

These records are from CDER's historical file of information previously disclosed under the Freedom of Information Act (FOIA) for this drug approval and are being posted as is. They have not been previously posted on Drugs@FDA because of the quality (e.g., readability) of some of the records. The documents were redacted before amendments to FOIA required that the volume of redacted information be identified and/or the FOIA exemption be cited. These are the best available copies.

NDA 20-428 1 ~ f 3

DDA 220-428

AP Ltr

N/A Ltr

LBC

MOR

Micra

Chem

Memo

AP Ltr

LBC

NDA 20-428

Allergan Herbert
Division of Allergan, Inc.
Attn: Mr. Steve Buxbaum
Director, Worldwide Regulatory Affairs
P.O. Box 19534
Irvine, CA 92713-9534

SEP 3 1995

Dear Mr. Buxbaum:

Please refer to your February 28, 1994, new drug application (NDA) and to your March 9, 1995, amendment submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azelex (azelaic acid cream) 20%.

Please also refer to the not approvable letter dated February 28, 1995. We acknowledge your correspondence dated May 17, July 25, August 3, 10, 18, and 31, and September 12 and 13, 1995.

We acknowledge your correspondence dated August 18, 1995, in which a commitment was made to submit the following:

1. Within 60 days of approval, a supplement will be submitted that establishes an x-ray powder diffraction method and appropriate specifications for polymorphs A (α) and B (β) of azelaic acid.
2. Within 60 days of approval, a supplement will be submitted that establishes a particle size and/or agglomeration specification for azelaic acid.
3. Within 60 days of approval, a supplement will be submitted that amends the content uniformity protocol.

In addition, a commitment was made to collect and submit data to establish a correlation between viscosity and penetration.

We also acknowledge your correspondence dated August 31, 1995, in which a commitment was made to revise the storage conditions shown on the tubes and cartons to conform to the draft labeling after the initial production run. The initial production run consists of the following lots: 58A00 through 58A07, 58A08 through 58A22, and 75B00 through 75B14.

Finally, we acknowledge your commitment dated March 9, 1995, to conduct a Phase 4 study to investigate hypopigmentation as a possible adverse event.

We have completed the review of this application as amended, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted draft labeling dated February 24, 1994, (carton and container labels) and September 13, 1995 (package insert). Accordingly, the application is approved, effective as of the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling. Marketing the product with FPL that is not identical to the draft labeling may render the product misbranded and an unapproved new drug.

Please submit fifteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-428. Approval of this labeling is not required before it is used.

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

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications HFD-240
5600 Fishers Lane
Rockville, MD 20857

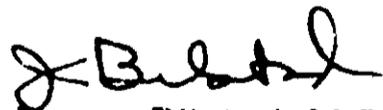
Please submit one market package of the drug product when it is available.

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

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

Should you have questions regarding this application please contact Ms. Kennerly K. Chapman, Project Manager, at 301-594-0301.

Sincerely yours,

 9/13/95

James Bilstad, M.D.

Director

Office of Drug Evaluation II

Center for Drug Evaluation and Research

NDA 20-428

4

cc:

Concurrence only:

Orig NDA 20-428

HFD-540/DDir/Wilkin

HF-2 (w/labeling)

HFD-540/SPMS/Cook/rd8/15/95 *more 7/3/95*

HFD-2/Lumpkin (w/labeling)

HFD-540/SCchem/DeCamp/rd/8/24/95

HFR-PA240/LOS-DO (w/labeling)

HFD-540/SPharm/Jacobs/8/16/95

HFD-613 (w/labeling)

HFD-735/Baresh (w/labeling)

HFD-500 (w/labeling)

HFD-85 (w/labeling)

HFD-540/DptyDir/Katz

HFD-540/MO/Vaughan (w/labeling) 9/6/95

HFD-540/Pharm/Mainigi

HFD-540/Chem/Rejali

HFD-540/Chem/Hathaway/rd/8/17/95

HFD-540/Micro/King/rd/8/17/95

HFD-426/Biopharm/Pelso:

HFD-710/Biostat/Harkins

HFD-540/ClinRev/Joyce (w/labeling) *not 9/13/95*

HFD-540/SMO/Chambers/9/6/95

HFD-540/PMS/Chapman/n20428.ap (w/labeling)/9/6/95 *266 11/2/95*

Revised: Ripper/9/7/95

Ripper 9/13/95

Revised: Chambers/8/31/95

Revised: Chapman:9/5/95

Revised: DeCamp/Chambers: 9/6/95

APPROVAL WITH POST-APPROVAL COMMITMENTS (6)

Attachment (labeling)

AZELEX™
(azelaic acid cream) 20%

NDA 20-428
ALLERGAN Herbert

For Dermatologic Use Only
Not for Ophthalmic Use

DESCRIPTION:

AZELEX™ (azelaic acid cream) 20% contains azelaic acid, a naturally occurring saturated dicarboxylic acid.

Structural Formula: $\text{HOOC}-(\text{CH}_2)_7-\text{COOH}$
Chemical Name: 1,7-heptanedicarboxylic acid
Empirical Formula: $\text{C}_9\text{H}_{16}\text{O}_4$
Molecular Weight: 188.22

Active Ingredient: Each gram of AZELEX™ contains azelaic acid.....0.2 gm (20% w/w).
Inactive Ingredients: cetearyl octanoate, glycerin, glyceryl stearate and cetearyl alcohol and cetyl palmitate and cocoglycerides, PEG-5 glyceryl stearate, propylene glycol and purified water. Benzoic acid is present as a preservative.

CLINICAL PHARMACOLOGY:

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.

Pharmacokinetics: 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.

INDICATIONS AND USAGE:

AZELEX™ is indicated for the topical treatment of mild-to-moderate inflammatory acne vulgaris.

CONTRAINDICATIONS:

AZELEX™ is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS:

AZELEX™ is for dermatologic use only and not for ophthalmic use.

There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexions, these patients should be monitored for early signs of hypopigmentation.

PRECAUTIONS:

General: If sensitivity or severe irritation develop with the use of AZELEX™, treatment should be discontinued and appropriate therapy instituted.

Information for patients: Patients should be told:

1. To use AZELEX™ for the full prescribed treatment period.
2. To avoid the use of occlusive dressings or wrappings.
3. To keep AZELEX™ away from the mouth, eyes and other mucous membranes. If it does come in contact with the eyes, they should wash their eyes with large amounts of water and consult a physician if eye irritation persists.
4. If they have dark complexions, to report abnormal changes in skin color to their physician.
5. Due in part to the low pH of azelaic acid, temporary skin irritation (pruritus, burning, or stinging) may occur when AZELEX™ is applied to broken or inflamed skin, usually at the start of treatment. However, this irritation commonly subsides if treatment is continued. If it continues, AZELEX™ should be applied only once-a-day, or the treatment should be stopped until these effects have subsided. If troublesome irritation persists, use should be discontinued, and patients should consult their physician. (See ADVERSE REACTIONS.)

Carcinogenesis, mutagenesis, impairment of fertility: 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, animal studies to evaluate carcinogenic potential with AZELEX™ Cream were not deemed necessary. 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. Animal studies have shown no adverse effects on fertility.

Pregnancy: Teratogenic Effects: Pregnancy Category B.

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.

Nursing Mothers:

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.

Pediatric Use:

Safety and effectiveness in pediatric patients under 12 years of age have not been established.

ADVERSE REACTIONS:

During U.S. clinical trials with AZELEX™, adverse reactions were generally mild and transient in nature. The most common adverse reactions occurring in approximately 1-5% of patients were pruritus, burning, stinging and tingling. Other adverse reactions such as erythema, dryness, rash, peeling, irritation, dermatitis, and contact dermatitis were reported in less than 1% of subjects. There is the potential for experiencing allergic reactions with use of AZELEX™.

In patients using azelaic acid formulations, the following additional adverse experiences have been reported rarely: worsening of asthma, vitiligo depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris), and exacerbation of recurrent herpes labialis.

DOSAGE AND ADMINISTRATION:

After the skin is thoroughly washed and patted dry, a thin film of AZELEX™ should be gently but thoroughly massaged into the affected areas twice daily, in the morning and evening. The hands should be washed following application. The duration of use of AZELEX™ can vary from person to person and depends on the severity of the acne. Improvement of the condition occurs in the majority of patients with inflammatory lesions within four weeks.

HOW SUPPLIED:

AZELEX™ is supplied in collapsible tubes in a 30 gm size:
30 g - NDC 0023-8694-30

Note: Protect from freezing. Store between 15° - 30° C (59° - 86° F).

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

Distributed under license; U.S. Patent No. 4,386,104.

September 1995

ALLERGAN Herbert
Skin Care Division of ALLERGAN, INC.
Irvine, California 92715, U.S.A.

©1995 Allergan, Inc.
Printed in U.S.A.
(PM#)(copy code)

MEMORANDUM OF A TELEPHONE CONVERSATION

March 23, 1994

Between: Stephen Buxbaum
Director Regulatory Affairs
(714)-752-4500

And: Nahid Mokhtari-Rejali, Ph.D.
HFD-540

Subject: Filing NDA

I called Stephen Buxbaum to request the following information for the purpose of filing the application:

- 1) The Statement regarding when for pre-approval inspection. ready
- 2) English translation of batch record.
- 3) An extra copy of Method Validation Package

Mr. Buxbaum stated that facilities could be inspected any time after June 1, 1994. He promised to provide me the English translation of the batch record and an extra copy of MVP.

