CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-470

PHARMACOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY COVER SHEET

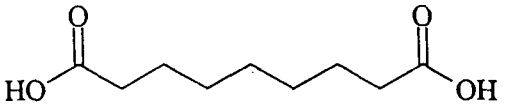
NDA number:	21-470
Review number:	2
Sequence number/date/type of submission:	C / 11-19-02 / Phase 4 commitment
Information to sponsor:	Yes (X) No ( )
Sponsor and/or agent:	Berlex Laboratories, Inc. 340 Changebridge Road P.O. Box 10000 Montville, NJ 07045-1000
Manufacturer for drug substance :	Schering AG

Reviewer name:	Barbara Hill
Division name:	Dermatologic and Dental Drug Products
HFD #:	HFD-540
Review completion date:	12-10-02

Drug:

Trade name:	Finacea™ gel, 15%
Generic name (list alphabetically):	Azelaic acid gel, 15% or Skinoren gel
Code name (for gel):	SH H 655BA, SH H00655BA
Code name (for active):	ZK 95421
Chemical name:	1,7-Heptanedicarboxylic acid
CAS registry number:	123-99-9
Mole file number:	N/A
Molecular formula/molecular weight:	$C_9H_{16}O_4$ / 188.2

Structure:



UV Absorption:

UV max (SH H00655BA {azelaic acid 15% gel} in methanol) –

{azelaic acid 15% gel

Note: A comparison of the absorbance from . of the azelaic acid 15% gel, vehicle gel and azelaic acid alone suggests that these two peaks appear to be due to the gel formulation.

Relevant INDs/NDAs/DMFs:

1) IND (; HFD-540; Sponsor
2) IND 61,324 (Azelaic acid 15% gel; papulo-pustular rosacea; HFD-540; Sponsor – Berlex)

3) IND [redacted]; HFD-540; Sponsor – Berlex)
4) NDA 20-428 (Azelex {Azelaic Acid} 20% cream; acne; HFD-540; approved 9-13-95; Sponsor – Allergan)

Drug class: Anti-keratinizing, anti-bacterial and anti-inflammatory agent

Indication: Treatment of inflammatory papules and pustules [redacted] of rosacea

Clinical formulation:

Finacea™ gel is formulated for clinical use as a 15% azelaic acid gel formulation. The composition of the Finacea™ gel is provided in the following table. The quantities listed in the table are g per 100 g of gel formulation.

Ingredient	% w/w
Azelaic Acid	15.00
Lecithin, NF	[redacted]
Medium chain triglycerides	[redacted]
Polysorbate 80, NF	[redacted]
Propylene glycol, USP	[redacted]
Polyacrylic acid *	[redacted]
Sodium hydroxide, NF	[redacted]
Edetate disodium, USP	[redacted]
Benzoic acid, USP	[redacted]
Purified Water, USP	[redacted]

* - The sponsor states that no USP/NF monograph is available for polyacrylic acid [redacted] The sponsor states that release tests are conducted according to the Ph. Eur. Monograph on [redacted] The quality corresponds to [redacted]

Reviewer's comments: It is known that the related [redacted] can potentially contain [redacted] due to the limits of allowable [redacted] contained in the specifications. It is not acceptable to have any level of [redacted] in topical drug products. The reviewing chemist, Mamta Gautam Basak, informed me that the specification [redacted] for [redacted] that was contained in the NDA, was NMT (not more than) [redacted] This is an acceptably low level for the specification for [redacted] to basically consider [redacted] as [redacted] free.

Route of administration: Topical

Proposed use: FINACEA™ is indicated for topical application in the treatment of inflammatory papules and pustules [redacted] of rosacea. A thin layer of FINACEA™ should be applied twice daily, in the morning and evening, to the entire affected areas and gently massaged into the skin. The duration of use of FINACEA™ can vary from person to person and depends on the severity of rosacea. In the majority of patients, improvement of the dermatosis was observable after 4 weeks.

The sponsor states that the maximum daily clinical dose of azelaic acid 15% gel is expected to be 1.0 g gel formulation containing 150 mg azelaic acid. This represents a daily dose of 2.5 mg/kg for a 60 kg individual, corresponding to 92.5 mg/m^2 based upon body surface area. It is to be applied daily over several months. Azelaic acid 15% gel was applied bid for 12 weeks in the two phase 3 clinical studies conducted to support the rosacea indication.

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

Introduction and drug history:

The pharmacology/toxicology review for Finacea gel was completed on 9-25-02 and received final sign off in DFS on 10-20-02. It was determined that the NDA is approvable from a pharmacology/toxicology perspective provided that the recommended labeling changes contained in the original NDA pharmacology/toxicology review are incorporated into the label. The sponsor stated in the NDA submission that they agreed to conduct a study to determine the photoco-carcinogenic potential of Finacea gel and a dermal carcinogenicity study with Finacea gel as phase 4 commitments. The agreed upon phase 4 commitments with recommended timelines were relayed to the sponsor on November 8, 2002. This submission contains the sponsor's response to the timelines recommended for the phase 4 commitments. The sponsor's response and review of the adequacy of the response is contained in the "Carcinogenicity" section of this review.

Studies reviewed within this submission:

No new nonclinical studies were included in this submission.

Executive Summary

I. Recommendations

A. Recommendation on Approvability
The NDA is approvable from a pharmacology/toxicology perspective provided that the recommended labeling changes provided in the original NDA pharmacology/toxicology review are incorporated into the label.

B. Recommendation for Nonclinical Studies
The sponsor has agreed to conduct the recommended photoco-carcinogenicity and dermal carcinogenicity studies for azelaic acid 15% gel as phase 4 commitments. The proposed timeline and study protocol included in this submission appear to be adequate.

C. Recommendations on Labeling
Recommended wording for the nonclinical portions of the label are provided in the labeling recommendations section in the original NDA pharmacology/toxicology review.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings
No major nonclinical toxicological findings were noted in the nonclinical toxicology studies conducted to support azelaic acid.

B. Pharmacologic Activity
Azelaic acid possesses some anti-keratinizing, anti-bacterial and anti-inflammatory activity.

C. Nonclinical Safety Issues Relevant to Clinical Use
No nonclinical safety issues were identified that would be relevant to clinical use of azelaic acid 15% gel for the rosacea indication.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:
HFD-540/DIV DIR/WILKIN
HFD-540/ PHARM SUP/JACOBS
HFD-540/PHARM/HILL
HFD-540/MO/VAUGHAN
HFD-540/CHEM/GAUTAMBASAK

APPEARS THIS WAY
ON ORIGINAL

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:

Carcinogenicity summary:

No long term carcinogenicity studies have been conducted with either azelaic acid, the approved 20% azelaic acid cream or 15% azelaic acid gel. The sponsor was informed that a study to determine the photoco-carcinogenic potential of azelaic acid 15% gel and a dermal carcinogenicity study for the 15% azelaic acid gel are recommended for the final development of this drug product. The sponsor agreed to the conduct of these recommended studies as phase 4 commitments in the original NDA submission. The recommended phase 4 commitments and timelines for the conduct of these studies were relayed to the sponsor on November 8, 2002 via Fax. Each of the recommended phase 4 commitments and timelines followed by the sponsor's response and evaluation of this response is provided below.

First recommended phase 4 commitment and timeline:

1. The applicant commits to conducting a photoco-carcinogenicity study in male and female mice with the azelaic acid 15% gel.

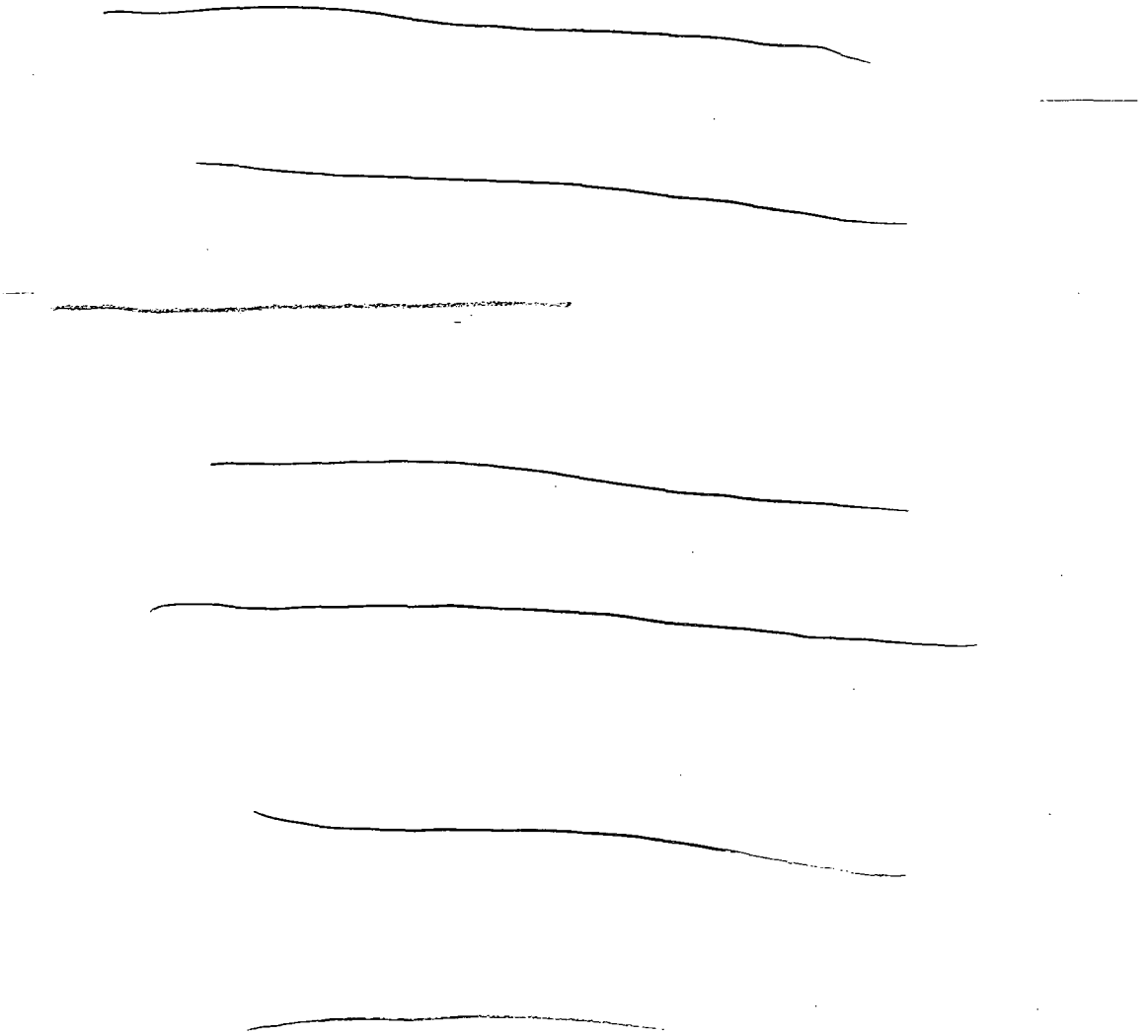
   Protocol submission: Within 4 months of the date of the approval letter for this NDA
   Study Start: Within 6 months of the date of the approval of the protocol
   Final Report Submission: Within 12 months after the study completion

Sponsor's Response:

The sponsor requests postponement of the first commitment until the division has reviewed the

The sponsor provides the following information in the submission concerning the

Reviewer's Comments:



Second recommended phase 4 commitment and timeline:

2. The applicant commits to conducting an alternative, dermal carcinogenicity study in transgenic mice (Tg.AC assay) with the azelaic acid 15% gel.

   Protocol submission: Within – months of the date of the approval letter for this NDA
   Study Start: Within 6 months of the date of the approval of the protocol
   Final Report Submission: Within 12 months after the study completion

Sponsor's Response:

The sponsor commits to conduct of an alternative, dermal carcinogenicity study in transgenic mice (Tg.AC assay) with azelaic acid 15% gel. However, the sponsor requests that the protocol submission time be changed to [redacted] 5 months after the anticipated date of the Approval Letter for this NDA (January 21, 2003)".

