CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-470

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Reviewer's Comments:

In the NDA 21-470 the firm has provided compositions of Investigational Formulations SH S 655 BA corresponding to the batch no. 03002 (Milan, Italy) and batch DA0171 (Berlin, Germany).

The batch DAO171 manufactured in Berlin was used in only one pharmacokinetic study Protocol ——— (Report AU36). This study was conducted to assess the urinary excretion of azelaic acid ((AzA) in 29 patients with mild or moderate papulopustular facial acne treated twice daily with AzA 20% cream or 15% gel. The data from Report AU36 showed that although the urinary excretion of AzA was highly variable, no specific difference between AzA 20% cream and 15% gels were noted. Additionally, the levels from this study were within the range of endogenous daily urinary excretion in subjects on a normal regular diet. Based on these, the firm has concluded that treatment with AzA 15% gel or 20% cream did not result in a distinctly higher body burden than from daily dietary exposure.

In the reviewer's opinion, the pharmacokinetic profile in Report AU36 (using batch DA0171) is a supportive study, and will not impact significantly the outcome of other important clinical studies where batch 03002 was used. Thus, if the manufacturing site for the proposed product is going to be in Milan, Italy, a comparative in vitro release testing between the clinical and to-be-marketed batches is not essential for the approval of this NDA. However, if the manufacturing site is going to be in Berlin, Germany, an in vitro study is required to assure the product "sameness", quality and performance between the two batches.

III. Recommendations

The Agency concurs with the sponsor's view for not performing a comparative in vitro release testing between the clinical and to-be-marketed formulations provided the manufacturing site for the to-be-marketed product is **Milan, Italy**. However, if the manufacturing site is **Berlin, Germany**, the sponsor is requested submitting in vitro release data to assure "sameness", product quality and performance of the clinical and to-be-marketed batches of azelaic acid gel, 15%. The Agency encourages the sponsor conducting an in vitro release testing on its proposed product to facilitate approval process in the future by having an in vitro test already validated and ready to use in such a situation.

The above recommendations should be forwarded to the sponsor.

Chandra S. Chaurasia, Ph. D. _____ Date: _____
Biopharm Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initiated by E. Dennis Bashaw, Pharm. D. _____ Date: _____

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/s/

Chandra S. Chaurasia
10/17/02 05:03:52 PM
BIOPHARMACEUTICS

Dennis Bashaw
10/17/02 05:19:11 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: **21-470**	Submission Date(s): 03/21/02
Brand Name	Finacea Gel 15%
Generic Name	Azelaic acid gel 15%
Reviewer	Chandra S. Chaurasia, Ph. D. and Jang-IK Lee, Pharm D., Ph. D.
Team Leader	E. Dennis Bashaw, Pharm.D.
OCPB Division	DPE III (HFD-880)
OND division	ODE V (HFD-540)
Sponsor	Berlex Laboratories
Relevant IND(s)	61,324
Submission Type; Code	New formulation (3S), new indication (6S)
Formulation; Strength(s)	Gel 15%
Indication	Topical treatment of inflammatory papules and pustules [redacted] of rosacea

1. EXECUTIVE SUMMARY

Finacea 15% Gel contains azelaic acid, a naturally occurring, straight-chained, saturated 9 carbon aliphatic dicarboxylic acid. Dietary intake of just one ounce of cereal such as wheat, rye, and barley provides 11 to 196 mg of azelaic acid and its potential precursors. Azelaic acid is also endogenously formed from longer chain dicarboxylic acids, metabolism of oleic acid, and ω-oxidation of C9 monocarboxylic acid. Endogenous plasma concentration and daily urinary excretion of azelaic acid are highly dependent on dietary intake and endogenous metabolism. Schering AG has marketed azelaic acid 20% cream in Europe under the tradename, Skinoren since 1988 as a treatment for mild to moderate acne vulgaris. Allergan Herbert and Berlex introduced the cream to the United States as Azelex (NDA 20-428, 1995) and Finevin (NDA 20-428, 2001), respectively. In this submission, the sponsor pursues the approval of azelaic acid gel 15% for the treatment of inflammatory papules, pustules, [redacted] of rosacea.

1.1. Recommendations

- The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information submitted to the Human Pharmacokinetics and Biopharmaceutics Section of NDA 21-470. The information submitted is acceptable and supports approval of the proposed azelaic acid 15% gel formulation.

- Although not a requirement for approval, the Agency strongly recommends the applicant to develop an in vitro release test and specifications so as to facilitate future formulation changes.

_____ Date: _____

Chandra S. Chaurasia, Ph.D.
Clinical Pharmacology Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by E. Dennis Bashaw, Pharm.D. _____ Date: _____

2. TABLE OF CONTENTS

3. OVERVIEW OF CPB SECTION

Item 6 of this NDA presents *in vitro* and *in vivo* human pharmacokinetic data for azelaic acid (Table 1) from 6 studies using either 15% gel, 20% cream or oral dosage forms of azelaic acid. Of these, only two reports A03125 and AU36 contain data using azelaic acid 15% gel formulation.

- The pharmacokinetic data in Report A03125 and Report AU36 were obtained concurrently with clinical efficacy and safety data.

- Report A03125 shows the serial plasma concentrations of azelaic acid following topical application of azelaic acid 15% gel for 8 weeks in comparison with vehicle treatments.