MEMORANDUM OF A TELEPHONE CONVERSATION

June 8, 1994

Between: Stephen Eastham
CIN-DO Inspector
(513)-684-3501 xt. 140

And: Nahid Mokhtari-Rejali, Ph.D.
HFD-540

Subject: Pre-approval Inspection at

On June 8, 1994, Stephen Eastham called me on the first day of his inspection to discuss status in regard to the purity of the azelaic acid. He stated that is a manufacturer of crude azelaic acid for polymer industry and only 0.1% is used by the applicant. He added that does not perform any specification or testing for azelaic acid.

I told Mr. Eastham that further purification and processing is going to be performed at . And I'm reviewing the related DMF right now. He noted that does not have any DMF in hand; however, they are in the process of preparing a DMF to file azelaic acid. I stated that I'm aware of this problem; and it has been communicated to the applicant.

Finally, he added that he will sent me a copy of the EIR when is completed.

MEMORANDUM OF A TELEPHONE CONVERSATION

October 11, 1994

Between: Henry Drew
Chief, Drug Monitoring Branch
(314)-539-2168 xt. 109

And: Nahid Mokhtari-Rejali, Ph.D.
HFD-540

Subject: Method Validation

I called Mr. Henry Drew to inform him of our concern regarding the E-Mail I received from him on September 29, 1994. I recommended the following:

Drug substance method:

1. The first assay for the drug substance is titration and the second is an HPLC assay on page 5 65. This is the same assay method submitted in the DMF and NDA for drug substance and drug product.
2. No validation is required for clarity of solution, color of solution, heavy metals, and sulfated ash methods. These are the USP methods.

Drug products method:

1. No microbial contamination test and microbial challenge test is required (per Dr. King, the microbiologist).
2. The special equipment for micro-penetration test may be accomplished through a contractor laboratories since you don't have access to this equipment.

error

Medical Officer's Review of NDA 20-~~482~~⁴²⁸
Original

⁴²⁸
NDA 20-~~482~~
M.O. Review #1

Submission Date: 3/ 1/94
Review Date: 11/15/94

Drug Name:

Generic Name: Azelaic acid
Proposed Trade Name: AZELEX™ 20% Cream
Chemical Name: 1,7-heptanedicarboxylic acid

Sponsor:

Allergan Herbert Division of Allergan Inc
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92713-9534

Pharmacologic Category:

Topical anti-acne (antimicrobial)

Proposed Indication:

Acne Vulgaris

**Dosage Form
and Route of Administration:**

Topical cream

NDA Drug Classification:

1 S

Related Drugs:

None

Related IND/NDA:

IND

Materials Reviewed:

Volumes 1, 2, 40-72, and 95

**Chemistry and
Manufacturing Controls:**

See Chemistry Review

**Animal Pharmacology
and Toxicology**

See Pharm/Tox Review

6. Clinical Background

6.1 Relevant Human Experience

The product proposed in this NDA is azelaic acid 20% topical cream for the treatment of acne vulgaris. Azelaic acid is a naturally occurring medium-chain dicarboxylic acid found in wheat, rye, and barley. Azelaic acid is endogenously formed, and detected as a normal constituent of human urine. Azelaic acid 20% cream has been marketed in Europe by _____ under the tradename Skinoren since 1989 as a treatment for acne vulgaris. In these countries, the product has demonstrated an excellent safety profile and has established itself as an effective therapy.

The basic cause of acne is unknown, however, four major etiological factors have been associated with the disease: growth of microbial flora, hyperkeratinization of the pilosebaceous duct, the induction of inflammation, and increased sebum production.

Antimicrobial effects of azelaic acid (Primary mechanism of action)

Azelaic acid is a naturally occurring, 9-carbon, straight-chain dicarboxylic acid that has microbistatic/microbiocidal properties especially against the cutaneous bacteria implicated as causative agents of inflammatory acne vulgaris. The numbers of the bacterium *Propionibacterium acnes* are known to be elevated in acne vulgaris and successful antibacterial treatment of acne causes a decline in *P. acnes* populations.

Overall, the non-clinical pharmacology studies show that azelaic acid 20% cream is an effective antimicrobial agent, and that it also has a beneficial effect upon the process of keratinization within the follicle and potential anti-inflammatory effects. These pharmacological actions are believed to account in large measure for the drug's clinical activity in acne. In addition, non-clinical pharmacology studies examining the effects of azelaic acid on metabolism, smooth muscle and renal function, as well as effects on cardiovascular and neurotropic activity, have revealed no significant untoward actions. These studies, together with the toxicologic and pharmacokinetic evaluation of the drug, point to no effects which would preclude the use of azelaic acid in humans for the treatment of acne vulgaris using the proposed 20% topical product.

In vivo studies demonstrated that topical application of azelaic acid 20% cream to acne-affected skin for 2-3 months resulted in pronounced reductions in the densities of superficial cutaneous microflora, as well as intrafollicular *Propionibacteria* species (greater than or equal to 99.9% reduction for micrococaceae and 97.7% for *P. acnes*). Additionally, after a single topical application of azelaic acid 20% cream, the follicular concentration of azelaic acid was found to be comparable with the concentration required to inhibit the growth of *P. acnes* and *S. epidermidis in vitro*.

It appears, therefore, that the efficacy of topical azelaic acid in the treatment of acne is due, in large part, to the reduction of the acne lesion microbial flora.

Effects on follicular hyperkeratinization (Secondary mechanism of action)

The initial follicular change in acne is a progressive accumulation of keratinous material in the infundibular region of the follicle (the microcomedo). In the normal sebaceous follicle, the keratinous build-up does not occur, and cellular turnover in the wall of the comedo is less rapid.

Azelaic acid can reduce the thickness of the horny layer of the infundibular epidermis. The number and size of keratohyalin granules are also reduced, and there is a marked decrease in filaggrin. These effects of azelaic acid on keratinocytes are suggested to play a beneficial role in the treatment of acne by normalizing the disordered keratinization in the acroinfundibulum.

Support for this hypothesis is shown in a rabbit ear model of comedone formation. Azelaic acid was shown to produce a dose-dependent inhibition of tetradecane-induced comedone formation. Topical application of azelaic acid 20% cream reduced the median comedonal area while 10% azelaic acid had no apparent effect.

Anti-inflammatory effects (Secondary mechanism of action)

The development of inflammatory lesions in acne seems to result from the release of biologically active mediators from resident bacteria or from the generation (due to the activities of bacteria) of extracellular inflammatory substances, such as free fatty acids from triglycerides in sebum.

Although direct anti-inflammatory activity has not been demonstrated for azelaic acid in the treatment of acne, azelaic acid has been shown to inhibit the generation and action of reactive oxygen species *in vitro*, and to decrease superoxide anion and hydroxy radical generation by neutrophils.

Effects on the sebaceous gland (No effect demonstrated)

Although it has been shown that individuals with acne have increased sebaceous gland activity, it is considered unlikely that azelaic acid exerts its clinical actions through direct effects on sebaceous gland activity. In an *in vivo* animal model, no effect on hamster flank weight was observed after topical application of azelaic acid. In addition, there were no effects on ear tissue lipid profiles, serum total cholesterol, HDL cholesterol, triglycerides or free fatty acids. Although azelaic acid 20% cream inhibits bacterial lipase activity in humans, it does not appear to inhibit sebum production, or alter sebum composition or sebaceous gland morphology when applied for up to 6 months.

Sponsor's Summary:

"Based on human clinical data, as well as animal toxicology data, azelaic acid 20% cream has an excellent safety profile. Azelaic acid is a naturally occurring compound commonly found in the diet. It is also endogenously formed in humans, and is detected as a normal constituent of human urine. Pharmacokinetic studies in humans demonstrate a low systemic burden after topical application of azelaic acid 20% cream. The systemic absorption of the 20% concentration of azelaic acid cream after topical dosing was estimated to be approximately 4%, which is similar to that of other topical agents. Additionally, minimal cutaneous metabolism of azelaic acid occurs after topical applications. The estimated daily systemic load from percutaneous application of a 20% cream is well within the normal fluctuations of dietary exposure.

Signs and symptoms of local irritation are the most common adverse effects associated with the use of azelaic acid 20% cream. The majority of local adverse events were mild to moderate in severity and transient in nature. In comparison with other topical preparations, azelaic acid 20% cream was shown to have a comparable or superior tolerability profile. Benzoyl peroxide and tretinoin-treated subjects generally had a higher incidence of erythema and scaling. Furthermore, azelaic acid is pleasant to use and cosmetically acceptable, and subjects treated with azelaic acid did not report problems with bleaching or staining, as can occur with some topical acne medications.

The regimen of twice daily dosing is simple and easy for patients to follow. The application at equidistant time intervals is the dosing regimen generally used for the majority of topical medications in order to provide a sufficient drug concentration over a 24-hour period. Patients with acne vulgaris using azelaic acid 20% cream should experience clinical improvement in their condition within four weeks of beginning therapy.

Azelaic acid 20% cream represents a new class of therapy for the treatment of acne vulgaris and offers physicians a very safe and effective alternative therapy for this very common, chronic disease."

6.2 Related INDs and NDAs

Data on Azelaic acid (AGN 191861 20% Cream) was submitted under IND

6.3 Foreign Experience

Azelaic acid 20% Cream was first approved for marketing in Denmark on October 27, 1988 under the tradename Skinoren® (Schering AG/Berlin, BRD).