The sponsor states that the dose range-finding study for the Tg.AC assay with the 15% azelaic acid gel will start in [redacted]. The audited draft report will be available in [redacted] The sponsor intends to submit this report to the division with the protocol for the definitive Tg.AC study. Therefore, the sponsor states that this submission cannot be made before [redacted]

Reviewer's Comments:

The proposed change for the protocol submission time from "within [redacted] months" to [redacted] 5 months" after the approval letter is acceptable. It is interesting that the sponsor has inserted a date for the approval letter for this NDA of [redacted] 3. It appears that the sponsor anticipates that the division will meet the 10 month review cycle for this NDA.

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:

The sponsor's request to postpone the study to determine the photoco-carcinogenic potential of the 15% azelaic acid gel until the division has reviewed the [redacted] is acceptable. It would be preferable to submit the [redacted] to the NDA when it becomes available instead of submitting the [redacted] The sponsor's proposal for [redacted] appears to be reasonable. The sponsor has made an attempt to follow recommendations for [redacted] The final determination as to whether the [redacted] is acceptable to determine the photoco-carcinogenic potential of the 15% azelaic acid gel will be determined after review of the [redacted]

The sponsor's request to change the timeframe for submission of the protocol for the dermal carcinogenicity study conducted in transgenic mice (Tg.AC assay) with the 15% azelaic acid gel to [redacted] 5 months after the approval letter for this NDA is acceptable.

Recommendations:

External Recommendations (to sponsor):

It is recommended that the following information be relayed to the sponsor for NDA 21-470 concerning the submission received on 11-19-02.

1) The sponsor's request to postpone the study to determine the photoco-carcinogenic potential of the 15% azelaic acid gel until the division has reviewed the [redacted] is acceptable. It would be preferable to submit the [redacted] to the NDA when it becomes available instead of submitting the [redacted] The sponsor's proposal for [redacted] appears to be reasonable. The sponsor has made an attempt to follow recommendations for use of [redacted] The final determination as to whether the [redacted] is acceptable to determine the photoco-carcinogenic potential of the 15% azelaic acid gel will be determined after review of the study report.

2) The sponsor's request to change the timeframe for submission of the protocol for the dermal carcinogenicity study conducted in transgenic mice (Tg.AC assay) with the 15% azelaic acid gel to [redacted] 5 months after the approval letter for this NDA is acceptable.

Labeling with basis for findings: Label recommendations are provided in the original NDA pharmacology/toxicology review.

X. APPENDIX/ATTACHMENTS:

Addendum to review: N/A

Other relevant materials (Studies not reviewed, appended consults, etc.): N/A

Any compliance issues: N/A

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
12/12/02 08:58:42 AM
PHARMACOLOGIST

Abby Jacobs
12/12/02 10:37:15 AM
PHARMACOLOGIST

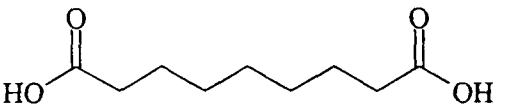
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number:	21-470
Review number:	1
Sequence number/date/type of submission:	000 / 3-21-02 / Original NDA submission 000 / 5-14-02 / Letter of reference
Information to sponsor:	Yes ( ) No (X)
Sponsor and/or agent:	Berlex Laboratories, Inc. 340 Changebridge Road P.O. Box 10000 Montville, NJ 07045-1000
Manufacturer for drug substance :	Schering AG

Reviewer name:	Barbara Hill
Division name:	Dermatologic and Dental Drug Products
HFD #:	HFD-540
Review completion date:	9-25-02

Drug:

Trade name:	Finacea™ gel, 15%
Generic name (list alphabetically):	Azelaic acid gel, 15% or Skinoren gel
Code name (for gel):	SH H 655BA, SH H00655BA
Code name (for active):	ZK 95421
Chemical name:	1,7-Heptanedicarboxylic acid
CAS registry number:	123-99-9
Mole file number:	N/A
Molecular formula/molecular weight:	$C_9H_{16}O_4$ / 188.2
Structure:	



UV Absorption:

UV max (SH H00655BA {azelaic acid 15% gel} in methanol) – [redacted]
[redacted] [azelaic acid 15% gel does not absorb in the UVB/UVA/visible range]

Note: A comparison of the absorbance from [redacted] of the azelaic acid 15% gel, vehicle gel and azelaic acid alone suggests that these two peaks appear to be due to the gel formulation.

Relevant INDs/NDAs/DMFs:

1) IND [redacted] ([redacted] HFD-540; Sponsor – [redacted])

2) IND 61,324 (Azelaic acid 15% gel; papulo-pustular rosacea; HFD-540; Sponsor – Berlex)
3) IND [redacted] HFD-540; Sponsor – Berlex)
4) NDA 20-428 (Azelex {Azelaic Acid} 20% cream; acne; HFD-540; approved 9-13-95; Sponsor – Allergan)

Drug class: Anti-keratinizing, anti-bacterial and anti-inflammatory agent

Indication: Treatment of inflammatory papules and pustules [redacted] of rosacea

Clinical formulation:

Finacea™ gel is formulated for clinical use as a 15% azelaic acid gel formulation. The composition of the Finacea™ gel is provided in the following table. The quantities listed in the table are g per 100 g of gel formulation.

Ingredient	% w/w
Azelaic Acid	15.00
Lecithin, NF	[redacted]
Medium chain triglycerides	[redacted]
Polysorbate 80, NF	[redacted]
Propylene glycol, USP	[redacted]
Polyacrylic acid ([redacted]	[redacted]
Sodium hydroxide, NF	[redacted]
Edetate disodium, USP	[redacted]
Benzoic acid, USP	[redacted]
Purified Water, USP	[redacted]

* - The sponsor states that no USP/NF monograph is available for polyacrylic acid [redacted] The sponsor states that release tests are conducted according to the Ph. Eur. Monograph on [redacted] The quality corresponds to [redacted]

Reviewer's comments: It is known that the related [redacted] can potentially contain [redacted] due to the limits of allowable [redacted] contained in the specifications. It is not acceptable to have any level of [redacted] in topical drug products. The reviewing chemist, Mamta Gautam Basak, informed me that the specification for [redacted] for [redacted] that was contained in the NDA, was NMT (not more than) [redacted]. This is an acceptably low level for the specification for [redacted] to basically consider [redacted] as [redacted] free.

The sponsor included a letter of reference from [redacted] to DMF [redacted] on file for [redacted] Mamta informed me that the DMF [redacted] submission (dated April 6, 1999) contains results of an [redacted]

Route of administration: Topical

Proposed use: FINACEA™ is indicated for topical application in the treatment of inflammatory papules and pustules ——— of rosacea. A thin layer of FINACEA™ should be applied twice daily, in the morning and evening, to the entire affected areas and gently massaged into the skin. The duration of use of FINACEA™ can vary from person to person and depends on the severity of rosacea. In the majority of patients, improvement of the dermatosis was observable after 4 weeks.

The sponsor states that the maximum daily clinical dose of azelaic acid 15% gel is expected to be 1.0 g gel formulation containing 150 mg azelaic acid. This represents a daily dose of 2.5 mg/kg for a 60 kg individual, corresponding to 92.5 mg/m^2 based upon body surface area. It is to be applied daily over several months. Azelaic acid 15% gel was applied bid for 12 weeks in the two phase 3 clinical studies conducted to support the rosacea indication.

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

Introduction and drug history:

Rosacea is a chronic dermatosis characterized by facial flushing, erythema, telangiectasia, inflammatory episodes with papules and pustules, and in severe cases, rhinophyma. It most commonly becomes manifest in patients between the ages of 30 to 50 years. Clinically, but not pathologically, rosacea shares some features in common with acne, particularly the occurrence of inflammatory papules and pustules, some facial redness and the responsiveness to certain antibiotics.

Azelaic acid is a naturally occurring dicarboxylic acid. Currently, azelaic acid is used as a 20% cream in the topical treatment of acne. Azelaic acid 20% cream has been approved for marketing for this indication in multiple counties. In the US, azelaic acid 20% cream was approved for the treatment of mild to moderate forms of acne vulgaris under NDA 20-428 with a trade name of Azelex® and Finevin™ under the sponsorship of Allergan. Berlex Laboratories is an approved distributor of Finevin™ under NDA 20-428. Berlex and Allergan co-market the drug product under NDA 20-428 using the tradenames Finevin™ and Axelex®, respectively. Berlex's parent company, Schering AG, Berlin, Germany, manufactures the drug substance that is used in both the approved cream formulation and gel formulation that is the subject of this NDA.

It is believed that the antibacterial and comeodolytic activity of azelaic acid is responsible for its beneficial effects in the treatment of acne. The sponsor noted that controlled comparisons with either placebo or topical metronidazole suggested that azelaic acid 20% cream may have some efficacy in the treatment of rosacea. The sponsor proposed that a direct anti-inflammatory effect of azelaic acid by inhibition of neutrophil generated reactive oxygen radicals may account for this beneficial effect. The sponsor has developed an azelaic acid 15% gel formulation. The scope of this NDA was to investigate the efficacy of the sponsor's azelaic acid 15% gel in the treatment of moderate, papulo-pustular rosacea by comparison with its vehicle.

It was determined during the review of IND 61,324 that the need for a nonclinical photoirritation test of azelaic acid 15% gel could be waived. The rationale for this decision was that the UV spectrum for the 15% azelaic acid gel submitted to IND 61,324 did not show any significant absorption in the UVB/UVA/VIS spectrum.

The following studies were recommended to the sponsor as Phase 4 commitments after the review of IND 61,324.

1) A study to determine the photoco-carcinogenic potential associated with azelaic acid 15% gel.
2) A dermal carcinogenicity study that could be conducted as an alternative assay in the Tg.AC mouse model.

The sponsor proposed to conduct a photoco-carcinogenicity study in hairless mice and a dermal carcinogenicity study in Tg.AC mice as phase 4 commitments during a pre-NDA meeting conducted for IND 61,324 on August 30, 2001. The division concurred that this was acceptable. The sponsor included more specific information concerning proposed timelines for conduct of these studies in the NDA. The acceptability of the sponsor's proposal will be discussed in the "Carcinogenicity" section of this review.

Studies reviewed within this submission:

This NDA was a totally electronic NDA submission. Electronic copies of study reports for nonclinical studies that were conducted by Schering AG or were included in this NDA submission. The sponsor for NDA 20-428 (azelaic acid 20% cream) is Allergan. Some nonclinical repeat dose toxicology studies that have been conducted with systemic azelaic acid and topical azelaic acid 20% cream were not conducted by Schering AG or The sponsor submitted an electronic copy of a letter of authorization from Allergan which authorizes Berlex Laboratories to cross-reference Allergan's IND for and NDA 20-248 in support of their azelaic acid containing application. This letter of authorization allows Berlex Laboratories to have access to the nonclinical data generated by Allergan for the systemic azelaic acid and topical azelaic acid cream 20% nonclinical toxicology studies.

All of the nonclinical studies that have been conducted for azelaic acid are listed below. The results from these studies will be summarized in this review document. It will be annotated next to the study the IND or NDA where the original review of the study was performed and the contact lab that conducted the study. The two repeat dose toxicology studies included in NDA 20-428 that Allergan conducted are the six month oral toxicity study in dogs and the six month dermal toxicity study in rats. The results from both of these studies are summarized in this review.

Two new nonclinical pharmacokinetic studies were included in this NDA submission for the azelaic acid 15% gel. The review of these studies is provided in the appropriate section of this review document.