- Report AU36 reports the comparison between azelaic acid 20% cream and 15% gel applied topically to patients with papulo-pustular facial acne in terms of systemic exposure of azelaic acid determined by daily urinary excretion.

- Report 5999 and Report 6083 contain *in vitro* data regarding the protein binding and skin penetration of azelaic acid (Franz cell) and support the human pharmacokinetic data.

- Report 5299 shows the absorption and elimination of azelaic acid administered orally in gelatin capsules as pure substance to healthy volunteers.

- Report 6138 demonstrates the bioavailability of azelaic acid 20% cream applied topically to healthy skin relative to azelaic acid suspension administered orally.

To-be-marketed formulation was used in both pivotal clinical and PK studies. Schering AG, Berlex's parent company, manufactures the drug substance.

Reviewer's Note: Studies in Reports # 5299, 6138, 5999 and 6083 are not necessarily relevant to this application and were not reviewed for the following reasons:

In Table 1, the sponsor cites four additional studies (reports # 5299, 6139, 5999 and 6083) done in support of this application. These study reports were reviewed as part of NDA 20-428, AZELEX Cream, 20%. Two of these (report #5299 and 6139) were in vivo studies done in normal volunteers with healthy skin, the relevance of these data to patients with rosacea are unknown. The other two studies, report #5999 was done using radio-labeled azelaic acid solution to determine in vitro protein/RBC binding, and report #6083 was done using radio-labeled 20% azelaic acid cream to determine in vitro PK parameters (skin uptake, systemic absorption).

Table I: Pharmacokinetic Studies in NDA 21-470, Azelaic Acid Gel, 15%

Report No.	Objective	Design	Subjects (M/F)	Dosage Form	Dose and Duration	Route	Remark
A03125	to determine systemic exposure by plasma concentration (pre-dose, 1, 2, 4 hr after 8 wk dose)	Randomized, double-blind	14 patients with stage 2 rosacea (4/10)	15% gel	~ 0.75 g gel, bid x 12 wks	Topical	Concurrently with clinical study Plasma concentrations were higher with 15% gel than vehicle, but still in normal range
			13 patients with stage 2 rosacea (3/11)	Vehicle gel	~ 0.75 g gel, bid x 12 wks	Topical	
AU36 (Same formulation as in A03125: Different manufact-uring site)	to compare systemic exposure by daily urinary excretion (predose, Days 8, 15, 29, 57)	Randomized, double-blind	14 patients with papulo-pustular facial acne (4/10)	20% cream, (marketed in Europe as Skinoren™)	~ 0.75 g cream, bid x 8 wks	Topical	Concurrently with clinical study Similar daily urinary excretion
			15 patients with papulo-pustular facial acne (8/7)	15% gel	~ 0.75 g gel, bid x 8 wks	Topical	
5299	to determine PK parameters	Ascending dose (1 wk washout), open label	5 healthy volunteers (3/2)	oral gelatin capsules (pure substance)	0.5 – 5 g	oral	Completely absorbed, linear Cmax and AUC up to 3.5 g, t1/2 < 1 h, CLr ~ 300 mL/min
6138	to determine relative bioavailability	single-dose, 2-way crossover, open label	6 healthy volunteers (6/0)	20% cream	5 g	Topical	Percutaneous absorption ~ 4% Not relevant to this submission -> Not reviewed
				Suspension	1 g in 100 mL	Oral	
5999	to determine in vitro PK parameters (protein/ RBC binding)			^{14}C-azelaic acid aqueous solution			
6083	to determine in vitro PK parameters (skin uptake, systemic absorption)			^{14}C-azelaic acid 20% cream			Used Franz cell and cadaver skin

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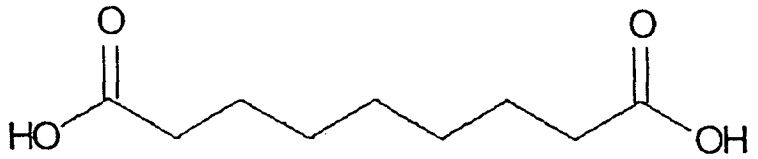
4. QUESTION-BASED REVIEW

4.1. General Attributes

What are the highlights of the physicochemical properties of azelaic acid?

Chemical Name: 1,7-heptanedicarboxylic acid

Structure: $HOOC-(CH_2)_7-COOH$



Molecular Weight: 188.22

Physicochemical Properties: white odorless crystalline solid, slightly soluble in water (2.4 g/L at 20 °C), slightly soluble in aqueous buffer at pH 4.5, freely soluble in aqueous buffer at pH 6.5

What are the highlights of the biochemical and pathophysiological roles of azelaic acid?

Exogenous Source: Azelaic acid is present in animals, humans, and plants. It is a natural constituent in whole grain cereals such as wheat, rye and barley, which contain azelaic acid in amounts of 0.4 to 7 mg/g. Dietary intake of just one ounce of cereal provides 11 to 196 mg of azelaic acid depending on the constituent grain. Dietary intake also includes potential precursors of azelaic acid such as odd-numbered fatty acids. Azelaic acid was the first dicarboxylic acid proposed as an alternative energy substrate in parenteral nutrition.

Endogenous Production: Azelaic acid is also endogenously formed from longer chain dicarboxylic acids, metabolism of oleic acid, and ω-oxidation of C9 monocarboxylic acid.