1. List of the countries where marketed:

<u>Country</u>	<u>Approval Date</u>	<u>Country</u>	<u>Approval Date</u>
Argentina	10/04/91	Honduras	11/01/91
Australia	??/05/93	Hong Kong	03/17/92
Austria	12/12/89	Indonesia	10/28/92
Belgium	02/21/89	Italy	12/20/88
Bolivia	01/12/93	Korea	09/05/90
Brazil	08/03/92	Nicaragua	01/16/92
Chile	07/13/92	Norway	02/17/92
Costa Rica	03/02/92	Pakistan	07/20/92
Curacao	09/09/92	Paraguay	08/08/91
Denmark	10/27/88	Peru	03/04/92
El Salvador	01/23/92	Philippines	06/18/91
Finland	02/27/91	Portugal	02/05/92
France	12/14/89	Singapore	10/12/92
Germany	08/30/90	South Africa	09/30/92
Greece	10/03/90	Sweden	03/20/92
Great Britain	12/12/89	Switzerland	08/13/90
		Thailand	02/26/92
		Turkey	05/10/92

2. List of countries where the drug has been withdrawn from marketing for any reason related to safety or effectiveness: None

6.4 Human Pharmacology, Pharmacokinetics, Pharmacodynamics

Humans are constantly exposed to azelaic acid from birth, the sources for systemic exposure being both endogenous and dietary. Dietary absorption of azelaic acid from one ounce of cereal is approximately 11 to 196 mg, and circulating levels of azelaic acid fluctuate according to dietary intake. Additional dietary sources include precursors of azelaic acid such as odd-number chain fatty acids. Endogenously, azelaic acid can also be formed from longer chain dicarboxylic acids, metabolism of oleic acid (18:1 ω -9) and ω -oxidation of C9 monocarboxylic acid.

Following a single application of azelaic acid 20% cream 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 (after 24 hours, approximately 10% of the dose is found in the epidermis and dermis). A single topical application of azelaic acid 20% cream in man led to follicular concentrations comparable to those required to inhibit growth of *P. acnes* and *S. epidermidis in vitro*. Additionally, minimal cutaneous metabolism of azelaic acid occurs after topical application. Following topical application of ^3H -azelaic acid to human skin samples, the major compound found in the skin is azelaic acid.

Percutaneous absorption of azelaic acid from a single application of 20% azelaic acid cream is estimated to be approximately 4%. Systemic absorption after topical application of 1 g of azelaic acid 20% cream to normal volunteers resulted in a mean C_{max} for azelaic acid of 2 and 2.5 times the baseline C_{max} after single and multiple doses, respectively (AZEL-153-8466/PK-1993-105). The relative magnitude between the C_{max} value post-dosing and the baseline concentration was similar to that observed in subjects on a regular diet (AZEL-150-8466/PK-1993-106). The urinary excretion of azelaic acid during the topical treatment and a regular diet was within the normal fluctuations observed in the literature for a standard North American diet. This indicates that the normal body burden of azelaic acid is not significantly altered by multiple applications of azelaic acid 20% cream. Additionally, treatment of facial acne for 12 weeks with azelaic acid 20% cream did not elevate azelaic acid plasma concentrations above baseline levels (AZEL-220-8466/ PK-1993-085).

Serum C_{max} and AUC of azelaic acid exhibited linear increases with single oral doses up to 3.5 g (AZEL-952-SCAG/5299). Once in the systemic circulation, azelaic acid distributes primarily to the extracellular water, is not extensively protein bound and is rapidly eliminated virtually unchanged in the urine, with a half-life of approximately 45 minutes. Renal clearance ranged from mL/min to approximately mL/min after intravenous (Bertuzzi et al. 1991) and oral administration (AZEL-952-SCAG/5299), respectively, indicating active tubular secretion. While there is evidence of β -oxidation of azelaic acid (AZEL-952-SCAG/5299) to shorter-chain dicarboxylic acids (e.g., pimelic acid), azelaic acid is primarily excreted unchanged in the urine. Mean urinary excretion of azelaic acid ranges from mg per day (from dietary and endogenous sources).

The results of the pharmacokinetic studies together with the fact that azelaic acid is a naturally occurring compound in the diet indicate that there is a large safety margin with azelaic acid 20% cream, and that systemic exposure due to topical treatment with azelaic acid 20% cream is well within the normal fluctuations of dietary exposure.

In AZEL-153-8466/PK-1993-105, systemic absorption of azelaic acid 20% cream after single dose (1 g of cream) and multiple dose (1 g of cream twice a day for 7 days) topical application in 12 healthy adult volunteers who were on a regular diet was assessed by comparing baseline plasma concentrations. The dose contained in each topical application was approximately mg azelaic acid/kg. Concentrations of azelaic acid and pimelic acid were measured by GC-MS. The baseline concentrations observed in this study were slightly higher than previously reported (AZEL-150-8466/PK-1993-106), reflecting normal fluctuations in plasma azelaic acid concentrations from a regular diet. The baseline and C_{max} values after a single dose and multiple doses were 52 ± 16 ng/mL, 112 ± 29 ng/mL, and 136 ± 29 ng/mL, respectively. The plasma AUC values after correction for the endogenous baseline were 613 and 686 ng•hr/ml after a single topical dose and during one dosing interval at steady state, respectively. The observed plasma $T_{1/2}$ of azelaic acid after a single topical dose was approximately 12 hours, a value much longer than that after oral dosing, indicating absorption-limited elimination. Elimination following multiple dosing appeared to be slower, but was not calculated due to the variability of the data. The urinary excretion of azelaic acid was 8.1 ± 2.7 mg after a single dose and 7.5 ± 3.4 mg during a dosing interval at steady state. Steady state was achieved within four days. Based upon values of the renal clearance mL/min to mL/min) and the unbound fraction in the plasma (57%), the involvement of active tubular secretion in renal excretion of azelaic acid was indicated.

Study results demonstrated systemic absorption of azelaic acid from topically applied 20% cream and a regular diet. The relative magnitude between the C_{max} value post-dosing and the baseline concentration in this study was similar to that observed in subjects who were on a regular diet only (AZEL-150-8466/PK-1993-106). The urinary excretion of azelaic acid during the topical treatment and a regular diet was within the normal fluctuations observed in the literature for a standard North American diet. Therefore, the normal body burden of azelaic acid was not significantly altered by multiple applications of a 20% azelaic acid cream to the skin.

In AZEL-220-8466/PK-1993-085, the systemic absorption of azelaic acid 20% cream was assessed after multiple topical applications (~ 1.25 mg azelaic acid/kg BID for up to 12 weeks) in 56 subjects with mild to moderate facial acne. The trough plasma concentrations of azelaic acid (measured by GC-MS) at baseline and at the end of treatment were ng/mL and ng/mL, respectively, indicating that treatment with azelaic acid 20% cream for facial acne does not significantly elevate plasma concentrations of azelaic acid above baseline levels. Therefore, the systemic exposure from topical treatment of azelaic acid in man does not alter the endogenous levels.

Oral Absorption Pharmacokinetic Studies

In AZEL-951-SCAG/6138, 6 young healthy male subjects were given 1 g of azelaic acid as an aqueous microcrystalline suspension of 100 mL. Urinary excretion of unchanged azelaic acid, measured by UV-HPLC, was complete within 24 hours and accounted for approximately 61% of the drug.

In AZEL-952-SCAG/5299, the oral absorption and metabolism of azelaic acid were assessed by HPLC-MS in an ascending single dose study with 0.5 to 5 g of azelaic acid in 5 healthy male and female volunteers. The serum C_{max} and AUC of azelaic acid exhibited linear increases with doses up to 3.5 g. The disproportionate increase in C_{max} and AUC at doses higher than 3.5 g indicated capacity-limited drug disposition. These saturation kinetics, however, are not anticipated at the low plasma concentrations achieved after topical dosing. The terminal $T_{1/2}$ was approximately 0.75 hr and remained constant for all oral doses. Renal clearance was about 10 mL/min, indicating tubular secretion. In addition, there was evidence of systemic β -oxidation of azelaic acid to dicarboxylic acid metabolites with 2 to 4 carbon atoms fewer (pimelic or glutaric acid). Since the percentage of the dose eliminated unaltered via the urine after oral and intravenous dosing was about 60% and 77%, respectively, azelaic acid was nearly completely absorbed after oral administration.

Intravenous Pharmacokinetic Studies

In Mingrone et al. (1989), the possible clinical use of azelaic acid in parenteral nutrition was explored. Six healthy subjects received an intravenous dose of azelaic acid, 10 g over 80 min. The respiratory quotient and the ATP/CO₂ ratio of azelaic acid were similar to palmitic acid. Plasma concentrations of azelaic acid were above 100 μ g/mL at the end of infusion and declined slowly over 120 minutes. Over 50% of the intravenous dose was excreted unchanged in the urine with additional urinary loss of 2 g in the form of pimelic acid.

In Tacchillo et al. (1990), a study to evaluate whether medium-chain dicarboxylic acid could be used as a source of calories was conducted. The metabolic response to intravenous administration of azelaic acid (10 g) and Intralipid (10 g) was compared in six healthy subjects. There was no significant difference between azelaic acid and Intralipid treatments in all respiratory and metabolic measurements. After an eighty-minute infusion period, the plasma concentration of azelaic acid was 100 μ g/mL and rapidly declined to 10 μ g/mL in four hours. Approximately 50 g of azelaic acid was excreted intact in the urine. Study results demonstrate rapid systemic elimination and significant renal excretion of azelaic acid in man.