Pharmacology Studies (previously reviewed):

1) Preliminary studies on the antimicrobial effect of azelaic acid (IND —— Schering AG Report 5465)
2) Antimicrobial effect of azelaic acid (in vitro investigation of a selected group of microorganisms) (IND —— , Schering AG Report 6386)
3) Studies on the comedolytic effect of azelaic acid and pimelic acid on the tetradecane treated rabbit ear (IND —— Schering AG Report 6932)
4) The effect of topically applied azelaic acid on the lipid metabolism of the hamster (lipogenesis of the hamster ear, fresh weights of flank organs, serum lipid level and lipid composition of hamster ear tissue) (IND —— ;chering AG Report 6819)

Safety Pharmacology Studies (previously reviewed):

1) Pharmacological characterization of sodium azelate: Influence on the intermediary metabolism of rats, as measured by the behavior of the glucose, free fatty acids and lactate in the blood (NDA 20-428; Schering AG Report 6094)
2) Pharmacological characterization of sodium azelate: Effect on rabbit intermediary metabolism and liver function after repeated intravenous injection (NDA 20-428; Schering AG Report 6519)
3) Neurotropic effects of sodium azelainate (ZK 95412) in the Irwin test in rats after single intravenous administration (NDA 20-428; Schering AG Report 6199)
4) Investigations on the cardiovascular action of AZ 95421 (disodium salt of azelaic acid) in conscious rats and in isolated atria and papillary muscles of the guinea pig (NDA 20-428; Schering AG Report 6204)
5) Influence of sodium azelate after i.v. injection on the renal Na^+-, K^+-, Ca^{++}- and water excretion of rats (NDA 20-428; Schering AG Report 6103)
6) Pharmacological characterization of sodium azelainate: In vitro effect on smooth muscle organs (NDA 20-428; Schering AG Report 6437)

Systemic Nonclinical Pharmacokinetic/Toxicokinetic Studies (previously reviewed):

1) Whole body autoradiographic studies after the intravenous administration of ^{14}C-azelaic acid to male and pregnant rats (IND —— , Schering AG Report 5194)
2) Whole body autoradiographic studies in male, pigmented rats after intravenous administration of ^{14}C-azelaic acid (IND —— , Schering AG Report 5442)
3) Pharmacokinetics of ^{14}C-azelaic acid after intravenous (10 m/kg) and oral administration (1000 mg/kg) in female rats (IND —— , Schering AG Report 5106)
4) The pharmacokinetics of ^{14}C-azelaic acid after intravenous (10 mg/kg) and intragastric (500 mg/kg) administration in rabbits (IND —— Schering AG Report 5708)
5) Transplacental passage of ^{14}C-azelaic acid in rabbits (NDA 20-428; Schering AG Report 9023)
6) The pharmacokinetics of ^{14}C-azelaic acid after intravenous (10 mg/kg) and intragastric (100 mg/kg) administration in beagle dog (IND —— Schering AG Report 5687)
7) The pharmacokinetics of ^{14}C-azelaic acid after intravenous (10 mg/kg) and intragastric (150 mg/kg) administration in monkeys (IND —— , Schering AG Report 5684)

Dermal Nonclinical Pharmacokinetic/Toxicokinetic Studies (previously reviewed):

1) Does salicylic acid increase the availability of azelaic acid in guinea pig skin? (IND 38,271; Schering AG Report 6195)
2) Percutaenous absorption of azelaic acid in beagle dogs following dermal application of ca. 1.5 g Skinoren® cream to 30 cm^2 of intact skin (NDA 20-428; Schering AG Report A269)
3) Study on the in vitro permeation of azelaic acid though intact skin of hairless mice using the FRANZ-flow-through-diffusion-cell (IND 61,324; Schering AG Report AY15)

Dermal Nonclinical Pharmacokinetic/Toxicokinetic Studies (included in this submission):

1) Comparative study of percutaneous resorption of ^{14}C-azelaic acid in Beagle dogs following 24 hours dermal application of Skinoren-cream and Finevin-gel (Schering AG Report A05699)
2) Comparative study of percutaneous resorption of ^{14}C-azelaic acid in rats following 24 hours dermal application of Skinoren-cream and Finevin-gel (Schering AG Report A05700)

Acute Toxicology Studies (previously reviewed):

1) Systemic tolerance test in male mice after a single intragastric application (IND [redacted] Schering AG Report 5651)
2) Systemic tolerance test in female mice after a single intragastric application (IND [redacted] Schering AG Report 5639)
3) Systemic tolerance test in male mice after a single intraperitoneal application (IND [redacted] Schering AG Report 5699)
4) Systemic tolerance test in female mice after a single intraperitoneal application (IND [redacted] Schering AG Report 5640)
5) Systemic tolerance test in male rats after a single intragastric application (IND [redacted] Schering AG Report 5652)
6) Comparative acute toxicity in rats following a single intraperitoneal application with approximate LD50 determination (IND [redacted] Schering AG Report 6231)
7) Systemic test in male and female dogs after a single oral (intragastric) administration (IND [redacted] Schering AG Report 5709)

Repeat Dose Systemic Toxicology Studies (previously reviewed):

1) Assessment of toxicity to rats by daily intragastric administration for 28-29 days (IND [redacted] Schering AG Report 5418)
2) Systemic tolerance test in rats after daily intragastric administration over a period of 27 weeks (IND [redacted] Schering AG Report 7079)
3) Systemic tolerance study in monkeys (*Macaca fascicularis*) after daily per os (intragastric) administration over 28-29 days (IND [redacted]; Schering AG Report 6517)
4) Six-month oral (capsule) toxicity study in dogs with azelaic acid with a recovery segment of one month (NDA 20-428; [redacted] -123022)

Repeat Dose Dermal Toxicology Studies (previously reviewed):

1) Systemic tolerance study in Beagle dogs after daily dermal administration over 26-27 weeks (IND —, Schering AG Report 7080)
2) Azelaic acid 20% cream: Six-month dermal and systemic safety evaluation in rats with a one-month recovery period (NDA 20-428; Report 1764-2530-1; Contract lab not specified in NDA review)

Genetic Toxicology Studies (previously reviewed):

1) Evaluation of ZK 062498 in the Ames Salmonella/microsome mutagenicity test (IND —, Schering AG Report 5239)
2) ZK 062498 Evaluation in the Ames Salmonella/microsome mutagenicity test (IND —; Schering AG Report 6874)
3) Test report of study LMP 146: ZK 062498 - Detection of gene mutations in somatic mammalian cells in culture: HGPRT-test with V79 cells (IND —→ —— Report 7081)
4) ZK 062498 - Evaluation of the clastogenic potential in the human lymphocyte test (IND —; Schering Report 7082)
5) Studies on the mutagenic potential of ZK 062498 in the mouse dominant lethal assay (IND — Schering AG Report 5461)
6) Study of the mutagenic potential of azelaic acid (ZK 62498) in the mouse micronucleus test (IND —, Schering AG Report A03118)

Reproductive and Developmental Toxicology Studies (previously reviewed):

1) Fertility study in the rat (IND —— Report 5943)
2) Oral (gavage) teratology study in the rat (IND —— Report 5643)
3) 2-week dose-finding study with ZK 62.498 following per os administration to rabbits in order to determine doses which appear suitable for the performance of a teratogenicity study (SII) (IND — Schering AG Report 5208)
4) Embryotoxicity including teratogenicity study in rabbits by intragastric administration from day 6 to 27 of gestation (IND —— Schering AG Report 5717)
5) 2-week dose-finding study with ZK 62.498 following per os administration to monkeys in order to determine which doses appear suitable for the performance of a teratogenicity study (SII) (IND — Schering AG Report 5236)
6) Teratology study in Cynomolgus monkeys (IND —— Report 5725)
7) Peri- and postnatal study in rats after daily intragastric administration from day 15 postcoitum to day 21 postpartum (IND —, Schering AG Report 5861)

Special Toxicology Studies (previously reviewed):

1) Local tolerance test of SH C 441 DA (ZK 62.498) on the rabbit conjunctiva after a single application (IND [redacted] Schering AG Report 5738)
2) Local tolerance test of the vehicle of SH C 441 DA on the rabbit conjunctiva after a single application (IND [redacted], Schering AG Report 5706)
3) SH C 441F Local tolerance test on the monkey's (*Macaca fascicularis)* conjunctiva after a single application (NDA 20-428; Schering AG Report 8639)
4) Azelaic acid: Maximization test in guinea pigs to determine the potential sensitizing effect (IND [redacted] Schering AG Report 5200)
5) Local tolerance test of SH H655BA on rabbit skin (M + F) after a single dermal administration (IND [redacted], Schering AG Report A03292)
6) Skinoren Gel versus Skinoren Cream local tolerance test in rabbits (M+F) after a daily dermal application over 4 weeks (28 applications) (IND [redacted], Schering AG Report A03309)

Executive Summary

I. Recommendations

A. Recommendation on Approvability
The NDA is approvable from a pharmacology/toxicology perspective provided that the recommended labeling changes are incorporated into the label.

B. Recommendation for Nonclinical Studies
The sponsor has agreed to conduct the recommended photoco-carcinogenicity and dermal carcinogenicity studies for azelaic acid 15% gel as phase 4 commitments.

C. Recommendations on Labeling
Recommended wording for the nonclinical portions of the label are provided in the labeling recommendations section located at the end of this review.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings
No major nonclinical toxicological findings were noted in the nonclinical toxicology studies conducted to support azelaic acid.

B. Pharmacologic Activity
Azelaic acid possesses some anti-keratinizing, anti-bacterial and anti-inflammatory activity.

C. Nonclinical Safety Issues Relevant to Clinical Use
No nonclinical safety issues were identified that would be relevant to clinical use of azelaic acid 15% gel for the rosacea indication.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:
HFD-540/ PHARM SUP/JACOBS
HFD-540/PHARM/HILL
HFD-540/MO/VAUGHAN
HFD-540/CHEM/GAUTAMBASAK
HFD-540/PM/CROSS

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Pharmacology summary:

The antimicrobial activity of azelaic acid was assessed in aerobic and anaerobic bacteria, yeasts and fungi. The effects of azelaic acid on the accumulation of keratinous material in the infundibular region of the sebaceous follicle (the microcomedo) were tested in an in vivo rabbit model. In addition, the effects of azelaic acid on the sebaceous gland and lipid metabolism were evaluated in a hamster model.

Azelaic acid has demonstrated in vitro bacteriostatic and bacteriocidal activity against a variety of aerobic and anaerobic bacteria including *Propionibacterium acnes* and *Staphylococcus aureus*. The numbers of *P. acnes* are known to be elevated in acne vulgaris and successful antibacterial treatment of acne causes a decline in *P. acnes* populations.

The effects of azelaic acid on the accumulation of keratinous material in the infundibular region of the sebaceous follicle (the microcomedo) were tested in an in vivo animal model (tetradecane-induced comedo formation in the rabbit ear). A statistically significant reduction of follicular epithelial hyperplasia (i.e. comedo size) was observed morphometrically after daily application of an ethanolic solution containing 20% azelaic acid or after daily application of azelaic acid 20% cream for 11 days to rabbit ears retreated with tetradecane. No effect was observed after similar application of an ethanolic solution of 20% pimelic acid, the initial metabolite formed in animals and humans by β-oxidation, for 11 consecutive days.

An in vivo experiment was conducted to determine if azelaic acid has a direct effect on the sebaceous gland. An ethanolic solution containing 10% azelaic acid or a cream formulation containing 20% azelaic acid was applied to the ear of intact Syrian hamsters and to castrated, testosterone propionate-substituted golden Syrian hamsters. No effects were noted on ear tissue lipid profiles, serum total cholesterol, triglycerides or fatty acids after daily application over 4 months.

Information is contained under the CLINICAL PHARMACOLOGY section of the Azelex® (azelaic acid cream, 20%) label

"The exact mechanism of action of azelaic acid is not known. The following *in vitro* data are available, but their clinical significance is unknown. Azelaic acid has been shown to possess antimicrobial activity against *Propionibacterium acnes* and *Staphylococcus epidermidis*. The antimicrobial action may be attributable to inhibition of microbial cellular protein synthesis.

A normalization of keratinization leading to an anticomedonal effect of azelaic acid may also contribute to its clinical activity. Electron microscopic and immunohistochemical evaluation of skin biopsies from human subjects treated with AZELEX® demonstrated a reduction in the thickness of the stratum corneum, a reduction in number and size of keratohyalin granules, and a

reduction in the amount and distribution of filaggrin (a protein component of keratohyalin) in epidermal layers. This is suggestive of the ability to decrease microcomedo formation."

Pharmacology conclusions:

The possible pharmacodynamic activities of azelaic acid were evaluated in several nonclinical models related to factors that may be associated with acne pathology. The clinical review team will make the final determination of the relevance, if any, of the results from these studies to the treatment of papulo-pustular rosacea.