Pathophysiological Role: The mechanisms by which azelaic acid interferes with the pathogenic events in rosacea are unknown but may include an anti-inflammatory effect. In acne, azelaic acid is claimed to have antikeratinizing and antibacterial activity. The normalization of the disturbed follicular keratinization and an antimicrobial activity against *Propionibacterium acnes* provides the rationale for the use of azelaic acid 20% cream in the topical therapy of mild to moderate forms of acne vulgaris.

What are the properties of the formulation of the drug product?

Formulation: 15% (w/w) gel containing ——— azelaic acid

Composition: See Table II.

Table II. Component and Compositions of Finacea 15% Gel

Component	Quantity (g) per 100 g
Azelaic acid,	15.0
Lecithin, NF	
Medium chain triglycerides	
Polysorbate 80, NF	
Propylene glycol, USP	
Polyacrylic acid	
Sodium hydroxide, NF	
Edetate disodium, USP	
Benzoic acid, USP	
Purified Water, USP	
Total	100.0

NF = National Formulary; USP = United States Pharmacopoeia.

What are the proposed therapeutic indication, dosage, route of administration, and mechanism of action of azelaic acid?

Indication: Finacea (azelaic acid) 15% gel is indicated for topical application in the treatment of inflammatory papules and pustules of rosacea.

Rosacea, previously referred to as acne rosacea, clinically has some features in common with acne, particularly the occurrence of inflammatory papules and pustules and facial redness. However, its pathogenesis differs from that of acne and does not involve abnormal keratinization or *P acnes*. Rosacea is a chronic inflammatory dermatosis mostly involving the centrofacial area. Early clinical symptoms include facial flushing. The progression of the disease to papulopustular rosacea is characterized by persistent erythema, telangiectasia, and inflammatory episodes with papules and pustules. In severe cases of rosacea, dermal and sebaceous gland hypertrophy causes the development of rhinophyma or other phymas. It most commonly becomes manifest between the ages of 30 to 50 years. Current modalities of treatment of rosacea include topical metronidazole, systemic antibiotics (tetracycline derivatives and erythromycin), and oral isotretinoin for severe cases. Telangiectasia are usually obliterated using either diathermy, light coagulation or laser surgery.

Dosage and Route of Administration: The daily clinical dose of azelaic acid 15% gel varies due to the size of the affected areas. A typical dose of 1.0 g gel formulation containing 150 mg azelaic acid, applied twice a day, represents a daily dose of 3.0 mg/kg for a 50 kg individual, corresponding to approximately 120 mg/m^2 body surface area.

Mechanism of Action: The pharmacological basis for the clinical effect of azelaic acid in rosacea is unclear but may to include an anti-inflammatory effect. In vitro findings indicate that azelaic acid inhibits the production and/or release of proinflammatory, reactive oxygen species from neutrophils. The release of reactive oxygen species, such as superoxide and hydroxyl radicals,

results in tissue destruction and may initiate or perpetuate inflammation processes. The clinical relevance of these in vitro results is unknown.

4.2. General Clinical Pharmacology

Are the active moieties in the plasma or other biological fluid appropriately identified and measured to assess pharmacokinetic parameters?

The concentration of azelaic acid (AzA) and its metabolite, pimelic acid in human plasma was determined by a validated LC/MS/MS method (**Report A03125**). Most values for the plasma concentration of pimelic acid were below the limit of detection for the assay (10 ng/mL).

The concentration of AzA and its possible metabolites ZK 27123 (Glutaric acid) and ZK 57818 (Heptanedioic acid) in human urine samples was measured by validated GC/MS method (**Report AU36**). For the metabolites, only semi-quantitative estimation was possible due the lack of accuracy and precision.

The assays are acceptable. Section 4.6 summarizes the analytical method validations.

What are the basic pharmacokinetic parameters of azelaic acid (ADME)?

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 (omega)-oxidation of monocarboxylic acids. The percutaneous absorption of azelaic acid after topical application of azelaic acid gel 15% could not be determined reliably. However, per the labeling of sponsor's approved product Finevin (NDA 20-428, 2001, Azelaic acid cream 20%), approximately 4% of the topically applied azelaic acid is systemically absorbed. Azelaic acid is mainly excreted unchanged in the urine but undergoes some (beta)-oxidation to shorter chain dicarboxylic acids.

Are the study populations relevant to the proposed indication?

Finacea is indicated for the treatment of inflammatory papules, pustules [redacted] of rosacea. The pharmacokinetic study (**A03125**) was conducted in patients with moderate rosacea with 10 to 50 inflammatory papules and pustules, persistent erythema and telangiectasia. Subjects without papules and pustules, subjects with nodules, rhinophyma, or ocular involvement, and subjects with a history of hypersensitivity to ingredients of the study drug were excluded.

Rosacea is a common disorder in fair-skinned Caucasian but occurs only rarely in dark-skinned persons including African-Americans. It most commonly becomes manifest between the ages of 30 to 50 years.