Azelaic acid was the first dicarboxylic acid proposed as an alternative energy substrate in total parenteral nutrition. In Bertuzzi et al. (1991), the disposition of azelaic acid was investigated in 12 healthy volunteers; 7 subjects received a constant intravenous infusion

g over min) and 5 others received a 1 g bolus injection. Plasma and urine concentrations were assayed by gas liquid chromatography. For the intravenous infusion, the C_{max} was $\mu\text{g/mL}$. Total clearance from the intravenous infusion data was estimated to be mL/min, with 77% of the dose excreted unchanged in the urine. The mean renal clearance was mL/min, indicating the presence of active tubular secretion. The mean volume of distribution for the central and peripheral compartments was 3.74 L and 5.93 L, respectively, as analyzed by a two compartment model. The sum of the central and peripheral compartment volumes was less than the volume of distribution for inulin, suggesting that azelaic acid mainly circulated in the extracellular water space. The fast drug elimination, large renal clearance and limited volume of distribution suggested that azelaic acid was not effectively utilized by the tissue and may not be suitable for total parenteral nutrition.

In Passi et al. (1989), in order to maintain effective serum-tissue concentrations in disseminated malignant disease states, intravenous or intra-arterial infusions of azelaic acid were tested in subjects. One hour intravenous infusions of 5 or 10 grams of azelaic acid were administered to 5 male human volunteers which resulted in peak plasma concentrations of about $\mu\text{g/mL}$, respectively. By 7 hours post-infusion, plasma concentrations returned to pre-dose levels. Plasma concentrations after intra-arterial administration paralleled those obtained by intravenous infusion. Urinary excretion of azelaic acid after intravenous or intra-arterial administration was 81% of the dose. Further, after longer infusions (20 g over 4 hours) plasma azelaic acid concentrations rose disproportionately indicating nonlinear elimination. However, plasma azelaic acid concentrations ($\mu\text{g/mL}$) at which capacity limited kinetics occurred were many fold higher than the anticipated plasma concentration after clinical topical dosing (ng/mL range) with 20% azelaic acid cream.

6.6 Directions For Use

After the skin is thoroughly washed and patted dry, a sufficient quantity of AZELEX™ Cream should be gently but thoroughly massaged into the affected areas twice daily, in the morning and evening. The hands should be washed following application. The duration of use of AZELEX™ can vary from person to person and depends on the severity of the acne. In general, an improvement of the condition becomes apparent within 4 weeks. To obtain the best results, however, AZELEX™ should be used regularly over several months or until the condition resolves.

7. Description of Clinical Data Source:

The data that serve as the basis for this review were obtained entirely from the Sponsor's development program.

Clinical Studies in Acne

Study Number	Investigator (Location)/ Start Date	Study Design/ Objectives	Treatment/ Dosing/ Duration	Number of Subjects Entered	Number of Subjects Completed	Age Range (Mean)	Sex (% M/F)	Race (% C/B/O)	Location of Study Docs/Full Report/Statistical Report/CRFs
U.S. Vehicle-Controlled Trials									
220	Elson (USA)	Double-blind, randomized, parallel-group	Azelaic acid 20% cream (8466X)	300 (AZA = 151, VEH = 149)	247 (AZA = 124, VEH = 123)	12-70 (19.5)	49/51	87/8/5	Volume 1.46, Page 21
	Jones (USA)	parallel-group	Azelaic acid 20% cream (8465X)						
	Jonizzo (USA)	To evaluate the safety and efficacy of azelaic acid 20% cream in comparison with vehicle cream	BID x 12 weeks						
	Lucky (USA)								
	My (USA)								
	Shumnes (USA)								
	Jan. 28, 1992 (Complete)								
Non-U.S. Vehicle-Controlled Trials (Single Center)									
221	Berger (USA)	Double-blind, randomized, parallel-group	Azelaic acid 20% cream (8466X)	299 (AZA = 150, VEH = 149)	246 (AZA = 127, VEH = 119)	12-47 (18.8)	55/45	93/3/4	Volume 1.51, Page 62
	Kligman (USA)	To evaluate the safety and efficacy of azelaic acid 20% cream in comparison with vehicle cream	BID x 12 weeks						
	Merchant (USA)								
	Swinyer (USA)								
	Williams (USA)								
	Whiting (USA)								
	Jan. 16, 1992 (Complete)								
Non-U.S. Vehicle-Controlled Trials (Multicenter)									
910	Cunliffe (United Kingdom)	Double-blind, randomized, matched pairs	Azelaic acid 20% cream (SHC 441F)	80	66	12-41 (18.4)	22/78	Volume 1.54, Page 202	
	October 1985 (Complete)	To demonstrate the efficacy of azelaic acid cream vs. vehicle in the treatment of acne vulgaris	BID x 3 months						
Non-U.S. Vehicle-Controlled Trials (Multicenter)									
911	Caputo, Giannetti, Giannotti, Stratigos (Italy, Greece)	Double-blind, randomized, parallel-group	Azelaic acid 20% cream (SHC 441F)	101	80	13-34 (20.2)	29/71	Volume 1.55, Page 1	
	October 1985 (Complete)	To demonstrate the efficacy of azelaic acid cream vs. vehicle in the treatment of acne	BID x 3 months						

Study Number	Investigator (Location)/ Start Date	Study Design/ Objectives	Treatment/ Dosing/ Dosage Duration	Number of Subjects Entered	Completed	Age Range (Mean)	Sex (% M/F)	Location of Study Documents Full Report/Statistical Report/Case Report Forms
Non-U.S. Active-Controlled Trials—Topical Comparison								
920	7234 Multicenter (Germany, Belgium, Austria, Switzerland, Italy, Denmark, Greece) October 1983 (Complete)	Single-blind, randomized, parallel group To demonstrate the efficacy of azelaic acid cream vs. tretinoin in the treatment of acne	Azelaic acid 20% cream (SHC 441DA) Tretinoin 0.05% cream (AiroI, Roche) QD x 2 weeks, then BID up to 6 months	337	204	11-47 (18.8)	47/53	Volume 1.55, Page 139
921	7232 Multicenter (France, Germany, Italy, Denmark, UK, Belgium, Austria, Switzerland, Greece) October 1983 (Complete)	Single-blind, random- ized, parallel-group To demonstrate the efficacy of azelaic acid cream vs. benzoyl per-oxide in the treatment of acne	Azelaic acid 20% cream (SHC 441DA) Benzoyl peroxide 5% gel (Pan OxyI 5, Stiefel Laboratories) QD x 2 weeks, then BID up to 6 months	341	159	13-48 (19.4)	72/28	Volume 1.56, Page 1
925	8943 Multicenter (Portugal, Germany, Switzerland, Denmark, Holland, Greece) November 1988 (Complete)	Double-blind, random- ized, parallel group To demonstrate the efficacy of azelaic acid cream vs. erythromycin in the treatment of acne	Azelaic acid 20% cream (SHC 441F) Erythromycin 2% ointment, (Akne Mycin 2000 [®] , Hermal) BID x 5 months	314	236	12-43 (21.2)	41/59	Volume 1.56, Page 136

Study Number	Investigator (Location)/ Start Date (Study Status)	Study Design/ Objectives	Treatment/ Dosing/ Dosage Duration	Entered	Number of Subjects Completed	Age Range (Mean)	Sex (% M/F)	Location of Study Documents Full Report/Statistical Report/Case Report Forms
907	6499 Cunliffe (UK) Sept. 1983 (Complete)	Double-blind, rando-mized, parallel group, active control	Azelaic acid 20% cream (SHC 441DA)	40	40	18-22 (18.8)	100/0	Volume 1.56, Page 248
		To compare the efficacy and safety of azelaic acid 20% cream with benzoyl peroxide 5% in the treatment of acne	Benzoyl peroxide 5% (Pannogel-5, Pannoc Chemie)					
			BID x 6 months					

909	6499 Cunliffe (UK) Sept. 1983 (Complete)	Double-blind, rando-mized, parallel group	Azelaic acid 20% cream (SHC 441DA)	42	42	15-23 (17.9)	100/0	Volume 1.57, Page 1
		To compare the safety and effectiveness of azelaic acid 20% cream vs tretinoin 0.05% cream in the treatment of acne	Tretinoin 0.05% cream (Atrul, Roche)					
			BID x 6 months					

Non-U.S. Active-Controlled Trials—Oral Comparison

923	7233 Multicenter (Germany, Italy, UK, Belgium, Switzerland, Denmark, Hungary, Austria) October 1983 (Complete)	Double-blind, rando-mized, parallel-group, double-dummy	Azelaic acid 20% cream (SHC 441DA) Vehicle cream (SHC 441DA vehicle) QD x 2 weeks, then BID Duration: up to 6 months	287	219	13-50 (21)	74/26	Volume 1.57, Page 114
		To demonstrate the efficacy of topical azelaic acid cream vs. oral tetracycline in the treatment of acne	Tetracycline capsules, 250 mg (Hoechst, Hoesstacycline) Placebo capsules 250 mg po QID month 1, TID month 2, BID month 3, then titrated Duration: up to 6 months					

Study Number	Investigator (Location)/ Start Date (Study Status)	Study Design/ Objectives	Treatment/ Dosing/ Dosage Duration	Entered	Number of Subjects Completed	Age Range (Mean)	Sex (% M/F)	Location of Study Documents Full Report/Statistical Report/Case Report Forms
924	7333 Multicenter (UK, Norway, Belgium, Switzerland, Germany, Denmark, Hungary) October 1985 (Complete)	Double-blind, randomized, parallel group, double-dummy To demonstrate the efficacy of topical azelaic acid cream vs. oral tetracycline in the treatment of acne	Azelaic acid 20% cream (SHC 441F) Vehicle cream (SHC 441F vehicle) Tetracycline HCl capsules, 250 mg (Hoechst) Placebo capsules	374	261	12-38	54/46	Volume 1.58, Page 1
908	6499 Cunliffe (UK) Sept. 1983 (Complete)	Double-blind, randomized, parallel group, double dummy, active control To compare the efficacy and safety of topical azelaic acid 20% cream with oral tetracycline in the treatment of acne	Azelaic acid 20% cream (SHC 441DA) Vehicle cream (SHC 441DA vehicle) Tetracycline HCl 250 mg (Hoechst, Hosiacycline) Placebo capsules	45	39	13-29 (18.2)	100/0	Volume 1.58, Page 150