II. SAFETY PHARMACOLOGY:

Safety pharmacology studies for azelaic acid were performed with the disodium salt of azelaic acid due to its higher water solubility. Safety pharmacology studies with sodium azelainate were evaluated in vivo in rats and rabbits and in vitro in isolated atria, papillary muscles and smooth muscle organs of the guinea pig.

Safety pharmacology summary:

Two in vivo studies were conducted to evaluate the effect of azelaic acid on intermediary metabolism. A single 1000 mg/kg intravenous dose of sodium azelainate in rats resulted in transient (15 to 30 minutes after dosing) increases in lactate concentration associated with reduced free fatty acid concentrations. In a similar study of rabbits dosed intravenously with 100 mg/kg/day of sodium azelainate for 6 consecutive days, glucose tolerance was slightly delayed but there was no effect on liver function or serum concentrations of lactate, pyruvate, glucose, urea and creatinine.

In safety pharmacology studies of sodium azelainate, neurotropic effects observed in rats following a single intravenous administration were limited to individual instances of mydriasis (400 mg/kg) and slightly reduced locomotor activity (800 mg/kg) in the Irwin test. Sodium azelainate had no chronotropic or inotropic effects on spontaneous or stimulated contractions in isolated guinea pig atria preparations at concentrations up to 10^{-3} M. Sodium azelainate did not effect stimulated contraction of isolated guinea pig papillary muscle at similar concentrations. Intravenous administration of sodium azelainate in conscious rats as doses of 10, 50 and 250 mg/kg did not influence heart rate or blood pressure up to 1 hour postadministration. Renal function of Wistar rats (monitored by excretion of Na^+, K^+, and Ca^{+2} and urinary flow over a 20 hour period) was not affected after single intravenous doses of sodium azelainate (up to 1000 mg/kg). Sodium azelainate had no clear effect on isolated smooth muscle preparations of guinea pig ileum, trachea or uterus with the exception of a moderate stimulatory effect at the highest in vitro concentration tested (25 mg/ml).

Safety pharmacology conclusions:

Nonclinical safety pharmacology studies did not indicate significant effects for azelaic acid on intermediary metabolism, liver function, renal function, cardiovascular function, smooth

muscle or the nervous system under the conditions used in these studies. No additional nonclinical safety pharmacology studies are recommended for Finacea gel at this time.

III. PHARMACOKINETICS/TOXICOKINETICS:

Pharmacokinetic/Toxicokinetic Study #1:

Study Title:	Comparative study of percutaneous resorption of ^{14}C-azelaic acid in Beagle dogs following 24 hours dermal application of Skinoren-cream and Finevin-gel
Study No:	A05699
Conducting laboratory:	Schering AG, Berlin, Germany
Date of study initiation:	12-18-00
GLP compliance:	No

The objective of this study was to compare the percutaneous absorption of ^{14}C-azelaic acid (^{14}C-AA) in Beagle dogs following 24 hours dermal application of Skinoren cream (20% azelaic acid) and Finevin gel (15% azelaic acid). Three groups of beagle dogs (2/sex/group) received a 24 hour non-occlusive topical application (covered loosely with dressing material) of either 150 mg/kg ^{14}C-AA as Skinoren cream or 150 mg/kg or 15 mg/kg ^{14}C-AA as Finevin gel. Skinoren cream was applied on a surface area of 15 cm^2/kg and Finevin gel was applied on a treatment area of 20 cm^2/kg. The area doses were 50 mg Skinoren cream (10 mg ^{14}C-AA/cm^2), 50 mg Finevin gel (7.5 mg ^{14}C-AA/kg) and 5 mg Finevin gel (0.75 ^{14}C-AA/cm^2).

All animals were kept individually in metabolism cages for 7 days. Urine and feces were collected daily for 7 days. Radioactivity was measured by liquid scintillation counting in urine, plasma, feces, cage wash, all dressing material and skin wash solution. In addition concentrations of radiolabeled ^{14}C- and non-labeled ^{12}C-azelaic acid (measure of endogenous levels of azelaic acid) and the metabolite pimelic acid were determined in plasma and urine by LC/MS.

The recovery rates of radioactive compound were much higher in the high dose groups (96.2% and 97.1%) compared to the low dose Finevin gel group (77%). The major part of the dose was recovered from the dressing material and skin wash at 24 hours post dose (non absorbed dose fraction). The study report states that recovery of the non-absorbed dose fraction in the low dose group may have been incomplete due to technical difficulties with extraction of small amounts of test article from the dressing material.

The following table provides a comparison of recovery (over a 7 day period) of ^{14}C-radiolabled compound (% of dose) after topical administration of the three doses of ^{14}C-AA in this study. Calculated values are provided as mean ± SD.

Measurement	Units	Skinoren-cream	Finevin-gel	Finevin-gel
Dose (drug)	mg/kg ^{14}C-AA	150	150	15
Dose (^{14}C)	KBq/kg	740	740	740
Dose (product)	mg cream, gel/kg	750	1000	100
Dose (product)	mg cream,gel/cm^2	50	50	5
Treatment area	cm^2/kg	15	20	20
Area dose	mg AA/cm^2	10	7.5	0.75
		Mean ± SD	Mean ± SD	Mean ± SD
Urine	% of dose	0.49 ± 0.13	0.34 ± 0.19	2.39 ± 1.62
Feces	% of dose	0.30 ± 0.30	0.01 ± 0.02	0.41 ± 0.52
Cage wash	% of dose	0.38 ± 0.22	0.08 ± 0.05	1.03 ± 0.58
Total absorbed	% of dose	1.16 ± 0.40	0.43 ± 0.25	3.83 ± 2.42
Mean flux	µg AA/cm^2/hr	4.8 ± 1.7	1.3 ± 0.8	1.2 ± 0.8
Dressing material	% of dose	84.24 ± 5.65	93.41 ± 1.99	47.77 ± 3.18
Skin wash	% of dose	10.83 ± 4.17	3.25 ± 0.72	25.42 ± 5.12
Total non-absorbed	% of dose	95.07 ± 2.39	96.66 ± 1.39	73.19 ± 3.45
Total recovery	% of dose	96.24 ± 2.20	97.13 ± 1.56	77.03 ± 4.13

The extent of percutaneous absorption (% dose from urine + feces) of azelaic acid was low in both high dose groups (Skinoren cream = 1.16% and Finevin gel = 0.43%). A ten fold reduction of the area of dose of Finevin gel yielded ~9 fold increase of the absorbed dose fraction (3.83%). The percutaneous AA fluxes were similar at both dose levels of Finevin gel in the dog. The difference in % absorbed dose between the low and high dose Finevin gel treatment groups is not a surprising result. The design of this study provided for an increase in dose by adding more of the Finevin gel to the same treatment area size that was used in the low dose group. This only increased the thickness of the layer of Finevin gel applied in the high dose group. Percutaneous flux would only occur at the point were test article was in contact with the skin. It can not be assumed that there would be a greater diffusion of azelaic acid through the thicker layer of gel applied to the skin in the high dose group. It would have been a more effective study design to have increased the treatment area in the high dose group while maintaining the same amount of Finevin gel applied per cm^2 of treatment area.

The study report states that formation of $^{14}CO_2$ was observed in previous pharmacokinetics studies conducted in rats. Release of $^{14}CO_2$ was not measured in this study. Therefore, it might be assumed that the percutaneous absorption could have been slightly underestimated in this study.

The level of ^{14}C-azelaic acid or ^{14}C-pimelic acid were below the limit of quantitation in plasma [redacted], at all measured timepoints following topical application of the radiolabeled compound. Mean plasma concentrations of endogenous ^{12}C-azelaic acid and the metabolite ^{12}C-pimelic acid did not change during or after the treatment period.

Percutaneous flux of azelaic acid in the dog was somewhat higher following application of Skinoren cream compared to Finevin gel (4.8 µg AA/cm^2/hr vs 1.3 µg AA/cm^2/hr, respectively). A corresponding higher total % absorbed dose was noted for Skinoren cream compared to Finevin gel (1.16% vs 0.43%, respectively). However, it is unclear if this relatively small difference would translate into a meaningful difference in systemic exposure under conditions of clinical use for both drug products.

Pharmacokinetic/Toxicokinetic Study #2:

Study Title:	Comparative study of percutaneous resorption of ^{14}C-azelaic acid in rats following 24 hours dermal application of Skinoren-cream and Finevin-gel
Study No:	A05700
Conducting laboratory:	Schering AG, Berlin, Germany
Date of study initiation:	12-18-00
GLP compliance:	No

The objective of this study was to compare the percutaneous absorption of ^{14}C-azelaic acid (^{14}C-AA) in rats following 24 hours dermal application of Skinoren cream (20% azelaic acid) and Finevin gel (15% azelaic acid). Four groups of female Wistar rats (4 females/group) received a 24 hour non-occlusive topical application (covered loosely with dressing material) of either 30 or 300 mg/kg ^{14}C-AA as Skinoren cream or 30 or 300 mg/kg ^{14}C-AA as Finevin gel. Skinoren cream was applied on a surface area of 30 cm^2/kg and Finevin gel was applied on a treatment area of 40 cm^2/kg. The area doses were 50 mg Skinoren cream (10 mg ^{14}C-AA/cm^2), 5 mg Skinoren gel (1 mg ^{14}C-AA/cm^2), 50 mg Finevin gel (7.5 mg ^{14}C-AA/kg) and 5 mg Finevin gel (0.75 ^{14}C-AA/cm^2).

All animals were kept individually in metabolism cages for 7 days. Urine and feces were collected daily for 7 days. Radioactivity was measured by liquid scintillation counting in urine, plasma, feces, cage wash, all dressing material and skin wash solution. In addition concentrations of radiolabeled ^{14}C- and non-labeled ^{12}C-azelaic acid (measure of endogenous levels of azelaic acid) and the metabolite pimelic acid were determined in the urine by LC/MS.

Two additional groups of 14 animals each (2 females/timepoint) received a 24 hour non-occlusive topical application (covered loosely with dressing material) of 300 mg/kg ^{14}C-AA as Skinoren cream or 300 mg/kg ^{14}C-AA as Finevin gel. Plasma concentrations of radiolabeled ^{14}C- and non-labeled ^{12}C- azelaic acid and pimelic acid were determined at 0, 1, 2, 4, 7, 24 and 26 hours after application of test article.

The recovery rates of radioactive compound were much higher in the high dose groups (90.9% or 92.3%) compared to the low dose groups (42.5 or 67.2%). The major part of the dose was recovered from the dressing material and skin wash at 24 hours post dose (non absorbed dose fraction). The study report states that recovery of the non-absorbed dose fraction in the low dose groups may have been incomplete due to technical difficulties with extraction of small amounts of test article from the dressing material.

The following table provides a comparison of recovery (over a 7 day period) of ^{14}C-radiolabled compound (% of dose) after topical administration of the four doses of ^{14}C-AA in this study. Calculated values are provided as mean ± SD.