All patients for the PK study were from site no. 10. The demographic summary of the study patients (N=28) is given below:

Ethnic Group:	Caucasian (AzA Gel, N = 14: 3 males, 11 females) Vehicle, N = 14: 4 males, 10 females)

Age (years):	AzA Gel: mean (± SD): 52.4 ± 15.1, range: 23-81
	Vehicle: mean (± SD): 56.8 ± 14.4, range: 35-77
Height (cm):	AzA Gel: mean (± SD): 165 ± 9.1, range: 154.9-185.4
	Vehicle: mean (± SD): 168.2 ± 7.5, range: 154.9-182.9
Weight (kg):	AzA Gel: mean (± SD): 77.5 ± 13.4, range 49.9-99.8
	Vehicle: mean (± SD): 76.0 ± 13.7, range 53.4-99.8
Body Mass Index:	AzA Gel: mean (± SD): 28.4 ± 5.1, range 19.5-36.5
	Vehicle: mean (± SD): 27.0 ± 5.4, range: 19.0-40.2

Are dose and dosing regimen appropriate for the treatment of the proposed indication?

Rosacea is chronic inflammatory dermatosis mostly involving the centrofacial area. The recommended dosage of FINACEA™ is a thin layer to be applied twice daily, in the morning and evening, to the entire affected areas and gently messaged 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 observed after 4 weeks.

In the current submission, plasma AzA concentrations (predose and 1, 2, and 4 hours postdose) were monitored in patients with moderate, papulopustular facial rosacea who had received approximately 0.75 g, twice daily topical treatments of AzA 15% gel or vehicle for at least 8 weeks (Report A03125). Additionally, urine AzA concentrations (at baseline, 1, 2, 4 and 8 weeks) were monitored in patients with mild to moderate, papulopustular facial acne treated twice daily with approximately 0.75 g AzA 20% cream or 15% gel (Report AU36).

Based on clinical trial outcome, the dose and dosing regimen seem appropriate for the treatment of the proposed indication.

4.3. **Intrinsic Factors:** Age, Sex, Race, Weight, Height and Disease States.

The PK study includes Caucasian population, both male and female adults 23-81 years of age. It is noted that rosacea is prevalent in this ethnic group.

Rosacea is typically manifested in adults 30-50 years old. PK study did not include sufficient numbers of subjects aged 65 and over to determine whether pharmacokinetics of FINACEA™ is different in geriatrics than those in younger subjects. Safety and effectiveness of FINACEA™ in pediatric patients have not been established. The firm's request for *Pediatric Waiver* is under consideration by the clinical review team.

As indicated in Section 4.2, azelaic acid is a dietary constituent and can also be formed endogenously. Furthermore, the drug product is a topical preparation, and approximately 4% of the topically applied azelaic acid has been shown to be systemically absorbed (data from Azelaic Acid 20% cream). Thus, in the reviewer's opinion pharmacokinetic studies in disease states (e.g., renal and hepatic impairments) adult population are not needed for the approval of this product.

4.4. **Extrinsic Factors:** Drugs, Diets and Smoking

No other topical or systemic medication affecting the course of rosacea and/or evaluability was to be applied during the studies. Patients were instructed to use very mild soap or soapless cleansing lotion for facial cleansing.

Patients were instructed to avoid spicy foods, extreme hot foods and drinks, alcoholic beverages during the study. Because of the wide distribution of azelaic acid in the diet, dietary restriction to control azelaic acid from diet was not feasible.

As indicated above, azelaic acid is a dietary constituent and the product is a topical preparation, thus, evaluation of the effect of any other extrinsic factors on azelaic acid pharmacokinetics is not needed.

4.5 General Biopharmaceutics

What are the differences between approved, clinical, and to-be-marked formulations?

The firm notes that the formulation number SH H 655 BA corresponding to Batch 03002 is the proposed commercial formulation (pp. 25, Summary Report). This batch was used in all clinical studies (listed in Summary Report, pp. 26) except one (——————— The batch was manufactured and packaged in the same facility (**Milan, Italy**) using the same equipment and nearly identical manufacturing process that will be used for the commercial product.

The batch used in protocol ———— is a —. batch (no. DA01710) of the same drug product formulation. This — batch was manufactured at — of production scale in the — plant (**Berlin, Germany**) using the same type of equipment and essentially the same manufacturing process that will be used for the commercial process.

The batch DAO171 manufactured in Berlin was used in only one pharmacokinetic study (Report AU36). This study was conducted to assess the urinary excretion of azelaic acid. In the reviewer's opinion, the pharmacokinetic profile in Report AU36 is a supportive study, and will not impact significantly the outcome of other important clinical studies where batch 03002 was used.

Are there any in vitro data for azelaic acid 15% gel formulation?

The sponsor has not provided any in vitro release testing data on this product. The in vitro release test is not required for the approval of this product. However, in a recent communication (in response to FDA request for information, NDA 21-470, submission date: 06/06//02), the Agency recommended the sponsor to develop an in vitro release testing on the proposed product to facilitate approval process in the future by having an in vitro test already validated and ready to use in such a situation.

4.6. Analytical

What bioanalytical methods are used to assess the amount of azelaic acid in blood, urine, or other study specimens?

Plasma Samples. The analysis of the human plasma samples to determine the concentrations of azelaic acid and pimelic acid was accomplished by use of a liquid chromatography/mass spectrometric/mass spectrometric method described in the validation report DSU Study No. 00-A024. Standard curve samples and quality control samples were generated by

The peak area ratios (PARs) of azelaic acid and pimelic acid to IS were calculated for each sample from the measured peak areas obtained by LC/MS/MS. Due to endogenous low levels of azelaic acid and pimelic acid,

Urine Samples. A GC-MS method was used for the determination of azelaic acid from human urine. The analytes and internal standard (sebacic acid) were isolated from pooled urine by means of a liquid/liquid extraction with ether.

