducted in rabbits. It is important to note that it would have been preferable if the daily treatment duration had been for 24 hours instead of for 6 hours in both of the dermal teratogenicity studies.

Higher systemic exposure levels were obtained in the oral reproductive toxicology studies. Fertility and general reproductive performance was assessed in the first part of the combined fertility and embryo-fetal development study in rats. No effect on mating or fertility was noted in males up to the dose of 45 mg/kg/day ($AUC_{0\text{-}24\ hr}$ = 872 ng·hr/ml). However, females at this dose showed prolonged estrus cycle or were acyclic. The NOAEL for female fertility and general reproductive performance was 10 mg/kg/day ($AUC_{0\text{-}6\ hr}$ = 194 ng·hr/ml). Compound related embryotoxicity as expressed by increased post implantation loss, reduced litter size, decreased fetal weights and increased rate of fetal retardation was noted at 45 mg/kg/day ($AUC_{0\text{-}6\ hr}$ = 620 ng·hr/ml). The disturbances of the estrus cycle and possibly also the post implantation loss could potentially be attributed to lower levels of sex hormones demonstrated in a special toxicology study. The low fetal weights and retardation might be due to direct toxic effects of ASM 981. ASM 981 crossed the blood-placental barrier in rats achieving mean embryonic tissue concentrations of 41 ng/g at the teratogenic NOAEL dose of 45 mg/kg/day (Maternal $AUC_{0-6\ hr}$ = 620 ng·hr/ml; extrapolated $AUC_{0-24\ hr}$ = 1448 ng·hr/ml).

Decreased body weight gain and food consumption were noted at the 20 mg/kg/day dose level in the embryo-fetal development study in rabbits. This dose was considered maternally toxic in this study. No effects on the development of the embryos was observed at the 20 mg/kg/day dose level in rabbits. ASM 981 crossed the blood-placental barrier in rabbits achieving mean embryonic tissue concentrations of 10 ng/g at the teratogenic NOAEL dose of 20 mg/kg/day (Maternal $AUC_{0-6\ hr}$ = 74 ng·hr/ml; extrapolated $AUC_{0-24\ hr}$ = 147 ng·hr/ml).

Similar prenatal findings as were observed in the oral fertility and embryofetal developmental study in rats were noted in the oral rat pre-post natal development study. At the high dose of 40 mg/kg/day only 2 of 22 females delivered live pups. Postnatal survival, development of the F1 generation, their subsequent maturation and fertility were not affected by treatment up to the highest dose evaluated in this study (10 mg/kg/day). Therefore, the NOAEL for postnatal development was 10 mg/kg/day. No AUC data was obtained in this study. However, the AUC data from the oral rat fertility and embryofetal developmental study could be used for this study since the 10 mg/kg/day dose level was tested in that study. Therefore, the AUC for the NOAEL for postnatal development can be set to equal the sponsor extrapolated value ($AUC_{0\text{-}24hr}$ = 465 ng·hr/ml) for labeling purposes.

In summary, reproductive toxicology studies conducted in rats and rabbits, by dermal or oral administration, gave no overt signal for teratogenic potential for ASM 981. However, an increase in embryofetal toxicity and postimplantation loss were noted in high dose (45 mg/kg/day) female rats. This could be interpreted as a potential signal for teratogenicity in this