Measurement	Units	Skinoren-cream		Finevin-gel	
Dose (drug)	mg/kg ^{14}C-AA	30	300	30	300
Dose (^{14}C)	KBq/kg	1480	1480	1480	1480
Dose (product)	mg cream, gel/kg	150	1500	200	2000
Dose (product)	mg cream,gel/cm^2	5	50	5	50
Treatment area	cm^2/kg	30	30	40	40
Area dose	mg AA/cm^2	1	10	0.75	7.5
		Mean ± SD		Mean ± SD	Mean ± SD
Urine	% of dose	4.23 ± 1.27	1.61 ± 0.55	8.96 ± 2.00	1.00 ± 0.38
Feces	% of dose	0.53 ± 0.15	0.12 ± 0.03	0.36 ± 0.30	0.12 ± 0.08
Cage wash	% of dose	0.82 ± 0.22	0.65 ± 0.40	1.27 ± 0.48	0.22 ± 0.03
Total absorbed	% of dose	5.58 ± 1.40	2.37 ± 0.93	10.59 ± 2.38	1.34 ± 0.38
Mean flux	µg AA/cm^2/hr	2.3 ± 0.6	9.9 ± 3.9	3.3 ± 0.7	4.2 ± 1.2
Dressing material	% of dose	18.1 ± 5.07	67.2 ± 7.96	41.4 ± 17.7	87.0 ± 2.2
Skin wash	% of dose	18.9 ± 20.9	21.3 ± 5.92	15.2 ± 7.84	4.01 ± 2.13
Total non-absorbed	% of dose	37.0 ± 16.4	88.5 ± 2.1	55.6 ± 14.6	91.0 ± 1.84
Total recovery	% of dose	42.5 ± 15.8	90.9 ± 1.39	67.2 ± 12.3	92.3 ± 1.66

The extent of percutaneous absorption (% dose from urine + feces) of azelaic acid was greater in the low dose treatments, irrespective of the formulation (low dose Skinoren cream = 5.6% versus high dose Skinoren cream = 1.4%; low dose Finevin gel = 10.6% versus high dose Finevin gel = 1.3%). A ten fold reduction of the area of dose of Finevin gel yielded ~9 fold increase of the absorbed dose fraction (3.83%). The difference in % absorbed dose between the low and high dose levels of the two azelaic acid formulations is not a surprising result. The design of this study provided for an increase in dose by adding more of the azelaic acid formulation to the same treatment area size that was used in the low dose group. This only increased the thickness of layer of azelaic acid formulation applied in the high dose group. Percutaneous flux would only occur at the point were test article was in contact with the skin. It can not be assumed that there would be a greater diffusion of azelaic acid through the thicker layer of azelaic acid formulation applied to the skin in the high dose group. It would have been a more effective study design to have increased the treatment area in the high dose group while maintaining the same amount of azelaic acid formulation applied per cm^2 of treatment area.

The study report states that formation of $^{14}CO_2$ was observed in previous pharmacokinetics studies conducted in rats. Release of $^{14}CO_2$ was not measured in this study. Therefore, it might be assumed that the percutaneous absorption could have been slightly underestimated in this study.

Neither ^{14}C-azelaic acid nor ^{14}C-pimelic acid were detectable in plasma at any measurement timepoint (limit of quantitation = ———, following the high dose application of either azelaic acid formulation. The endogenous ^{12}C-azelaic acid and ^{12}C-pimelic acid plasma and urine concentrations remained constant during the study.

Low levels of ^{14}C-azelaic acid and/or its metabolite ^{14}C-pimelic acid were measured in urine from all treatment groups on the day of treatment and the day after removal of the test article.

At the high dose level, percutaneous flux of azelaic acid in the rat was 2.4 fold higher following application of Skinoren cream compared to Finevin gel (9.9 µg AA/cm^2/hr vs 4.2 µg AA/cm^2/hr, respectively). At the low dose level, which corresponds to the area dose which is in general applied in the clinical situation, the percutaneous azelaic acid flux was 1.4 fold higher following application of Finevin gel compared to Skinoren cream (3.3 µg AA/cm^2/hr vs 2.3 µg AA cm^2/hr, respectively). It is unclear if this relatively small difference would translate into a meaningful difference in systemic exposure under conditions of clinical use for both drug products.

PK/TK summary:

All of the absorption, distribution, metabolism and excretion (ADME) studies were conducted using ^{14}C-labelled azelaic acid. [^{14}C] Azelaic acid contained the ^{14}C label at both carboxyl groups. Measurement of unchanged drug and its metabolites was performed using HPLC-[redacted] It is anticipated that the main process of elimination of azelaic acid is by biotransformation (since azelaic acid is a straight chain dicarboxylic acid). Systemically absorbed azelaic acid is metabolized by β-oxidation into shorter straight chain dicarboxylic acids (i.e.. pimelic and glutaric acids), malonyl-COA and acetyl-CoA. Released acetate enters the Krebs cycle for energy production or is used for lipid synthesis. Therefore, in these ADME studies, exhaled ^{14}C-label ($^{14}CO_2$) indicated catabolism of the released acetate.

ADME studies with [^{14}C] azelaic acid were conducted in the same species used in toxicology studies (rats, rabbits, dogs and monkeys). For each species, both the oral (gavage) and intravenous routes of administration were used to investigate absorption and systemic bioavailability by following the time course of plasma levels, distribution into organs and tissues, and pathways and rates of excretion.

[^{14}C] Azelaic acid was almost completely absorbed in rats, rabbits, dogs and monkeys when given as a single oral (gavage) administration of a microcrystalline suspension at doses (1000 mg/kg in rats, 500 mg/kg in rabbits, 100 mg/kg in dogs and 150 mg/kg in monkeys) which were comparable to those used in toxicology studies. Excretion of the label was mainly in the urine (~50%) across all species.

After a single oral (gavage) administration of 500 mg/kg to nonpregnant female rabbits or of 400 mg/kg to pregnant rabbits, the ^{14}C-label was excreted mainly in the urine (49% and 47%, respectively), with only trace amounts of radioactivity (1.5% and 0.5%, respectively) present in the feces. A trace amount of the administered radioactivity was able to pass the placental barrier (<0.1%).

The ^{14}C-label was rapidly distributed throughout rat body tissues after a single intravenous dose of 10 mg/kg [^{14}C] azelaic acid. High levels of radioactivity were found in the kidney (the main organ of excretion) and in the liver, and trace amounts of radioactivity appeared

to cross the blood/brain barrier (brain, spinal cord). No radioactivity was detected in the fetuses of pregnant rats given a single 10 mg/kg dose of [^{14}C] azelaic acid intravenously. No differences in distribution pattern were observed between albino and pigmented rats. The ^{14}C-label was rapidly excreted (within 24 hours of injection) mainly through the urine (64%) and with respiratory air (18%). Only a trace amount of radioactivity (1.5%) was present in the feces.

The ^{14}C-label was also rapidly excreted mainly with the urine (53% to 65%) and respiratory air (19%) in rabbits given a single intravenous dose (10 mg/kg) of [^{14}C] azelaic acid. Only a trace amount was found in the feces (0.7%). In dogs given the same intravenous dose, 64% of the label was excreted with the urine and 0.6% was excreted with the feces. Approximately equal amounts of the ^{14}C-label were excreted in the urine (48%) and respiratory air (49%) of Cynomolgus monkeys after a single intravenous dose of 10 mg/kg [^{14}C] azelaic acid. This result suggests that azelaic acid may be metabolized to a greater extent in monkeys than in other animals.

The metabolism of azelaic acid after single or repeated topical applications was evaluated by Matsumoto et al.[1] No detectable metabolism of azelaic acid was observed following single or repeated topical administration of azelaic acid 20% cream in the skin of rats, dogs or humans.

In vitro and in vivo nonclinical percutaneous absorption studies were conducted with azelaic acid 20% cream and azelaic acid 15% gel. The rate of in vitro permeation of azelaic acid though intact skin of hairless mice was compared in the cream versus two gel formulations using the FRANZ-flow-through-diffusion-cell. In this in vitro skin penetration model using hairless mouse skin, the gel formulation delivered a higher dose fraction (6 and 25%) into the skin than the cream formulation (3%), even though the average steady state percutaneous flux of [^{14}C] azelaic acid was greater for the cream formulation (8.9 $\mu g/cm^2/hr$) than for the gel formulations (2.8 and 4.4 $\mu g/cm^2/hr$). This result suggests a potential for lower systemic absorption and higher drug concentration in viable skin for the gel formulation compared with the cream formulation.

The in vivo percutaneous absorption of azelaic acid cream and gel formulations was compared in rats and dogs. In rats, at the highest dose (300 mg/kg), the absorption of the cream formulation was almost two-fold higher than the gel (2.4% and 1.3%, respectively). In the dog, the percutaneous absorption was 1.16% after a single dermal application of the 20% cream at 150 mg/kg azelaic acid. After a single dermal application of the gel formulation to dogs at 15 mg/kg or 150 mg/kg, the percutaneous absorption was 3.83% and 0.43%, respectively. This corresponded to nearly identical percutaneous fluxes of 1.2-1.3 μg azelaic acid/cm^2/hour. Since the treatment area was kept constant the 10-fold dose increase was achieved by an increase of the thickness of the gel layer applied to the skin. The constant percutaneous flux, independent of the area dose, indicated that the percutaneous absorption of azelaic acid occurred only from the most proximal layer of the gel. The average daily percutaneous flux was 2 to 4 fold greater with the 20% cream than from the 15% gel in both species. This result suggested that the movement of azelaic acid across the skin layer in vivo was enhanced in the cream formulation. However, it is unclear if this difference in percutaneous flux in rats and dogs would translate into a meaningful

[1] Matsumoto RM, Duff SB, Sun H, Lehman PA, Franz TJ, Tang-Liu D. Metabolism of 3H-azelaic acid in rat, dog and human skin. *Pharm Res.* 1993; 10 (Suppl): S328.

difference in systemic exposure under conditions of clinical use for both drug products. In summary, the data after a single non-occluded topical application of 20% azelaic acid cream or 15% azelaic acid gel indicated that the percutaneous absorption of azelaic acid was relatively low in both rats and dogs for both the cream and gel formulations.

Information is contained under the Pharmacokinetics section of the Azelex® (azelaic acid cream, 20%) label

"Following a single application of AZELEX® to human skin *in vitro*, azelaic acid penetrates into the stratum corneum (approximately 3 to 5% of the applied dose) and other viable skin layers (up to 10% of the dose is found in the epidermis and dermis). Negligible cutaneous metabolism occurs after topical application. Approximately 4% of the topically applied azelaic acid is systemically absorbed. Azelaic acid is mainly excreted unchanged in the urine but undergoes some β-oxidation to shorter chain dicarboxylic acids. The observed half-lives in healthy subjects are approximately 45 minutes after oral dosing and 12 hours after topical dosing, indicating percutaneous absorption rate-limited kinetics.

Azelaic acid is a dietary constituent (whole grain cereals and animal products), and can be formed endogenously from longer-chain dicarboxylic acids, metabolism of oleic acid and ω-oxidation of monocarboxylic acids. Endogenous plasma concentration (20 to 80 ng/mL) and daily urinary excretion (4 to 28 mg) of azelaic acid are highly dependent on dietary intake. After topical treatment with AZELEX® in humans, plasma concentration and urinary excretion of azelaic acid are not significantly different from baseline levels."

Reviewer's comment: The exact level of exposure to azelaic acid in the diet is questionable. Evidence in the literature suggests that azelaic acid can form as an artifact of urine analyses in small volumes in plastic containers[2]. In addition, it is unclear how much azelaic acid may be present as a dietary constituent in cereals or animal products.

Human pharmacokinetic information obtained in a clinical pharmacokinetic study conducted in patients with Rosacea

The sponsor conducted a clinical pharmacokinetics study in patients with rosacea. Patients applied 0.75 g of azelaic acid 15% gel or vehicle gel to the affected facial area twice daily for 12 weeks. Fourteen (4 males, 10 females) patients were treated with azelaic acid 15% gel and 13 patients (3 males, 11 females) were treated with vehicle gel. Plasma azelaic acid concentration were determined in all treated patients after 8 weeks of treatment at predose and 1, 2 and 4 hours postdose.

The azelaic acid concentrations (mean ± SD) at the various timepoints are provided in the following table.

[2] Bennett MJ, Ragni MC, Hood I, Hale DE. Azelaic and pimelic acids: Metabolic intermediates or artefacts? *J. Inher. Metab. Dis.* 1992; 15: 220-223.

Treatment	Azelaic acid concentration (ng/ml)			
	0 hr	1 hr	2 hr	4 hr
Azelaic acid 15% gel	42.1 ± 20.1	53.8 ± 18.4	62.2 ± 24.1	63.1 ± 27.6
Vehicle gel	17.2 ± 5.0	27.5 ± 20.2	29.2 ± 21.9	27.9 ± 19.8

Plasma azelaic acid concentrations in patients on azelaic acid 15% gel were ~2X higher at all measured timepoints than in vehicle gel treated patients. The sponsor states that even the higher levels noted in azelaic acid 15% gel patients were within the range of published endogenous values. The sponsor states that this indicates that twice daily application of azelaic acid 15% gel did not increase plasma azelaic acid concentrations beyond the normal range derived from dietary and endogenous sources.

PK/TK conclusions:

Nonclinical pharmacokinetic/toxicokinetic studies have been conducted for Finacea (azelaic acid) gel, 15%. No additional nonclinical pharmacokinetic/toxicokinetic studies are recommended for Finacea gel at this time.