Are analytical methods sensitive enough to determine the extent of azelaic acid absorption after topical application?

Analytical method validation results are summarized below:

For Human Plasma Samples.

Internal Standard:

Linearity Range:
Lower Limit of Quantitation:
Accuracy (QCs):
Precision (QCs):
Specificity:

Stability:

For Human Urine Samples

Internal Standard:
Linearity Range:
Lower Limit of

Quantitation:
Accuracy (QCs):
Precision (QCs):
Specificity:

Stability: Not submitted.

4.7. Pharmacokinetic Data:

Table I: Azelaic Acid Mean Plasma Concentrations (ng/mL) by Treatment Group and Sampling Time (N= 27: 13 AzA Gel and 14 Vehicle Treatments)

Sampling Time	Azelaic Acid 15% gel	Vehicle	Treatment Difference	95% CI for Treatment Difference
Time 0 (predose)				
N*	11(84.6%)	8 (57.1%)		
Mean	42.05	17.23	24.83	9.38, 40.28
SD	20.11	5.01		
Median	35.30	17.95		
Min-Max				
1 hour postdose				
N*	13 (100%)	12 (85.7%)		
Mean	53.8	27.53	26.28	10.31, 42.24
Median	56.90	25.00		
Min-Max				
SD	18.41	20.18		
2 hours postdose				
N*	13 (100%)	12 (85.7%)		
Mean	62.18	29.19	32.99	12.48, 53.50
SD	27.14	21.89		
Median	59.10	25.30		
Min-Max				
4 hours postdose				
N*	13 (100%)	13 (92.9%)		
Mean	63.11	27.94	35.17	15.71, 54.63
SD	27.62	19.82		
Median	68.00	19.50		
Min-Max				

The number of patients who had a quantifiable plasma level of azelaic acid at the specified sampling time.

Reviewer's Note: Individual plasma-azelaic acid-concentration vs. time plot (submitted in Clinical Study Report section, pp. 174-201) was analyzed by this reviewer. It is noted that plasma samples were collected only up to 4 hours post-dose and there were only 4 sampling times points (pre-dose at time 0, 1-, 2- and 4-hr post-dose). In addition, a) the Finacea gel did not show any appreciable percutaneous absorption, and b) plasma azelaic acid concentration appears

to reach a plateau at 2-hr sampling time point. Thus, the individual plasma concentration-time plots do not provide any meaningful information in the PK study.

5. Detailed Labeling Recommendations

Most of the information in the pharmacokinetic section of the label is acceptable.
The following changes are recommended for the pharmacokinetic section of the labeling. ~~ABC~~ suggests deletion of text and ABC does insertion of new text.

CLINICAL PHARMACOLOGY

The mechanisms by which azelaic acid interferes with the pathogenic events in rosacea are unknown.

Pharmacokinetics:

The percutaneous absorption of azelaic acid after topical application of FINACEA™ (azelaic acid 15% gel) could not be reliably determined.

Mean plasma azelaic acid concentrations in rosacea patients treated with FINACEA™ gel twice daily for at least 8 weeks are in the range of 42 to 63.1 ng/mL. These values are within the maximum concentration range of 24.0 to 90.5 ng/mL observed in rosacea patients treated with vehicle only. This indicates that FINACEA™ does not increase plasma azelaic acid concentration beyond the range derived from nutrition and endogenous metabolism.

In vitro animal and human data suggest negligible cutaneous metabolism of ^{3}H-azelaic acid 20% cream after topical application. Azelaic acid is mainly excreted unchanged in the urine, but undergoes some ß-oxidation to shorter chain dicarboxylic acids.

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ON ORIGINAL

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

APPENDIX II

Individual Study Reviews

Report A03125

A 12-Week, Randomized, Double-Blind Multicenter Study Comparing the Clinical Efficacy and Safety of Azelaic Acid 15% Gel with Its Vehicle in Patients with Moderate, Papulopustular Facial Rosacea

Objectives:

The objective of the pharmacokinetic part of this study was to compare the extent of azelaic acid absorption between azelaic acid 15% gel and its vehicle (gel base) after topical application to male and female patients with moderate, papulopustular, rosacea (stage 2 rosacea)

Methods:

This was a pharmacokinetic substudy of a multicenter, double-blind, randomized, parallel-group clinical study to evaluate the efficacy and safety of azelaic acid 15% gel in patients with moderate, papulopustular facial rosacea. Following eligibility evaluation, patients enrolled in the study applied either azelaic acid 15% gel (Batch No. 03002) or vehicle (Batch No. 03001) topically, twice daily to the entire facial area.

Plasma concentrations of azelaic acid and its metabolite, pimelic acid, were measured at steady state for patients enrolled in the pharmacokinetic substudy at one of the 15 clinical study sites. Blood samples (10 mL) were drawn predose, and at 1, 2, and 4 hours postdose. Summary descriptive statistics (mean, median, and standard deviation) of the concentration levels at each sampling time by treatment group were calculated. A 95% 2-sided confidence interval for the mean treatment difference in concentration levels was estimated for each of the 4 time points, and for both azelaic acid and pimelic acid.