U.S. Special Safety Studies

Investigator (Location)/ Study Number: SCAG (Study Status)	Study Design/ Objectives	Treatment/ Dosing/ Dosage Duration	Number of Subjects Completed	Age Range (Mean)	Sex (% M/F)	Race (% C/B/O)	Location of Study Docs/Full Report/Statistical Report/CRFs
--	--------------------------	------------------------------------	------------------------------	------------------	-------------	----------------	--

U.S. Irritation/Contact Sensitivity Trials

101	Not Applicable (USA) (Complete)	Shanahan (USA) Oct. 27, 1992	Investigator-masked, randomized-block	To determine the dermal irritation potential of azelaic acid 20% cream	Azelaic acid 20% cream, (8466X) Azelaic acid vehicle cream (8465X) AGN 190168 0.1% gel (7997X, 8606X) ALN 190168 0.05% gel (8225X, 8607X) AGN 190168 vehicle gel (8006X, 8608X) Retin-A™ 0.05% (8174X) and 0.1% (8175X) creams Benzac 5 gel (8556X) Sodium lauryl sulfate (0.5% in water) (7967X) QD x 21 days	30	29	20-64 (41.5)	17/83	100/0/0	Volume 1.62, Page 2
102	Not Applicable (USA) (Complete)	Shanahan (USA) Nov. 2, 1992	Investigator-masked, rando-mized-block	To determine the contact sensitization potential of azelaic acid 20% cream	Azelaic acid 20% cream (8466X) Azelaic acid vehicle cream (8465X) AGN 190168 0.1% gel (7997X, 8606X) AGN 190168 0.05% gel (8225X, 8607X) AGN 190168 vehicle gel (8006X, 8608X) Retin-A 0.1% cream (8175X) Three times per week for three weeks (nine induction applications), then once after a two week "rest" period (challenge application)	203	181	18-66 (41.7)	17/83	98/1/1	Volume 1.63, Page 1

Study Number	Investigator (Location)/ Start Date (Study Status)	Study Design/ Objectives	Treatment/ Dosing/ Dosage Duration	Entered	Number of Subjects Completed	Age Range (Mean)	Sex (% M/F)	Race (% C/B/O)	Location of Study Docs/Full Report/Statistical Report/CRFs
--------------	--	--------------------------	------------------------------------	---------	------------------------------	------------------	-------------	----------------	--

U.S. Phototoxicity/Photoallergy Trials

103	Not Applicable (USA) Nov. 23, 1992 (Complete)	Investigator-masked, randomized-block To determine the phototoxicity potential of azelaic acid 20% cream	Azelaic acid 20% cream (8466X) Azelaic acid vehicle cream (8465X) AGN 190168 0.1% gel (8606X) AGN 190168 0.05% gel (8607X) AGN 190168 vehicle gel (8608X) Retin-A 0.1% cream (8175X) Single application	10	10	22-48 (33.8)	6/100	100/0/0	Volume 1.60, Page 138
-----	---	---	---	----	----	--------------	-------	---------	-----------------------

104	Not Applicable (USA) Oct. 26, 1992 (Complete)	Investigator-masked, randomized-block To determine the photoallergic potential of azelaic acid 20% cream	Azelaic acid 20% cream (8466X) Azelaic acid vehicle cream (8465X) AGN 190168 0.1% gel (8606X) AGN 190168 0.05% gel (8607X) AGN 190168 vehicle gel (8608X) Retin-A 0.1% cream (8175X) Three times per week for three weeks (nine induction applications), then once after a two week "rest" period (challenge application)	28	22	18-64 (42.0)	18/87	100/0/0	Volume 1.61, Page 1
-----	---	---	---	----	----	--------------	-------	---------	---------------------

Non-U.S. Uncontrolled Clinical Studies in Acne

Study Number	Investigator (Location)/ Start Date (Study Status)	Study Design/ Objectives	Treatment/ Dosing/ Dosage Duration	Emerged	Number of Subjects Completed	Age Range (Mean)	Sex (% M/F)	Location of Study Documents Full Report/Statistical Report/Case Report Forms
--------------	--	--------------------------	------------------------------------	---------	------------------------------	------------------	-------------	--

AZEL SCAG (Study Status)

Non-U.S. Uncontrolled Trials

922	7231 Multicenter (France, UK, Belgium, Germany, Switzerland) October 1983 (Complete)	Open, randomized, parallel-group To demonstrate the efficacy of azelaic acid vs. isotretinoin in the treatment of acne	Azelaic acid 20% cream (SHC 441DA) QD x 2 weeks then BID up to 6 months <i>Isotretinoin 20 mg capsules</i> (Roche, Roaccutane) 0.5-1.0 mg/kg/day up to 6 months	102	57	15-60 (22.6)	89/11	Volume 1.59, Page 9
906	8587/ 7564 Ehlers, Gemy (Germany, Switzerland) January 1987 (Complete)	Open-label, multicenter, uncontrolled To investigate the long term (5 months) systemic tolerance of azelaic acid 20% cream	Azelaic acid 20% cream (SHC 441F) BID x up to 5 months	52	41	14-44	43/57	Volume 1.59, Page 158
933	4925 Nazzaro-Porto (Italy) 1977 (Complete)	Open-label, pilot study To examine the therapeutic effect of azelaic acid in the treatment of acne	Azelaic acid 15% cream (SHC 441A) BID x up to 9 months	82	Not Available	14-38	44/56	Volume 1.59, Page 259
934	5845 Multicenter (Germany, Belgium, Italy, UK, Austria, Switzerland) March 1982 (Complete)	Open-label, uncontrolled, multicenter study To compare efficacy of azelaic acid cream with standard therapy (unspecified) in subjects with severe acne	Azelaic acid 15% cream (SHC 441A) QD x 2 weeks then BID up to 6 months	120	99	13-53 (20.0)	100/0	Volume 1.60, Page 1

Clinical Pharmacology Studies

Study Number	Investigator (Location)/ Start Date	Study Design/ Objectives	Treatment/ Dosing/ Dosage Duration	Number of Subjects Entered	Completed	Age Range (Mean)	Sex (% M/F)	Race (% C/B/O)	Location of Study Docs/Full Report/Statistical Report/CRTs
AZEL SCAG	(Study Status)								

In Vitro Pharmacokinetic Studies

950	6083	Täuber (Germany) April 26, 1983 (Complete)	<i>In vitro</i> PK epicutaneous ¹⁴ C-Azelaic acid absorption 1 mg/cm ² human cadaver skin	Not Applicable	Volume 1 40, Page 160				
			To determine the penetration of ¹⁴ C-azelaic acid into human skin after topical application.						

PK-1992-071 ¹	Not Applicable	Franz, Lehman (U.S.) July 1992 (Complete)	<i>In vitro</i> metabolism, epidermal application	Not Applicable	Volume 1 40, Page 187				
			Technical report: determination of azelaic acid metabolism during its absorption through human skin.						

PK-1992-073 ¹	—	Franz, Lehman (U.S.) July 1992 (Complete)	<i>In vitro</i> metabolism, epidermal application	Not Applicable	Volume 1 40, Page 194				
			Technical report: determination of metabolism of ³ H-azelaic acid in rat, dog and human skin						

953 ¹	5999	Täuber (Germany) Feb. 15, 1984 (Complete)	<i>In vivo</i> PK plasma protein, human milk, and erythrocyte binding	Not Applicable	Volume 1 41, Page 389				
			To evaluate binding of radiolabeled azelaic acid to human plasma proteins, passage into maternal milk, and distribution in human erythrocytes						

Investigator (Location)/ Study Number	Start Date (Study Status)	Study Design/ Objectives	Treatment/ Dosing/ Dosage Duration	Number of Subjects Entered	Completed	Age Range (Mean)	Sex (% M/F)	Race (% C/B/O)	Location of Study Docs/Full Report/Statistical Report/CRFs
AZEL SCAG									

Pilot and Background Studies

150/PK- 1993-1061	Not Applicable	Keasal (U.S.) September 18, 1992 (Complete)	3 days normal diet vs. 18 hour subsequent fast 86 hours	20	20	19-39 (28)	100/0	95/0/5	Volume 1.40, Page 243
----------------------	-------------------	---	---	----	----	---------------	-------	--------	--------------------------

Literature Report	Not Applicable	Dias, et al. (Canada) Not Applicable (Not Applicable)	3 days high medium- chain triglyceride diet 3 days To examine the effect of low carbohydrate intake on levels of dicarboxylic acid and other plasma and urine organic acid levels	Not Applicable	8	8	25-35 (Not Available)	63/37	Not Available Page 212
----------------------	-------------------	--	--	----------------	---	---	-----------------------------	-------	------------------------------

Literature Report	Not Applicable	Parsons (Canada) Not Applicable (Not Applicable)	Baseline pediatric urinary excretion rates	Not Applicable	800	800	1 month to 18 yr (Not Available)	Not Available	Not Available Page 218
----------------------	-------------------	---	---	----------------	-----	-----	---	------------------	------------------------------

Literature Report	Not Applicable	Greut (Switzerland) Not Applicable (Not Applicable)	Urine chromatography To quantify the amount of azelaic acid excreted daily in human, rat, and canine urine	Not Applicable	10 (human)	10 (human)	25-63 (31.7)	70/30	Not Available Page 236
----------------------	-------------------	--	--	----------------	------------	------------	-----------------	-------	------------------------------