IV. GENERAL TOXICOLOGY:

Note: Azelaic acid microcrystalline suspension used in the oral toxicity studies consisted of 0.09% NaCl and 0.85% azelaic acid (w/v).

Toxicology summary:

Acute Toxicology Studies:

Azelaic acid was evaluated for its acute toxicological effects in male and female mice, male rats and male and female dogs following oral (gavage) and intraperitoneal administration. Following single oral (gavage) doses of azelaic acid administered as a microcrystalline suspension, the minimum lethal doses were 3750 mg/kg (male mice) and 5000 mg/kg (female mice and male rats). After intraperitoneal administration, the minimum lethal doses were 400 mg/kg (male rats) and 500 mg/kg (male and female mice). A separate intraperitoneal study was conducted in male rats to determine the acute toxicity of sodium azelainate vs azelaic acid administered as a microcrystalline suspension. No male rats died after intraperitoneal administration of up to 1000 mg/kg sodium azelainate. The main clinical signs noted in this study included apathy, disturbances in gait, prone position (conscious), eyelid closure, extended abdomen (mice and rats, intraperitoneal), accelerated respiration (rats, oral), unconsciousness and tremor (rats, intraperitoneal). Death occurred within 30 minutes to 7 days after intraperitoneal administration and 1.5 to 3 days after oral administration. The stomach and intestine were identified as potential target organs of toxicity in mice and rats. Necropsy findings in mice that died prematurely included punctiform black foci of the gastric glandular mucosa, white covering of the fatty tissue of the abdominal cavity and slight reddening of the intestine. Necropsy findings in rats that died prematurely included petechial hemorrhage of the gastric glandular

mucosa, hemorrhage in the mucosa of the small intestine and prominent vessels of the gastrointestinal tract.

Emesis was observed immediately to 4.5 hours following single oral (gavage) doses of azelaic acid (at doses of 250 mg/kg and higher) administered as a microcrystalline suspension in dogs. Diarrhea also occurred 2.5 to 3.5 hours after dosing in dogs given azelaic acid at a dose level of 5000 mg/kg.

Repeat Dose Systemic Toxicology Studies:

Azelaic acid was evaluated for its systemic toxicological effects in male and female rats (4 and 27 week repeat dose studies), monkeys (4 week repeat dose study) and male and female dogs (6 month repeat dose study with 1 month recovery) following oral (gavage) administration.

Azelaic acid [0, 500, 1500, 5000/3000 (reduced to 3000 after 2 days) mg/kg/day] was orally (gavage) administered as a daily microcrystalline suspension to male and female rats for 4 weeks. Four of ten males given 500 mg/kg/day azelaic acid died during the study. It was determined that at least two deaths were accidental based on the postmortem macroscopic and histological pulmonary changes. An additional six of ten males and nine of ten females given azelaic acid at the dose of 5000/3000 mg/kg/day died during the study. Postmortem findings in animals, which died prematurely, included macroscopic and microscopic evidence of gastric overload (stomach distension, hyperemia and/or hemorrhage of the glandular gastric mucosa and abnormal intestinal contents). Clinical findings that were attributed to the administration of a large (40 ml/kg) volume of the suspension included respiratory changes (respiratory distress at 500 and 1500 mg/kg) and retching of substance out of the mouth and nose (500 mg/kg/day and higher). Additional clinical signs observed included ruffled fur (500 mg/kg/day and higher), slight to severe apathy (1500 mg/kg/day and higher), and tremor, spastic gait, unconsciousness (5000/3000 mg/kg/day). Lower body weight gain and lower food consumption compared to control animals were observed in males given azelaic acid at dose levels of 1500 mg/kg/day and higher. Lower body weight gain (female) and higher water consumption compared to control animals were also observed in the high dose group. Lower non-esterified serum fatty acid levels (all dose groups), higher serum total cholesterol levels (high dose group), lower eosinophil polymorphonuclear leukocyte (mid dose group) and lymphocytes counts (mid dose group) in the body marrow, and slightly reduced partial thromboplastin time (mid and high dose groups) were noted in male animals compared to control animals. Organ weight changes included higher absolute kidney weights (low dose males) and lower pituitary weights (mid dose females) compared to control animals.

Reviewer's Comments: The effects noted at the high dose in the 4 week repeat dose toxicity study in rats are probably due to a gastric overload due to the large volume of drug substance that was administered in this study. Therefore, the results noted in high dose animals do not relate to the toxicity profile for azelaic acid. A NOAEL dose could not be established in this study.

Azelaic acid (0, 100 and 1000 mg/kg/day) was orally (gavage) administered as a daily microcrystalline suspension to male and female rats for 27 weeks. Lower body weight gain (1000 mg/kg/day), slightly lower food consumption (both dose groups) and slightly higher water

consumption (1000 mg/kg/day) were noted in treated animals compared to control animals. Postmortem findings included thickening of the cuticular ridge of the stomach (both dose levels) accompanied by evagination and epithelia overgrowth in the high dose animals. The NOAEL dose identified in this study was 100 mg/kg/day.

Azelaic acid (0 and 250 mg/kg/day) was orally (gavage) administered as a daily microcrystalline suspension to monkeys for 4 weeks. The dose for this study was selected to avoid vomiting in the monkeys. No treatment related effects were noted in this study.

Azelaic acid (0, 10, 100 and 800 mg/kg/day) in gelatin capsules was orally (gavage) administered daily to dogs for 6 months, with a one month recovery period. No treatment related effects were noted in this study. The NOAEL dose was identified as 800 mg/kg/day in this study.

Repeat Dose Dermal Toxicology Studies:

Azelaic acid was evaluated for its dermal toxicological effects in male and female rats (6 month repeat dose study with 1 month recovery) and male and female dogs (26 weeks repeat dose study) following dermal administration of the azelaic acid 20% cream.

Azelaic acid 20% cream (0, 50, 100 and 300 mg/kg/day) was applied dermally on a daily basis (bid for low and mid dose groups; tid for high dose group) to rats for 6 months, with a one month recovery period. No treatment related effects were noted in the study. Plasma drug levels for azelaic acid and pimelic acid (primary metabolite) were obtained at week 2 and month 6 in the study. Plasma levels for azelaic acid and pimelic acid increased proportionately following dermal application. After 2 weeks, the plasma azelaic acid concentrations were 158 ± 70, 490 ± 285 and 866 ± 523 ng/ml for the 50, 100 and 300 mg/kg/day dose groups, respectively. Azelaic acid plasma values after 6 months were 126 ± 27, 255 ± 126 and 791 ± 573 ng/ml, respectively. The plasma levels of pimelic acid ranged from —— ng/ml over the dose range tested in this study. The dermal NOAEL was identified in this study as 300 mg/kg/day.

Azelaic acid 20% cream (0 and 300 mg/kg/day) was applied dermally on a daily basis to dogs for 26 weeks. Each day the application site was occluded with gauze dressing for 24 hours after dosing. No treatment related systemic effects were noted in this study. Slight irritation was noted at the application site, which was observed more frequently in treated animals compared with control animals. The reason why the slight irritation was noted in dogs but not rats was probably related to the occlusion that occurred in dogs which was not done in the rat study. This study only tested the maximum feasible dose in dogs instead of the more comprehensive dose range tested in the rat. A possible explanation for this is provided in the following paragraph.

Reviewer's Comments: It is important to note that the 26 week dermal toxicity study in dogs, the 4 and 27 week oral toxicity study in rats and the 4 week oral toxicity study in monkeys were submitted under the IND for azelaic acid 20% cream (IND —— . The 6 month systemic toxicity study in dogs and the 6 month dermal toxicity study in rats were submitted with the NDA submission for azelaic acid 20% cream (NDA 20-428). The last two studies that were

submitted with the NDA were conducted with a more adequate dose range (low, mid and high dose groups).

Toxicology conclusions:

The toxicology of systemically administered microcrystalline suspensions of azelaic acid was assessed in acute studies conducted in mice, rats and dogs and repeat dose systemic toxicity studies in rats, monkeys and dogs. Dermal toxicology studies conducted with the azelaic acid 20% cream included repeat dose studies in rats and dogs.

The sponsor did not conduct any nonclinical repeat dose dermal toxicology studies with the azelaic acid 15% gel formulation. However, the sponsor included the results from two nonclinical in vivo percutaneous absorption studies conducted in rats and dogs in this submission. Both of these studies compared the percutaneous absorption of azelaic acid 20% cream and azelaic acid 15% gel. In rats, at the highest dose (300 mg/kg; equivalent to the high dose in the dermal toxicology study conducted in rats), the absorption of the cream formulation was almost two-fold higher than the gel (2.4% and 1.3%, respectively) after a single 24 hour non-occluded dose. In the dog, after a single dermal application of 150 mg/kg (~1/2 the high dose used in the repeat dose dermal toxicology study in dogs) of the azelaic acid 20% cream and the azelaic acid 15% gel, the percutaneous absorption was 1.16% and 0.43%, respectively. In summary, it appears that the results from these two in vivo percutaneous absorption studies indicate that the cream formulation provides a slightly higher systemic exposure after dermal administration compared to the gel formulation. This results suggests that the results from the repeat dose dermal toxicology studies conducted with azelaic acid 20% cream formulation would provide sufficient data to support the use of the azelaic acid 15% gel formulation. It would not be expected to see an increased level of systemic toxicity after repeat dose administration of the azelaic acid 15% gel formulation compared to the azelaic acid 20% cream formulation based on the results of the in vivo percutaneous absorption studies conducted in rats and dogs.

In addition, the sponsor submitted to IND ~~~ the results from two special toxicology studies that were conducted to assess the local tolerance of single and repeated (28 days) topical applications of azelaic acid 15% gel in rabbits. The local tolerance of repeated applications (28 days) in rabbits of azelaic acid 15% gel was compared with that of azelaic acid 20% cream. Azelaic acid 15% gel and vehicle gel were very slightly irritating on intact rabbit skin and more severely irritating on abraded rabbit skin after single topical application under semi-occlusion. Azelaic acid 15% gel and the vehicle gel formulation were slightly more irritating on intact rabbit skin than azelaic acid 20% cream during 4 weeks of repeat application. It is anticipated that the azelaic acid 15% gel would cause a slightly greater level of irritation in a repeat dose dermal toxicology study conducted in either rats or dogs.

In conclusion, the general toxicology studies conducted for azelaic acid appear to be adequate. No additional general toxicology studies are recommended for Finacea (azelaic acid 15%) gel at this time.

V. GENETIC TOXICOLOGY:

Genetic toxicology summary:

In vitro genotoxicity studies conducted for azelaic acid included two Ames tests, a HGPRT test in V79 cells (Chinese hamster lung cells) and a clastogenicity test in human lymphocytes. In vivo genotoxicity studies conducted for azelaic acid included a dominant lethal assay in the mouse and a mouse micronucleus assay.

The mutagenic potential of azelaic acid (0.01 to 10 mg/plate; 0.1 to 5 mg/plate) was evaluated in two in vitro Ames *Salmonella* tests with direct plate incorporation in the presence and absence of metabolic activation. Azelaic acid was not a bacterial cell gene mutagen when evaluated in either of these assays in the presence or absence of metabolic activation.

The potential for azelaic acid (0, 0.19, 0.75, 1.32, and 1.88 mg/ml) to induce gene mutations in mammalian cells was evaluated in vitro in the HGPRT test in V79 cells (Chinese hamster lung cells) in the presence and absence of metabolic activation. Azelaic acid was not a mammalian cell gene mutagen when evaluated in this assay in the presence and absence of metabolic activation.

The clastogenic potential of azelaic acid in mammalian cells was evaluated in vitro in human peripheral lymphocytes in the presence (0, 120, 240, 480 and 960 µg/ml) and absence (0, 60, 120, 240 and 480 µg/ml) of metabolic activation. Azelaic acid was not clastogenic in mammalian cells under the conditions of this assay in the presence or absence of metabolic activation.