Reviewer's Note on Sampling Time Points: *As mentioned above, the sponsor has used only four sampling time points – 0, 1, 2 and 4 hours post-dose. Normally, plasma sample collection at further time points would have been recommended in order to characterize the PK profile. However, the 4 time points in this study was considered appropriate for the following reasons:*

- *Although, the mean plasma azelaic acid levels at 1-, 2- and 4-hr sampling time-points in rosacea patients treated with azelaic acid 15% gel were significantly higher compared to those of the vehicle (54-63 ng/mL vs. 27-35 ng/mL, respectively, Table 1),* these values are within the maximum concentration range of *24.0 to 90.5 ng/mL observed in rosacea patients treated with vehicle only.*
- *The drug product FINACEA™ (azelaic acid 15% gel) is topically administered. There is a full PK profile of topically administered FINEVIN™ (azelaic acid cream 20%) in acne patients. It is noted that the surface area (face, back and chest regions) of acne is much larger than that in rosacea (facial only). The reported mean azelaic acid plasma concentration in acne patients is 89.6 ng/mL (FINEVIN™ data).*

- *Thus, even considering that percutaneous absorption of gel formulation (FINACEA™) could possibly be different from that of the cream formulation (FINEVIN™), further sampling after 4-hr time point is unlikely to provide any meaningful information with respect to the pharmacokinetic data.*

Azelaic acid and pimelic acid concentrations in plasma were determined using a validated LC/MS/MS assay. The performance of the method during sample analysis is described in analytical section of this review.

Inclusion/Exclusion Criteria: *Patients were eligible for inclusion in the study if they met all of the following criteria: moderate papulopustular facial rosacea (stage 2) with a minimum of 8 and a maximum of 50 inflammed papules and/or pustules and persistent erythema and telangiectasia, male and female patients aged 18 years or older, informed signed consent. Female patients of childbearing potential were allowed to participate in the study. Because azelaic acid is classified as Pregnancy Category B, patients were not required to practice a reliable hormonal or nonhormonal method of contraception. Exclusion criteria appear to be relevant to this study.*

Results:

All patients in the PK study were from Site No. 10. All PK blood samples were drawn on one day, after the patients had been treated with azelaic acid 15% gel or vehicle for at least 8 weeks. There were 30 patients who consented to participate in the PK study. Two patients failed to show up at the site on the morning of the study. Phlebotomists were unable to draw blood from a third patient (randomization number 249, AzA Gel), despite repeated attempts. In total, 27 patients participated in the PK evaluation. The demographic summary is provided below:

Ethnic Group:	Caucasian (AzA Gel, N = 14: 3 males, 11 females) Vehicle, N = 14: 4 males, 10 females)
Age (years):	AzA Gel: mean (± SD): 52.4 ± 15.1, range: 23-81 Vehicle: mean (± SD): 56.8 ± 14.4, range: 35-77
Height (cm):	AzA Gel: mean (± SD): 165 ± 9.1, range: 154.9-185.4 Vehicle: mean (± SD): 168.2 ± 7.5, range: 154.9-182.9
Weight (kg):	AzA Gel: mean (± SD): 77.5 ± 13.4, range 49.9-99.8 Vehicle: mean (± SD): 76.0 ± 13.7, range 53.4-99.8
Body Mass Index:	AzA Gel: mean (± SD): 28.4 ± 5.1, range 19.5-36.5 Vehicle: mean (± SD): 27.0 ± 5.4, range: 19.0-40.2

The steady-state predose plasma concentrations of azelaic acid were higher in the azelaic acid 15% gel group than in the vehicle group (Table I). At all sampling times after a single topical facial application, the azelaic acid plasma concentration was roughly twice as high in the azelaic acid-treated group as in the vehicle-treated group, increasing over time. There was an increase of plasma azelaic acid concentration in the vehicle group 1 hour after medication application that remained constant thereafter. At all 4 sampling times, the difference between the two treatment groups was statistically significant. No baseline values at the time the patients started treatment were obtained.

Table I: Azelaic Acid Mean Plasma Concentrations (ng/mL) by Treatment Group and Sampling Time (N= 27: 13 AzA Gel and 14 Vehicle Treatments)

Sampling Time	Azelaic Acid 15% gel	Vehicle	Treatment Difference	95% CI for Treatment Difference
Time 0 (predose)				
N*	11(84.6%)	8 (57.1%)		
Mean	42.05	17.23	24.83	9.38, 40.28
SD	20.11	5.01		
Median	35.30	17.95		
Min-Max				
1 hour postdose				
N*	13 (100%)	12 (85.7%)		
Mean	53.8	27.53	26.28	10.31, 42.24
Median	56.90	25.00		
Min-Max				
SD	18.41	20.18		
2 hours postdose				
N*	13 (100%)	12 (85.7%)		
Mean	62.18	29.19	32.99	12.48, 53.50
SD	27.14	21.89		
Median	59.10	25.30		
Min-Max				
4 hours postdose				
N*	13 (100%)	13 (92.9%)		
Mean	63.11	27.94	35.17	15.71, 54.63
SD	27.62	19.82		
Median	68.00	19.50		
Min-Max				

* The number of patients who had a quantifiable plasma level of azelaic acid at the specified sampling time.