					5 (rat)	5 (rat)	Not Applicable	100/0	Not Applicable
--	--	--	--	--	---------	---------	-------------------	-------	-------------------

Study Number	Investigator (Location)/ Start Date (Study Status)	Study Design/ Objectives	Treatment/ Dosing/ Duration	Number of Subjects Entered	Number of Subjects Completed	Age Range (Mean)	Sex (% M/F)	Race (% C/B/O)	Location of Study Docs/Full Report/Statistical Report/RFs
AZEL	SCAG								
Literature Report	Not Applicable (United Kingdom)	<i>In vivo</i> pharmacokinetics	Azelaic acid 20% cream (Skimont, Schering AG)	9	9	19-29 (24.1)	56/44	Not Available	Volume 1.44, Page 253
	Not Applicable (Not Applicable)	To determine the concentration of azelaic acid(SHC 441F) in pilosebaceous follicles after topical application of azelaic acid 20% cream	5 hours						

Topical Absorption Pharmacokinetic Studies

951	6138	Mathes, Tauber (Germany) May 9, 1984 (Complete)	Open-label, 2-way crossover, single-dose topical and oral	Topical: 5 g Azelaic acid 20% cream	6	6	22-24 (23)	100/0	100/0/0	Volume 1.42, Page 5
			To determine the percutaneous absorption and urinary excretion of azelaic acid after topical and oral dosing	Oral suspension: 1 g in 100 mL						
153/PK-1993-105	Not Applicable (USA) Dec. 4, 1992 (Complete)	Keasal (Complete)	Open-label, single- and multiple-dose, topical	Azelaic acid 20% cream (8466X)	16	16	20-33 (22.1)	100/0	100/0/0	Volume 1.42, Page 33
			Measurement of plasma concentrations of azelaic acid following single-dose and multiple-dose applications	Single-dose: 1 g of cream to 500 cm ² , removed after 12 hours						
				Multiple-dose: 1 g of cream to 500 cm ² , 15 doses over 8 days						

Study Number	Investigator (Location)/ Start Date (Study Status)	Study Design/ Objectives	Treatment/ Dosing/ Dosage Duration	Number of Subjects Entered	Number of Subjects Completed	Age Range (Mean)	Sex (% M/F)	Race (% C/B/O)	Location of Study Docs/Full Report/Statistical Report/CRFs
220/PK-1993-085	Not Applicable (USA) Elson, Lucky (Complete) Jan. 28, 1992	Double-blind, randomized, parallel group	Azelaic acid 20% cream (8466X) Vehicle cream (8365X)	56	42	13-70 (21)	48/52	95/4/2	Volume 1.44, Page 240
		Determination of plasma levels of azelaic acid following twice daily application for the treatment of acne vulgaris	BID x 12 weeks						

Oral Absorption Pharmacokinetic Studies

951	6138 Mathies, Täuber (Germany) May 9, 1984 (Complete)	Open-label, 2 way crossover, single-dose topical and oral	Topical: 5 g Azelaic acid 20% cream Oral suspension: percutaneous absorption and 1 g in 100 mL urinary excretion of azelaic acid after topical and oral dosing	6	6	22-24 (23)	100/0	100/0/0	Volume 1.44, Page 261
952	5299 Passi, Nazzaro-Porro (Italy) Not Available (Complete)	Open-label, oral, ascending single-dose, 1 week washout between doses	0.5-5.0 g Azelaic acid Single dose	5	5	30-45 (Not Available)	60/40	Not Available	Volume 1.44, Page 265
		To determine pharmacokinetics and biotransformation following oral administration of azelaic acid to humans							

Investigator (Location)/ Study Number	Start Date (Study Status)	Study Design/ Objectives	Treatment/ Dosing/ Dosage Duration	Number of Subjects Entered	Number of Subjects Completed	Age Range (Mean)	Sex (% M/F)	Race (% C/B/O)	Location of Study Docs/Full Report/Statistical Report/CRFs
---	------------------------------	-----------------------------	--	----------------------------------	------------------------------------	------------------------	----------------	-------------------	---

Mechanism of Action Pharmacodynamic Studies

908	6499	Cunliffe (United Kingdom) September 1983 (Complete)	Double-blind, parallel group, randomized, double- dummy, active control	Azelaic acid 20% cream (SHC 441DA)	21 (azelaic acid)	15 (azelaic acid)	13-29 (18)	100/0	Not Available Page 9	Volume 1.45.
			Surface bacteria subset; determination of change in surface bacteria from baseline in subjects following treatment of acne with azelaic acid; to assist in defining the mechanism of action of azelaic acid	Vehicle cream (SHC 441DA vehicle)	19 (tetra- cycline)	19 (tetra- cycline)				
				Oral tetracycline 250 mg						
				Placebo capsules						
				BID x 6 months (cream)						
				TID x 6 months (capsules)						

909	6499	Cunliffe (United Kingdom) September 1983 (Complete)	Double-blind, parallel group, randomized, active control	Azelaic acid 20% cream (SHC 441DA)	11 (azelaic acid)	11 (azelaic acid)	15-23 (18)	100/0	Not Available Page 181	Volume 1.45.
			SER subset: determination of sebum excretion rate in subjects following treatment of acne with azelaic acid cream; to assist in defining the mechanism of action of azelaic acid	Tretinoin 0.05% cream	11 (tretinoin)	10 (tretinoin)				
				BID x 3 months						

Study Number	Investigator (Location)/ Start Date (Study Status)	Study Design/ Objectives	Treatment/ Dosing/ Dosage Duration	Number of Subjects Entered	Number of Subjects Completed	Age Range (Mean)	Sex (% M/F)	Race (% C/B/O)	Location of Study Docs/Full Report/Statistical Report/CRFs
954	Orfanos (Germany) September 1984 (Complete)	Double-blind, randomized paired comparison, vehicle control	Azelaic acid 20% cream (SHC 441DA)	47 (SER subset)	47	18-43 (Not Available)	Not Available	Not Available	Volume 1, 45, Page 124
AZEL	SCAG	SEB subset, sebaceous gland size and keratinization subsets. To elucidate the mechanism of action of azelaic acid in the treatment of acne vulgaris	Vehicle cream	25 (sebaceous gland size and keratinization subsets)	25				

7.1 Extent of Exposure

Based on a daily application rate of 1.5 g (twice 0.75 g), a treatment duration of 4 to 6 months, and the total Skinoren™ brand name for azelaic acid cream sales volume recorded for the period July 1989 to August 1993, an estimated 749,000 to over 1 million people were treated with Skinoren™ during this period.

7.2 Post-Marketing Experience

Spontaneous reports of adverse events provided to covers the reporting period from July 1989 to August 16, 1993.

<u>Event</u>	<u>Number</u>
Contact Dermatitis/Allergy	8
Burning sensation	2
Vitiloid depigmentation one-side on the chin	1
Small depigmented spots	1
Hypertrichosis	1
Reddening; signs of keratosis pilaris	1
Recurrent exacerbation of herpes labialis	1
Shock (tachycardia hypotension)	1
Extrasystoles (2-3/day, up to 15-20/day)	1
Headache	1
Asthma (re-exposure positive)	1

Reviewer's comment: *Spontaneous reports of post-marketing adverse events should be included in the labeling.*

8.0 Clinical Studies:

Clinical trials were conducted to provide evidence of azelaic acid's safety and effectiveness in the treatment of acne vulgaris in the United States by the Allergan Herbert Division of Allergan Inc and outside the United States by Schering AG. Each United States study is identified with an Allergan Herbert (AZEL) study number and an Allergan study drug formulation number (e.g., 8466)--e.g., AZEL-220-8466. Each clinical trial conducted by outside the United States is identified with an Allergan Herbert (AZEL) study number and a report number (e.g., AZEL-911-SCAG/7332).

Two multicenter, randomized, double-blinded, parallel-group comparison studies (Azel-220-8466 and Azel-221-8466) were conducted in the United States by the Allergan Herbert. These studies were designed to evaluate the safety and efficacy of azelaic acid 20% cream in comparison with the vehicle cream (control). The study designs were identical for the two studies except that blood samples were taken before and after treatment in a subset of subjects to measure the systemic absorption of azelaic acid. The test medications were applied twice daily (morning and evening) to the faces of patients with mild to moderate acne vulgaris for twelve weeks. Patients were evaluated at baseline and at weeks 4, 8, and 12.