A single dose of azelaic acid (0, 500, 1000 and 2000 mg/kg) was orally (gavage) administered as a microcrystalline suspension to male mice to determine its clastogenic potential in the dominant lethal assay. Following treatment, males were mated with untreated females for a mating period of 4 days. Females were replaced eleven times for a total of 48 days of breeding. Four of fifty males died in the high dose group. Azelaic acid was not mutagenic during any mating interval and no compound related effects on fertility index, total implants, numbers of liver or dead implants or death index was observed in this study.

A single dose of azelaic acid (0, 500, 1000 and 2000 mg/kg) was orally (gavage) administered as a microcrystalline suspension to male and female mice to determine its clastogenic potential in the mouse micronucleus assay. Bone marrow was obtained for analysis at 24 and 48 hours after dosing. Azelaic acid did not demonstrate clastogenicity in the mouse micronucleus test under the conditions used in this assay.

Information contained under the "Carcinogenesis, mutagenesis, impairment of fertility" section of the Azelex® (azelaic acid 20% cream) label

"In a battery of tests (Ames assay, HGPRT test in Chinese hamster ovary cells, human lymphocyte test, dominant lethal assay in mice), azelaic acid was found to be nonmutagenic."

Reviewer's Comments: The information contained in the label under this section was adequate for the genetic toxicology studies that had been conducted to support the azelaic acid 20% cream. The sponsor of the azelaic acid 15% gel conducted an in vivo mouse micronucleus test for azelaic acid to bring the conducted genetic toxicology studies up to the current ICH guidelines. The final study report for the in vivo mouse micronucleus test for azelaic acid was submitted to and reviewed under IND [redacted] The results of the mouse micronucleus test should be added to the updated label for azelaic acid 15% gel.

Genetic toxicology conclusions:

Azelaic acid did not demonstrate any genotoxicity potential in a battery of genetic toxicology assays. The dominant lethal assay in the mouse is not a currently recommended in vivo genotoxicity assay according to ICH guidelines. It was recommended that the sponsor conduct an in vivo mouse micronucleus assay. The sponsor conducted an in vivo mouse micronucleus study and submitted the results from this study to IND [redacted] This is the currently accepted in vivo genotoxicity study according to ICH guidelines. Therefore, the sponsor has conducted an appropriate battery of genotoxicity studies for azelaic acid. No additional genetic toxicology studies are recommended for azelaic acid at this time.

Labeling recommendations:

It is recommended that the results of the battery of in vitro and in vivo genetic toxicology studies conducted with azelaic acid be incorporated into the Finacea gel label.

VI. CARCINOGENICITY:

Carcinogenicity summary:

No long term carcinogenicity studies have been conducted with either azelaic acid or the approved 20% azelaic acid cream. The sponsor was informed that a study to determine the photoco-carcinogenic potential of azelaic acid 15% gel and a dermal carcinogenicity study for the azelaic acid 15% gel are recommended for the final development of this drug product. The sponsor included a proposal for conduct of these studies in a pre-NDA briefing package for a pre-NDA meeting that was conducted for IND 61,324 (azelaic acid 15% gel for the treatment of papulo-pustular rosacea) on August 30, 2001. In the briefing package for this pre-NDA meeting, the sponsor proposed to conduct a photoco-carcinogenicity study in mice and a dermal carcinogenicity study in Tg.AC transgenic mice for the azelaic acid 15% gel as phase 4 commitments for the NDA. The division concurred that this would be adequate to address the photoco-carcinogenic potential and dermal carcinogenic potential associated with azelaic acid 15% gel. It was recommended that the sponsor include information concerning the conduct of the dermal carcinogenicity study in Tg.AC mice and the photoco-carcinogenicity study in mice with the NDA submission. In addition, it was recommended that the sponsor include a proposed timeline for completion of these studies as phase 4 commitments with the NDA submission. It was agreed upon during the pre-NDA meeting that this would be acceptable to fulfill the division's recommendations for determining the carcinogenic potential of azelaic acid 15% gel.

The sponsor provided the following information for conduct of the photoco-carcinogenicity study and the dermal carcinogenicity study in a transgenic animal model in the NDA submission.

The carcinogenic potential of the to-be-marketed drug product, azelaic acid 15% gel, will be assessed in a photoco-carcinogenicity study in male and female mice and in an alternative, carcinogenicity study in transgenic mice (Tg.AC assay), to be conducted as a Phase 4 commitment.

The photoco-carcinogenicity dose range-finding study, including relevant toxicokinetics, will be conducted in [redacted] Results of this dose range-finding study and a protocol for the definitive study will be submitted to the IND for review by the Division and to seek concurrence on dose selection for the definitive study.

The Tg.AC dose range-finding study, including relevant toxicokinetics, will also be conducted [redacted] Results of this dose range-finding study and a protocol for the definitive study will be submitted to the IND for review and presentation to the Executive Carcinogenicity Assessment Committee to seek concurrence on dose selection for the definitive study.

Reports for the definitive Tg.AC study and the definitive photoco-carcinogenicity study will be submitted after the NDA is filed, as a completion of our Phase 4 commitment. If completion of the dose range-finding studies and review of the protocols and dose selection for the definitive studies occurs as scheduled, targeted dates for submission of the reports for the definitive studies are [redacted]

Reviewer's comments: The sponsor's proposal for conduct of a photoco-carcinogenicity study and dermal carcinogenicity study in Tg.AC mice, with supporting dose-range studies, is acceptable. The timeline proposed by the sponsor for conduct of these studies appears to be reasonable.

Carcinogenicity information contained under the "Carcinogenesis, mutagenesis, impairment of fertility section" of the Azelex® (azelaic acid 20% cream) label

"Azelaic acid is a human dietary component of a simple molecular structure that does not suggest carcinogenic potential, and it does not belong to a class of drugs for which there is a concern about carcinogenicity. Therefore, animals studies to evaluate carcinogenic potential with AZELEX® Cream were not deemed necessary."

Reviewer's Comments: This was the agreed upon wording for this section at the time of approval of the 20% azelaic acid cream. However, it does not incorporate the current state of knowledge and it is not our current policy. It is recommended that this wording be changed in the Finacea gel label. More specific recommendations are contained in the "Labeling Recommendations" section below.

Carcinogenicity conclusions:

The sponsor's proposal to conduct a photoco-carcinogenicity study and a dermal carcinogenicity study in Tg.AC mice, with supporting dose-range studies, as a phase 4 commitment is acceptable to fulfill the division's recommendations for determining the carcinogenic potential of azelaic acid 15% gel. The timeline proposed by the sponsor for conduct of these studies appears to be reasonable.

Labeling Recommendations:

It is recommended that the reference to azelaic acid [redacted] and therefore [redacted] be removed from a label for the Finacea gel. It is recommended that a statement that [redacted] be included in the Finacea gel label. After completion of the photoco-carcinogenicity and carcinogenicity studies with the azelaic acid 15% gel, it is recommended that the results from these studies be incorporated into an updated label for Finacea gel.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Reproductive and developmental toxicology summary:

A combined oral fertility and embryofetal developmental study was conducted in male and female rats with azelaic acid. Oral embryofetal developmental studies were performed in rats, rabbits and Cynomolgus monkeys to assess the embryotoxic and teratogenic potential of azelaic acid. An oral peri- and post-natal developmental study was conducted in rats with azelaic acid.

Azelaic acid (0, 50, 500 and 2500 mg/kg/day) was orally (gavage) administered as a microcrystalline suspension to rats in a combined fertility and embryofetal developmental study. The high dose for this study was based on the results of the 4 week oral repeat dose study conducted in rats. High mortality was noted at 5000 mg/kg/day in the 4 week oral repeat dose study, so the sponsor selected 2500 mg/kg/day as the high dose in this study. Male rats were treated once daily for ~84 days (70 days prior to mating through 14 days of mating). Female rats were treated once daily for ~48 or 71 days (14 days prior to mating through day 20 of gestation or day 21 postpartum). No effects were noted on the fertility of the P-generation or their offspring and the general reproductive performance of the F-generation. No teratogenicity was observed in the F-1 or F-2 generation pups. Two of thirty high dose males died during the study. Stertorous breathing was noted as a clinical sign in mid (1/30) and high dose (6/30) P-generation males. Lower body weight gain was noted in mid and high dose P-generation males (↓4 and ↓20%, respectively). Lower body weight gain was noted in mid and high dose P-generation females (↓3 and ↓15%, respectively). The total intra-uterine deaths (post-implantation loss) were 3.7 times higher in the high dose group compared to the control group. Pup weight in the offspring of high dose dams was slightly lower (1 – 6%) than controls on days 7, 14 and 21. The increase in embryolethality and decreased pup weight noted in the high dose group may have been due to the decrease in maternal body weight gain noted in the high dose group.

Azelaic acid (0, 50, 500 and 2500 mg/kg/day) was orally (gavage) administered as a microcrystalline suspension to pregnant female rats from gestation day 6 to 15 inclusive in an embryofetal developmental study. The mean number of early intra-uterine deaths (post-implantation loss) was 4 times higher in the high dose group than in the control group. Eight animals in each of the mid and high dose groups exhibited some clinical signs of toxicity (retching reflex and/or stertorous breathing). Lower body weight gain was noted in the high dose group (↓17%) compared to control animals. No teratogenicity was observed in any of the dose groups. Embryolethality was noted in the high dose group only. The increase in embryolethality in the high dose group may have been due to the maternal toxicity (clinical signs and decreased in body weight gain) noted in the high dose group.

An oral two week repeat dose range finding study was conducted with azelaic acid in rabbits to determine appropriate dose levels for the definitive embryofetal developmental study in rabbits. Azelaic acid (0, 500, 1000, 1500, 2500 and 5000 mg/kg/day) was orally (gavage) administered as a microcrystalline suspension to female rabbits for two weeks. Four females were treated in each group. All animals in the 5000, 2500, 1500 and 1000 mg/kg/day groups died after 1, 2, 2 and 9 days after treatment, respectively. All animals in the 500 mg/kg/day group survived the two week treatment period. No effects in body weight gain were noted in the 500 mg/kg/day group over the two week treatment period. It was recommended that the high dose in the rabbit definitive embryofetal developmental study should not exceed 500 mg/kg/day.

Azelaic acid (0, 50, 150 and 500 mg/kg/day) was orally (gavage) administered as a microcrystalline suspension to pregnant female rabbits from gestation day 6 to 27 inclusive in an embryofetal developmental study. A slight decrease in maternal body weight gain was noted in all treatment groups compared to control animals. The incidence of embryolethality was slightly higher in the mid (↑4.1%) and high (↑4.5%) dose groups compared to control animals. The slight increase in embryolethality noted in mid and high dose groups may have been related to the slight decrease in maternal body weight gain noted in these dose groups. An increased incidence of incomplete or no ossification of the 5th sternebra was observed in fetuses from all dose groups. No other effects were noted and this slight variation was considered not biologically relevant. Therefore, it was determined that no teratogenicity was observed in rabbits under the conditions of this study.

An oral two week repeat dose range finding study was conducted with azelaic acid in monkeys to determine appropriate dose levels for the definitive embryofetal developmental study in monkeys. Azelaic acid (0, 500, 1000, 1500, 2500 and 5000 mg/kg/day) was orally (gavage) administered as a microcrystalline suspension to female monkeys for four weeks. Four females were treated in each group. Treatment started with the highest dose first to determine tolerability. Monkeys did not tolerate the 5000, 2500 and 1500 mg/kg/day dose levels. Animals vomited the drug substance, which caused the dose to be gradually decreased to 1500 mg/kg/day in the first group of treated animals. Two of the four animals were sacrificed moribund on day 5 and treatment of the remaining 2 animals were discontinued at this time. It was determined that doses between 1500 and 5000 mg/kg may be lethal to monkeys. At the 500 and 1000 mg/kg/day dose levels, animals vomited the drug substance more frequently on the first 8 treatment days

than during the remaining 2 week period. It was recommended that the high dose in the monkey definitive embryofetal developmental study should not exceed 500 mg/kg/day.

Azelaic acid (0, 50, 150 and 500 mg/kg/day) was orally (gavage) administered as a microcrystalline suspension to pregnant female monkeys from gestation day 19 to 50 inclusive in an embryofetal developmental study. A slight decrease in food consumption was noted in mid and high dose animals compared to control animals. Emesis was noted as a clinical sign in high dose animals. A higher incidence of spontaneous abortions was noted in high dose animals compared to control animals. The higher incidence of spontaneous abortions noted in the high dose group may have been related to the slight maternal toxicity noted in high dose animals (slight decrease in food consumption and emesis). No teratogenicity was observed in this study.