Most values for the plasma concentration of pimelic acid were below the limit of detection for the assay. The remaining values show that the concentration of pimelic acid was higher at predose in the patients treated with azelaic acid 15% gel (Table II). Over time, the concentration remained constant in the azelaic acid 15% gel group but increased slightly in the vehicle group. At no time was there a statistically significant difference in the concentration of pimelic acid between the 2 treatment groups.

Table II: Pimelic Acid Concentrations (ng/mL) by Treatment Group and Sampling Time

Sampling Time	Azelaic Acid 15% gel, N=13	Vehicle, N=14	Treatment Difference	95% CI for Treatment Difference
Time 0 (predose)				
N*	4 (30.8%)	2 (14.3%)		
Mean	15.68	10.70	4.98	-10.44, 20.39
SD	7.39	0.71		

Median	12.55	10.70		
Min-Max				
1 hour postdose				
N*	6 (46.2%)	4 (28.6%)		
Mean	13.60	14.48	-0.88	-6.57, 4.82
SD	3.91	3.68		
Median	12.25	13.45		
Min-Max				
2 hours postdose				
N*	9 (69.2%)	4 (28.6%)		
Mean	14.70	15.50	-0.80	-6.27, 4.67
SD	4.14	4.12		
Median	14.50	14.20		
Min-Max				
4 hours postdose				
N*	7 (53.8%)	6 (42.9%)		
Mean	16.80	14.67	2.13	-4.90, 9.17
SD	6.94	3.85		
Median	13.70	13.75		
Min-Max				

* The number of patients who had a quantifiable plasma level of azelaic acid at the specified sampling time.

Conclusion:

Mean plasma concentrations of azelaic acid were twice as high in the patients treated with azelaic acid 15% gel compared with that from the vehicle at all 4 sampling times.

Reviewer's Comment:

- Although the mean plasma azelaic acid concentrations in rosacea patients treated with azelaic acid were consistently higher compared with those in the vehicle group, these values are within the maximum concentration range of 24.0 to 90.5 ng/mL observed in rosacea patients treated with vehicle only. This indicates that the topical treatment with azelaic acid did not affect significantly any systemic function beyond that derived from dietary and endogenous sources.

- As noted, most values for the plasma concentration of pimelic acid were below the limit of detection for the assay. It is noted that at no time was there a statistically significant difference in the levels of pimelic acid in the AzA 15% gel-treated group than those from the vehicle-treated group.

- For a better comparison of the plasma azelaic acid levels in the AzA 15% gel-treated and vehicle-treated subjects, ideally baseline values at the time the patients started treatment should have been obtained. However, in light of the results of this study, absence of the baseline values may not have any significant impact on the outcome.

Report AU36

A 8-Week, Controlled, Double-Blind Pilot Study Comparing the Initial Clinical Effect of 15% Azelaic Acid Hydrogel SH H 655 BA with 20% Azelaic Acid Cream (Skinoren) During Twice-Weekly Topical Treatment of Patients with Papulopustular Facial Acne.

Objectives:

The objective of this pilot study was to investigate the effect of 15% azelaic acid gel formulation on acne lesions during an 8-week treatment period, as compared with that of 20% azelaic acid cream, in order to establish a time-response relationship during the initial phase of therapy of mild to moderate papulopustular facial acne. Additionally, the steady-state percutaneous absorption of azelaic acid from both formulations was to be assessed by measuring the amounts of AzA excreted with the urine.

Methods:

This was a pharmacokinetic exploratory investigative single center, double-blind, randomized, parallel-group comparison between 15% AzA gel SH H 655 BA and 20% AzA cream SH C 441 F (Skinoren®. *see reviewer's comment at the end*) to evaluate steady-state percutaneous absorption of azelaic acid 15% gel in patients with mild to moderate, papulopustular facial acne. The study was conducted at [redacted]. Following eligibility evaluation, patients enrolled in the study applied either azelaic acid 15% gel (Batch No. DA 0171) or azelaic acid cream 20% (Batch No. 732941) topically, twice daily to the entire facial area.

Percutaneous absorption of azelaic acid from the gel and cream was estimated from the daily excreted amount of AzA in the urine of the patients of both treatment groups on day 1 (pre-treatment value), and after 1 week, 2 weeks, 4 weeks and 8 weeks using the following formula:

[redacted] *(described in detail in the submission, Section 9.5, pp. 22-23 of study report no. AU36).*

Summary descriptive statistics (mean, median, and standard deviation) of the concentration levels at baseline 1, 2, 4 and 8 weeks by treatment group were calculated.

Azelaic acid concentrations in urine were determined using a validated GC/MS assay. The performance of the method during sample analysis is described in analytical section of this review.

Inclusion/Exclusion Criteria: *Patients were included in the study according to predefined inclusion and exclusion criteria described in section 9.3, pp. 13-15 of the study report No. AU36. The inclusion/exclusion criteria appear to be relevant to this study.*

Results:

All urinary excretion samples were estimated at the baseline and had been treated with azelaic acid 15% gel or vehicle for at least 8 weeks. There were 30 patients (15 each treatment group,

12 males and 18 females, mean age 23.6 years, range:16-43-years) who consented to participate in the PK study. One patient (#15) discontinued the study after 5 weeks. In total, 29 patients (15 in 15% gel- and 14 in 20% cream-treatment) completed the PK evaluation.