Inclusion criteria:

The following were prerequisites for enrollment into the study:

1. Male or female patients, ages 12 years of age or older
2. Written informed consent; patients under the legal age of consent in the state where the study was conducted must have the written informed consent of a parent or guardian
3. Presence of mild to moderate facial acne vulgaris (refer to publication by Pochi, 1991)
4. A minimum of 10 but no more than 60 facial inflammatory lesions (papules plus pustules)
5. A minimum of 10 but no more than 200 facial noninflammatory lesions (open and closed comedones)
6. No more than six facial nodular cystic lesions (\geq 5mm in diameter)
7. Anticipated ability to complete the study and to comply with appropriate instructions
8. Negative urine pregnancy test results (in women of childbearing potential)
9. Anticipated normal blood and urine laboratory test results (Azel- 220-8466)

Exclusion criteria:

Any of the following conditions excluded subjects from participating in the study:

1. Known hypersensitivity to any of the components of the study medications
2. Concomitant systemic or topical therapy with antibiotics or other anti-acne medications (e.g., benzoyl peroxide or tretinoin)
3. Topical anti-acne therapy with antibiotics or other anti-acne medications (e.g., benzoyl peroxide or tretinoin) within the 14 days prior to study entry
4. Systemic therapy with antibiotics within the 4 weeks prior to study entry
5. Previous treatment with systemic retinoids (e.g., Accutane™, Roche Dermatologics)
6. Treatment with estrogens for 12 weeks or less immediately preceding study entry (patients treated with estrogens for more than 12 consecutive weeks immediately prior to study entry were not excluded unless the patient expected to discontinue estrogen use during the study)
7. Presence of acne vulgaris known to be resistant to oral antibiotics
8. Presence of any skin disease that interfered with the diagnosis or evaluation of acne vulgaris
9. Females who were pregnant, nursing, or planning a pregnancy during the study, or who thought they might be pregnant at the start of the study (throughout the course of the study, females of childbearing potential were required to use reliable forms of contraception, e.g., abstinence, oral contraceptives for more than 12 consecutive weeks, or spermicide and condoms)
10. Concurrent involvement in another drug research or participation in such a study within 30 days prior to study entry

Reviewer's Comment:

1. *The criteria established for entry and exclusion seem reasonable and in keeping with the scheme generally employed in acne clinical studies. However, a 6-month washout period for prior use of systemic retinoids would have been preferable to a total exclusion from the study.*
2. *A urine pregnancy test with a sensitivity of at least 50 mIU/mL would have been preferred.*

Efficacy Variables:

The two key efficacy variables were:

1. changes from baseline in lesion counts
2. treatment success rates derived from the investigators' global response rating.

Facial lesions (papules, pustules, nodules, open and closed comedones) were counted at the initial visit and after 4, 8, and 12 weeks of treatment.

At weeks 4, 8, and 12, investigators made a global evaluation of each patient's response to treatment according to the following six-point scale:

5 =	Completely cleared,	no sign or symptom of disease
4 =	Excellent response,	75% -99% improvement
3 =	Good response,	50 - 74% improvement
2 =	Fair response,	25 - 49% improvement
1 =	Poor response,	1 - 24% improvement
0 =	Condition unchanged or worsened	

Patients who had a good or excellent response to treatment or who were completely cleared of acne were judged to be a treatment success.

Reviewer's Comment:

The efficacy variables are acceptable. However, a patient response to treatment of excellent or completely cleared would have been preferred as a treatment success.

Safety Variables:

At two investigational sites (Drs. Elson [investigator # 1938] and Lucky [investigator # 1900]), blood samples were taken at the initial visit and week 12 for determination of plasma levels of azelaic acid.

Any adverse experiences occurring during the study were recorded by the investigator, graded for severity, and assessed for relationship to the study treatment.

Women of childbearing potential were given a urine pregnancy test at the initial visit and week 12, and the results were recorded on case report forms.

Twelve hour fasting blood and urine samples were taken for all subjects at the initial visit and week 12 and sent to _____ for analysis.

At each visit, the overall clinical severity grade was recorded as none, mild, moderate, or severe for the following signs or symptoms:

- 1) dryness
- 2) erythema
- 3) oiliness
- 4) peeling
- 5) burning
- 6) pruritus

At the week 12 visit, patients rated the cosmetic characteristics of their assigned study medication in the following terms:

- 1) overall impression
- 2) texture
- 3) ease of application
- 4) appearance
- 5) odor

Criteria for effectiveness

Overall clinical severity grade was not included in any power calculations. The sensitivity of the 4-point scale for the overall clinical severity grade (none, mild, moderate, or severe) proved to be inadequate to detect meaningful differences between treatment groups because all of the subjects entered the study with mild or moderate acne. Thus, the inflammatory lesion counts (the sum of papules, pustules, and nodules), non-inflammatory lesion counts (the sum of open and closed comedones), total lesion counts (the sum of inflammatory and non-inflammatory lesions), and treatment success rates were considered the key efficacy variables in this study.

Reviewer's Comment:

Hypopigmentation should have been listed on the sign and symptoms check-list of the case report forms since this is a possible known side effect of azelaic acid.

Evaluability of Patients and Data

Upon study exit, each patient was placed into one of four disposition categories based on the following definitions:

- Disqualified - not included in the analysis because of significant deviation from protocol specified procedures, and/or baseline laboratory values that were outside the reference ranges defined by the laboratory
- Terminated - exited early from the study because of lack of efficacy or adverse experiences, whether or not these were judged to be treatment-related
- Discontinued - exited early from the study for reasons other than disqualification or termination from the study (e.g. missed visits)
- Completed - completed the 12-week course of treatment as specified in the protocol

Terminated, discontinued, and completed patients with evaluable data from at least one follow-up visit were considered to be evaluable subjects and were included in the preferred analysis.

Disqualified patients were considered to be non-evaluable.

Patients could voluntarily withdraw from the study at any time they chose. Also, investigators could elect to remove patients from the study for reasons of medical prudence unrelated to the study treatment. Patients who could not complete the study for other reasons (e.g., failure to comply with the visit schedule) could also be removed from the study. In addition, any patient who had an unacceptable response to treatment that affected his or her welfare, was removed from the study and received appropriate therapy at the discretion of the investigator.

To be considered evaluable, data at each visit had to pass criteria associated with "time elapsed since baseline" and protocol adherence. The criteria for "time elapsed since baseline" put limits on the number of days elapsed between the baseline visit and a given follow-up visit. Visit numbers were indicated on the case report forms along with the visit date. If the visit date corresponding to a given visit number satisfied the bounds describe in the following table, the data from that visit were considered evaluable.

<u>Visit Number</u>	<u>Admissible Range of Days Beyond Baseline for evaluability of Visit Data</u>
2	20 -47 days inclusive
3	48 -73 days inclusive
4	74 -102 days inclusive

The criteria for protocol adherence were applied and monitored by _____ and by the sponsor.

Reviewer's Comments:

1. *Acceptable. However, the protocol should have addressed how data would be handled if a patient made two visits within the same inclusive day period.*
2. *An initial follow-up visit of 14 days would have been preferable.*

Statistical Considerations

Key efficacy variables were:

1. changes from baseline in facial lesion counts of the inflammatory lesion counts (the sum of papules, pustules, and nodules), non-inflammatory lesion counts (the sum of open and closed comedones), total lesion counts (the sum of inflammatory and non-inflammatory lesions)
2. treatment success rates derived from the investigators' global response ratings.

The results are based on the preferred statistical analysis, which consisted of two parts:

1. analysis by week of evaluable data only
2. analysis of each subject's last observation carried forward (LOCF).

In the LOCF analysis, data from the last visit for all patients who had at least one follow-up visit were carried forward, and total inflammatory lesions, total non-inflammatory lesions, and global response ratings were statically analyzed.

Intent-to treat analysis

An intent-to-treat analysis by week, based on all data collected from patients who had lesion count data from at least one follow-up visit was performed.

Reviewer's Comments:

This is not a true intent-to-treat analysis, it is a modified intent-to-treat analysis. The classical intent-to-treat analysis is based on all data collected from all patients randomized to treatment.

Analytical methods

A p-value less than or equal to 0.05 was considered to be statistically significant for main effects. A p-value less than or equal to 0.10 was considered to be statically significant for treatment group-by-investigator interactions. Two-sided tests were performed in all cases.

The study protocol specified that the analysis of lesion counts be based on the computation of percent change from baseline, a two-way analysis of variance, and an analysis of variance method for repeated-measures designs to determine overall effect over time. However, because the data were not normally distributed, the percent change data were converted to an ordinal scale and then analyzed for differences in distribution.

For comparisons involving categorical data (such as demographic variables) and ordinal data (such as categorical percent lesion reduction), primary reliance was placed upon the generalized Cochran-Mantel-Haenszel (CMH) procedure with modified riddit weights controlling for investigator by stratification.

Differences in mean age between treatment groups were tested with a two-way analysis of variance, with treatment and investigator as main effects in the model and treatment group-by-investigator as the interaction term. Differences in distribution of sex and race (Caucasian

versus non-Caucasian) categories were tested with the CMH procedure.

Baseline (week 0) lesion counts were categorized as 0, 1 - 50, 51 - 100, or greater than 100, and were evaluated for between-group differences with the CMH procedure. Percent changes in lesion counts were tabulated by treatment group and follow-up visit. Percent change was calculated by subtracting the baseline count from the follow-up count, dividing the result by the baseline count, and then multiplying the result by 100%. Percent improvement was calculated as zero minus percent change.

Improvement rates at each scheduled follow-up visit were categorized into one of the following groups:

- ≥ 75 - ≤ 100% improvement
- ≥ 50 - < 75% improvement
- ≥ 25 - < 50% improvement
- ≥ 0 - < 25% improvement
- < 0% improvement

Global evaluation of response to treatment was recorded at follow-up visits with the following scale: 0 = condition unchanged or worsened, 1 = poor response, 2 = fair response, 3 = good response, 4 = excellent response, or 5 = completely cleared. Treatment success rates were calculated from the global evaluation ratings by computing the percentage of patients per treatment group with a good or excellent response or complete clearing of acne. Between-group differences in treatment success rates were analyzed with Fisher's exact test. Between-group differences in global response distributions were analyzed with the CMH procedure. A LOCF analysis was undertaken for both treatment success rates and global categories.

Adverse experiences were tabulated for each treatment group by body part, reaction term, and relationship to treatment. Associated listings include the investigator description, maximum severity, and subject disposition. Overall differences in adverse experience incidence rates within each treatment group were analyzed by demographic subgroup (age and sex cross-tabulated with race) with Fisher's exact test. Fisher's exact test was also used to analyze overall differences in sign or symptom groups.