Azelaic acid (0, 50, 500 and 2500 mg/kg/day) was orally (gavage) administered as a microcrystalline suspension to rats from day 15 of gestation through day 21 postpartum in a peri- and post-natal developmental study. Mortality was noted in the mid (1/25) and high (2/25) dose group F_0 dams. A significant decrease in body weight gain was observed in the mid (↓25%) and high dose (↓24%) group F_0 dams on day 20 post coitum. The mortality rate of high dose group young was significantly higher (↑21%) than control animals. The body weights of F_1 animals were moderately lower (↓16% males; ↓9% females) in the high dose group on day 90 postpartum compared to control animals. The preimplantation loss was increased (↑20%) in high dose F_1 females compared to control animals. A slightly higher incidence of delayed ossification of single fetal bones was observed in the high dose F_2 generation rats compared to control animals. This change was attributed to a slight disturbance in the reproductive performance of the high dose F_1 females. This may have been associated with the toxicity noted in the high dose group. In summary, the mid and high dose levels expressed toxicity in F_0 females (slightly increased mortality rates and decreased body weight gain) which produced slight disturbances in the postnatal development of F_1 rats and in the reproductive performance of F_1 females.

Reviewer's Comments: During the pre-IND meeting for the papulo-pustular rosacea indication (conducted on 9-27-00), the sponsor was asked to address the issue of inhibition of 5α-reductase activity by azelaic acid and the impact on development of the fetus. The 5α-reductase enzyme converts testosterone to dihydrotestosterone. This is considered the most important enzymatic process involved in androgen activity. The primary concern was the possibility of anti-androgenic effects on male offspring. The critical in utero exposure period for effects on fetal sexual differentiation is during late gestation (days 15 – 21 post coitum). The design of the peri- and post-natal developmental study in rats described above covers the critical period of concern (period of sexual maturation). No effects were noted on the development (or sexual maturation) of the male or female fetus in this study. In addition, pharmacokinetic studies have demonstrated that after oral administration of azelaic acid, very little (<0.1%) or no azelaic acid crosses the placenta in rabbits and rats, respectively. It would be anticipated that after topical administration of the 15% azelaic acid gel, the fetus would probably not be exposed to azelaic acid, which provides an additional measure of comfort for not being concerned about the possible inhibition of 5α-reductase in the fetus during development.

Reproductive and developmental toxicology information contained under the Pregnancy: Teratogenic Effects section of the Azelex® (azelaic acid 20% cream) label (Azelex® is designated as a Pregnancy Category B drug product)

"Embryotoxic effects were observed in Segment I and Segment II oral studies with rats receiving 2500 mg/kg/day of azelaic acid. Similar effects were observed in Segment II studies in rabbits given 150 to 500 mg/kg/day and in monkeys given 500 mg/kg/day. The doses at which these effects were noted were all within toxic dose ranges for the dams. No teratogenic effects were observed. 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 during pregnancy only if clearly needed."

The following information is contained under the Nursing Mothers section of the label.

"Equilibrium dialysis was used to assess human milk partitioning *in vitro*. At an azelaic acid concentration of 25 µg/ml, the milk/plasma distribution coefficient was 0.7 and the milk/buffer distribution was 1.0, indicating that passage of drug into maternal milk may occur. Since less than 4% of a topically applied dose is systemically absorbed, the uptake of azelaic acid into maternal milk is not expected to cause a significant change from baseline azelaic acid levels in the milk. However, caution should be exercised when AZELEX® is administered to a nursing mother."

The following information is contained under the Carcinogenesis, mutagenesis, impairment of fertility section of the label.

"Animal studies have shown no adverse effects on fertility."

Reviewer's Comments: The information in the label concerning the amount of azelaic acid in milk is potentially misleading. The potential amount of systemic azelaic acid after topical application is dependent on the extent of body surface area covered. A better determination of potential levels of azelaic acid in milk would be to determine if there was no detectable human exposure after clinical use under maximal conditions. It is recommended that the wording in this portion of the label be updated to current standards for the Finacea gel label.

Reproductive and developmental toxicology conclusions:

It appears that adequate reproductive and developmental toxicology studies have been conducted for azelaic acid. No additional reproductive and developmental toxicology studies are recommended for the Finacea gel at this time.

Labeling recommendations:

Pregnancy Category B would be appropriate for Finacea (azelaic acid 15%) gel based on the results of the oral reproductive and developmental toxicology studies conducted for azelaic acid. It is recommended that the results of the oral reproductive and developmental toxicology

studies be included in the label with the corresponding multiples of human exposure calculations based on body surface area comparisons (i.e., mg/m^2).

VIII. SPECIAL TOXICOLOGY STUDIES:

Special Toxicology Summary:

Azelaic acid was evaluated for its potential to induce delayed hypersensitivity in guinea pigs. Azelaic acid was intradermally or topically administered to male and female guinea pigs to determine its contact sensitization potential. The maximization test consisted of two induction phases (days 1 and 9) followed by a challenge phase on day 22. For the first induction phase, two injections each of azelaic acid (0.5% azelaic acid), Freund's Complete Adjuvant or azelaic acid (0.5% azelaic acid), in a 1:1 combination with Freund's Complete Adjuvant, were intradermally administered (0.1 ml/injection) on day 1. All animals were treated with 10% sodium lauryl sulfate on day 8. A single dose of azelaic acid (25% azelaic acid, aqueous suspension, 0.2 ml) was then topically applied on day 9 and occluded for 48 hours for the second induction phase. For the challenge phase, a single dose of azelaic acid (15% azelaic acid, oil suspension, 0.1 ml) was topically applied to the flank on day 22 and occluded for 24 hours. No evidence of contact sensitization potential was observed in this study.

Reviewer's Comments: The maximization test was not conducted with the final formulation for the 20% azelaic acid cream. A nonclinical delayed hypersensitivity test has not been conducted for the 15% azelaic acid gel. However, European and US clinical studies have been conducted with the 15% azelaic acid gel formulation. No apparent signal for delayed hypersensitivity was noted in the European and US clinical studies. Therefore, the need for a nonclinical delayed hypersensitivity test is waived for the 15% azelaic acid gel.

Primary ocular tolerance studies conducted in rabbits revealed moderate to severe ocular irritation with a preservative-free formulation of azelaic acid 20% cream. This irritation was judged to be mainly due to azelaic acid itself because only a slight irritation was noted with the vehicle alone. Administration of a single dose of azelaic acid 20% cream to the monkey eye led to pain reactions immediately after dosing that disappeared after rinsing with water.

Reviewer's Comments: A primary ocular tolerance study in rabbits for the azelaic acid 15% gel probably would not provide any additional useful information. It has been determined that the azelaic acid itself appears to be an ocular irritant. Therefore, it can be presumed that the azelaic acid 15% gel formulation will be an ocular irritant as well.

Two special toxicology studies (that were submitted to and reviewed under IND : —, were conducted to assess the local tolerance of single and repeated (28 days) topical applications of azelaic acid 15% gel. The local tolerance of repeated applications of azelaic acid 15% gel was compared with that of azelaic acid 20% cream. Azelaic acid 15% gel and vehicle gel were very slightly irritating on intact rabbit skin and more severely irritating on abraded rabbit skin after single topical application under semi-occlusion. Azelaic acid 15% gel and the vehicle gel formulation were slightly more irritating on intact rabbit skin than azelaic acid 20% cream during 4 weeks of repeat application.

Photoirritation potential of azelaic acid 15% gel in animals

The UV spectrum submitted in IND 61,324 for azelaic acid 15% gel did not show any significant absorption in the UVB/UVA/VIS spectrum. Therefore, the need for nonclinical photoirritation testing was waived for azelaic acid 15% gel.

Special Toxicology Conclusions:

It appears that adequate special toxicology studies have been conducted for the azelaic acid 15% gel. No additional special toxicology studies are recommended for the Finacea gel at this time.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions:

Based on the nonclinical data available for oral azelaic acid, topical azelaic acid 20% cream and topical azelaic acid 15% gel, my recommendation for NDA 21-470 is that it is approvable from a pharmacology/toxicology perspective provided that the recommended changes in the label discussed in the Labeling section below are incorporated into the label.

General Toxicology Issues:

Outstanding general toxicology issues for azelaic acid 15% gel include the following:

1) The sponsor has agreed to conduct a photoco-carcinogenicity study in ——— as a Phase 4 commitment.

2) The sponsor has agreed to conduct a dermal carcinogenicity study in TG.AC mice as a Phase 4 commitment.

The carcinogenic potential of the to-be-marketed drug product, azelaic acid 15% gel, will be assessed in a photoco-carcinogenicity study in male and female mice and in an alternative, carcinogenicity study in transgenic mice (Tg.AC assay), to be conducted as a Phase 4 commitments.

The photoco-carcinogenicity dose range-finding study, including relevant toxicokinetics, will be conducted ——— Results of this dose range-finding study and a protocol for the definitive study will be submitted to the IND for review by the Division and to seek concurrence on dose selection for the definitive study.

The Tg.AC dose range-finding study, including relevant toxicokinetics, will also be conducted ——— Results of this dose range-finding study and a protocol for the definitive study will be submitted to the IND for review and presentation to the Executive Carcinogenicity Assessment Committee to seek concurrence on dose selection for the definitive study.

Reports for the definitive Tg.AC study and the definitive photoco-carcinogenicity study will be submitted after the NDA is filed, as a completion of our Phase 4 commitment. If completion of the dose range-finding studies and review of the protocols and dose selection for the definitive studies occurs as scheduled, targeted dates for submission of the reports for the definitive studies are :

Reviewer's comments: The sponsor's proposal for conduct of a photoco-carcinogenicity study and a dermal carcinogenicity study in Tg.AC mice, with supporting dose-range studies, is acceptable. The timeline proposed by the sponsor for conduct of these studies appears to be reasonable.

Recommendations:

The following wording is recommended for the potential Approval letter for Finacea gel concerning nonclinical phase 4 commitments.

1. The applicant commits to conducting a photoco-carcinogenicity study in male and female mice with the azelaic acid 15% gel.

   Protocol submission: Within 4 months of the date of this letter
   Study Start: Within 6 months of the date of the approval of the protocol
   Final Report Submission: Within 12 months after the study completion

2. The applicant commits to conducting an alternative, dermal carcinogenicity study in transgenic mice (Tg.AC assay) with the azelaic acid 15% gel.

   Protocol submission: Within months of the date of this letter
   Study Start: Within 6 months of the date of the approval of the protocol
   Final Report Submission: Within 12 months after the study completion

Labeling with basis for findings:

The entire electronic version Finacea™ label submitted to the NDA is inserted below. Comments about the portions that relate to nonclinical pharmacology/toxicology will be inserted directly in the appropriate sections. Recommended sections to be deleted are marked by ~~strikeout.~~ Recommended sections to be added are marked by highlight. Reviewer's comments in support of recommended labeling changes are provided in *italics*.

8 pages redacted from this section of the approval package consisted of draft labeling

DOSAGE AND ADMINISTRATION

[redacted]

HOW SUPPLIED

FINACEA™ is supplied in [redacted] tubes in the following size:

30 g – NDC 50419-825-01

50 g – NDC 50419-825-02

Storage

Store at 25°C (77°F) with excursions permitted between 15°-30° C (59°-86°F) [See USP Controlled Room Temperature].

Distributed under license; *U.S. Patent No 4,713,394*

Component code number

] [redacted]

Distributed by:
Berlex Laboratories, Wayne, NJ 07470

X. APPENDIX/ATTACHMENTS:

Addendum to review: N/A

Other relevant materials (Studies not reviewed, appended consults, etc.): N/A

Any compliance issues: N/A

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
9/30/02 03:08:44 PM
PHARMACOLOGIST

Abby Jacobs
9/30/02 03:47:38 PM
PHARMACOLOGIST

Jonathan Wilkin
10/20/02 05:07:03 PM
MEDICAL OFFICER