A baseline azelaic acid concentrations of 0.94 and 1.19 mg/day was noted in urine samples of treatment groups 15% azelaic acid gel and 20% azelaic acid cream, respectively (Table III). The sources for this pretreatment systemic exposure are endogenous and dietary. After one week of twice daily treatment the median AzA excretion increased to approximately 12 and 13 mg/day from gel and cream, respectively. At the end of the second week of treatment the AzA excretions decreased in both treatment groups to values of 2.5 and 2 mg, respectively, and remained rather stable in both treatment groups during weeks 4 to 8 (with outputs of approximately 6-9 mg/day in the group treated with AzA gel and 12-14 mg/day in the group treated with AzA cream).

Table III. Urinary excretion of AzA (mg/day) during treatment with Azelaic acid 15% gel and 20% cream. Excretion was determined before starting treatment (baseline) and after 1, 2, 4 and 8 weeks of twice daily treatment with AzA gel and cream, respectively.

Azelaic Acid 15% Gel	Baseline	1 week	2 weeks	4 weeks	8 weeks
Mean	1.46	16.02	4.18	6.99	9.08
SD	1.45	11.18	5.80	4.61	6.16
Median	0.94	11.77	2.49	6.80	6.15
Q25					
Q75					
Min					
Max					
Azelaic Acid 20% Cream	Baseline	1 week	2 weeks	4 weeks	8 weeks
Mean	2.85	16.44	2.79	14.01	12.31
SD	5.02	14.22	2.66	15.98	9.03
Median	1.19	13.03	1.94	8.32	9.21
Q25					
Q75					
Min					
Max					

Conclusion:

There was no hint that systemic exposure to azelaic acid after treatment with the 15% AzA gel is essentially different form that after treatment with 20% AzA cream.

Reviewer's Comment:

After 8 weeks' topical treatment, the daily urinary excretion of azelaic acid in acne patients treated with azelaic acid 15% gel or 20% cream were similar and within the range derived from the dietary sources (4 to 28 mg). Long-term systemic exposure from topical application of AzA 15% gel is about the same as 20% AzA cream and does not cause a distinctly higher body burden

than from daily nutrient intake. However, it is noted that the study was conducted in Germany, and the amount of azelaic acid from dietary source is expected to be different than that in general US population based on variability of diet. Furthermore, it is also to be noted that the exact composition of 20% azelaic acid cream (Skinoren®) used in this study may be different (in terms of inactive ingredients) from the US marketed FINEVIN™ (azelaic acid 20% cream) product. Nevertheless, this was a [redacted] study and the data are used for supportive purpose only.

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OCPB Filing Review Form

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	21-470	Brand Name	Finacea
OCPB Division (I, II, III)	III	Generic Name	azelaic acid
Medical Division	HFD-540	Drug Class	topical anti-acne medication
OCPB Reviewer	Jang-Ik Lee and Chandra S. Chaurasia	Indication(s)	topical treatment of inflammatory papules and erythema of rosacea
OCPB Team Leader	E. Dennis Bashaw	Dosage Form	gel 15%
		Dosing Regimen	BID ?, up to 4 wks?
Date of Submission	03/21/02	Route of Administration	topical
Estimated Due Date of OCPB Review	09/21/02	Sponsor	Berlex Laboratories
PDUFA Due Date	01/21/03	Priority Classification	3S, 6S
Division Due Date	TBD		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:	X	1		in vitro study
Isozyme characterization:				
Blood/plasma ratio:	X	1		in vitro study
Plasma protein binding:	X	1		in vitro study
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				

single dose:	X	1		
multiple dose:	X	1		ascending dose
Patients-				
single dose:				
multiple dose:	X	2		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	X	1		
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				

Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			PK article including IV
Total Number of Studies		6		Includes in vitro studies

Filability and QBR comments		
	"X" if yes	Comments
Application fileable?	X	Reasons if the application is not fileable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	What are the highlights of the physicochemical properties of azelaic acid? What are the highlights of the biochemical and pathophysiological roles of azelaic acid? What are the properties of the formulation of the drug product? What are the proposed therapeutic indication, dosage, route of administration, and mechanism of action of azelaic acid? Are the active moieties in the plasma or other biological fluid appropriately identified and measured to assess pharmacokinetic parameters? What are the basic pharmacokinetic parameters of azelaic acid (ADME)? Are the study populations relevant to the proposed indication? Are dose and dosing regimen appropriate for the treatment of the proposed indication? What are the differences between approved, clinical, and to-be-marked formulations? What bioanalytical methods are used to assess the amount of azelaic acid in blood, urine, or other study specimens? Are analytical methods sensitive enough to determine the extent of azelaic acid absorption after topical application?	

Other comments or information not included above	Need clarification in the existence of population PK data, the existence of in vitro drug release study (Franz cell release rates) the waiver of pediatric information
Primary reviewer Signature and Date	Jang-Ik Lee (5/8/02) and Chandra S. Chaurasia
Secondary reviewer Signature and Date	

CC: NDA 21-470, HFD-850 (P. Lee), HFD-540 (CSO), HFD-880 (TL, DD, DDD), CDR

End of Document

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/s/

Chandra S. Chaurasia
12/9/02 01:53:32 PM
BIOPHARMACEUTICS

Dennis Bashaw
12/9/02 05:30:19 PM
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