For overall clinical severity grade, changes from baseline were calculated by treatment group and visit, and between-group differences were analyzed with the CHM procedure. A negative change from baseline indicates improvement. Incidence rates for signs and symptoms were tabulated for subjects who showed an increase in severity at any follow-up visit. Between-group differences in sign or symptom rates were tested with CHM procedure, and treatment group-by-investigator interactions with the Breslow-Day test for homogeneity.

A tabulation of the patients' evaluation of cosmetic characteristics was created from each cosmetic variable and each treatment group. Differences in response rates were analyzed with the CMH procedure.

Reviewer's Comment:

The global response was not balanced and the proposed method of data analysis of lesion counts is questionable. See the statistical review.

8.1 Indication Acne Vulgaris**8.1.1 Reviewer's Trial #1 Sponsor's protocol #AZEL-220-8466****8.1.1.1 Objective/Rationale**

The objective of this clinical trial was to evaluate the safety and efficacy of azelaic acid 20% cream in comparison with vehicle cream (control) applied twice daily in the treatment of mild to moderate acne vulgaris of the face.

8.1.1.2 Study Design

This was a twelve week multicenter, double-masked, parallel-group comparison study with patients randomly assigned to an azelaic acid 20% cream group or a vehicle cream group. Patients applied medication to their faces twice daily for twelve weeks and were evaluated at baseline and at weeks 4, 8, and 12.

8.1.1.3 Protocol**8.1.1.3.1 Population/Procedures - See Section 8.0**

Three hundred patients with mild to moderate facial acne vulgaris were enrolled into the study at six investigational sites. The study was conducted from January 28, 1992 to June 29, 1992.

Study Formulations:

Azelaic acid 20% cream (8466X)
Vehicle cream (8465X)

Randomization and Blinding

After giving their informed consent, qualified patients within each investigator's population were assigned to blinded treatment groups (azelaic acid 20% cream or vehicle cream) in numerical order, corresponding to a randomization schedule generated by the sponsor and using a blocking factor of four.

Investigators:

Joseph L. Jorizzo, M.D.	Winston-Salem, NC	(#1275)
Ann W. Lucky, M.D.	Cincinnati, OH	(#1900)
Lawrence S. Moy, M.D.	Los Angeles, CA	(#1966)
Edward Shmunis, M.D.	Columbia, SC	(#1558)
Melvin L. Elson, M.D.	Nashville, TN.	(#1938)
Terry M. Jones, M.D.	Bryant, TX	(#1967)

Reviewer's comment: *The investigators are all qualified.*

Treatment Regimen and Patient Compliance

At the initial visit, each patient received two 30g tubes of either azelaic acid 20% cream or vehicle cream and a bar of non-medicated cleanser (Dove™, Lever Brothers CO.). Patients received additional 30g tubes of their assigned medication after 4 and 8 weeks.

After washing with Dove or another non-medicated cleanser, rinsing thoroughly, and drying with a soft towel, patients applied the assigned medication to their faces. Medication was applied twice daily (morning and evening), at least 30 minutes after washing the face.

As a means of monitoring patient compliance with the regimen, patients were requested at each follow-up visit to return the tube of medication (whether unused, partially used, or empty) dispensed at the previous visit.

Concomitant Medications

With the exception of antibiotics or other anti-acne medications, concomitant systemic or topical medications were allowed if the investigator considered them necessary for the patients welfare, provided that they would not interfere with the response to treatment. The use of any concomitant medication was recorded on the patient's case report forms.

Patients were allowed to use non-medicated shampoos as often as they liked. Patients who were using non-medicated cosmetics were allowed to continue to do so, as long as their regimen did not change during the course of the study. Patients were not allowed to use other lotions, creams, powders, or solutions on the treatment area.

Reviewer's comment: *Acceptable.*

Data Quality Assurance

During the study period, personnel from _____ monitored the study sites via study site visits and periodic telephone contact with the investigators and their respective staffs.

8.1.1.3.2 Endpoints

8.1.1.3.3 Statistical considerations

Based on *a priori* power calculations, the planned sample size was a total of 300 patients enrolled at a total of six investigational sites. With 150 patients per treatment group, the power to detect a 15% difference between azelaic acid and its vehicle in the percent change from baseline in total lesion counts was calculated as 0.90. The power to detect a 20% difference between the treatment groups in the treatment success rates was calculated as greater than 0.90.

8.1.1.4 Results

Of the 300 patients enrolled into the study:

247	(82%) completed the study
44	(15%) were discontinued
7	(2%) were terminated due to adverse events
2	(1%) were disqualified due to improper enrollment

The completion rate:

82% for patients in the azelaic acid group
83% for patients in the vehicle group.

A total of 273 patients were judged to be evaluable and were included in the preferred analysis.

Evaluable patients:

138 (evaluable rate, 91%) - azelaic acid group
135 (evaluable rate, 91%) - vehicle group

8.1.1.4.1 Population enrolled/analyzed

The 273 evaluable patients (127 males and 146 females) ranged in age from _____ years (mean age, 19 years). Eighty-eight percent of the evaluable patients were Caucasian, 7% were Black, 4% Hispanic, and 1% were Oriental or Polynesian.

	<u>Treatment Group</u>	<u>Number Enrolled</u>	<u>Number Eligible</u>	<u>Number Evaluable</u>
Investigator 1275	Azelaic Acid Cream	25	25	22
	Vehicle Cream	25	25	24
Investigator 1558	Azelaic Acid Cream	25	25	25
	Vehicle Cream	25	24	23
Investigator 1900	Azelaic Acid Cream	30	30	27
	Vehicle Cream	30	30	27
Investigator 1938	Azelaic Acid Cream	26	26	22
	Vehicle Cream	24	23	19
Investigator 1966	Azelaic Acid Cream	15	15	14
	Vehicle Cream	15	15	12
Investigator 1967	Azelaic Acid Cream	30	30	28
	Vehicle Cream	30	30	30

* Screened, enrolled, eligible, and evaluable are defined as follows:

Screened: any potential subject considered for the study.

Enrolled: any subject who signed the subject consent form.

Eligible: any enrolled subject who was not disqualified.

Evaluable: any eligible subject with at least one evaluable follow-up visit.

Protocol Deviations

There were several categories of protocol deviations of note. They are as follows:

1. The following subjects were enrolled, but were not eligible for study inclusion (preferred analysis):

<u>Treatment Group</u>	<u>Investigator Number</u>	<u>Subject Number</u>	<u>Reason</u>
Vehicle	1558	531	Baseline papules + pustules > 60
	1938	614	Baseline lab results unacceptable

2. The following subjects were considered to be not evaluable (eligible subjects who did not have at least one evaluable follow-up visit) and were not used in any analyses:

<u>Investigator Number</u>	<u>Azelaic Group</u>	<u>Vehicle Group</u>
1275	231, 237, 243	206
1558		511, 531
1900	305, 311, 325	301, 306, 360
1938	619, 645, 649, 650	606, 614, 622, 627, 632
1966	415	401, 413, 421
1967	149, 152	

3. The following patients were not ITT evaluable since they did not have at least one follow-up visit with lesion count data:

Investigator Number	Azelaic Group	Vehicle Group
1275	243	
1558		511
1900	305, 311, 325	301
1938	619, 645, 649, 650	606, 622, 627, 632
1966	415	401, 413, 421
1967		

Reviewer's Comment:

1. *The modified intent-to-treat analysis should include any patient who was randomized to treatment and who had any follow-up recorded lesion count data. The following patients should also be included in the modified intent-to-treat analysis :*

Azelaic Acid Group

1900-325 (Adverse event with lesion count at interim visit)

1938-619 (Adverse event with lesion count at interim visit)

Vehicle Cream Group

1558-511 (Adverse event with lesion count at interim visit)

1558-531 (Improper entry but completed all visits)

1938-614 (Improper entry but completed two visits)

2. *The following patient's should be included in the LOCF analysis:*

Vehicle Cream Group

1938-614 (Completed two visits)

1558-531 (Completed all visits)

3. *Clarification is needed regarding the exclusion of patients from all analyses and then including some of these same patients in the intent-to-treat analyses:*

Demographic Characteristics of Evaluable Subjects

Analysis of evaluable patients with respect to mean age indicated no interaction between treatment group and investigator nor any significant group effect, but there was a significant investigator effect.

Group	Age (Years):				
	N	Mean	SD	Minimum	Maximum
azelaic acid	138	19.4	8.1	12	70
vehicle	135	18.8	7.0	12	50
total	273	19.1	7.5	12	70

Group	Total	Male		Female	
		N	(%)	N	(%)
Azelaic acid cream	138	62	(45%)	76	(55%)
Vehicle Cream	135	65	(48%)	70	(52%)
Total	273	127	(47%)	146	(53%)

Group	Azelaic acid		Vehicle cream	
	N	(%)	N	(%)
Caucasian	121	(88%)	119	(88%)
Black	12	(9%)	8	(6%)
Hispanic	3	(2%)	7	(5%)
Oriental	2	(1%)	-	-
Polynesian	-	-	1	(1%)
Total	138	(100%)	135	(100%)

Reviewer's Comment:

An attempt to recruit more pigmented patients should have been made in order to assess hypopigmentation as a possible adverse event.

Reasons For Dropouts

Reason for Exit	Azelaic acid cream	Vehicle cream
<u>Terminated</u>		
Adverse Event (treatment related)	5	2
<u>Discontinued</u>		
Concomitant antibiotics	8	7
Missed visits	5	6
Personal reasons	5	3
Topical steroid use	1	0
Started oral birth control	1	0
Noncompliance	1	0
Unable to make appointment	1	0
Fractures	0	2
Relocated	0	3
<u>Disqualified</u>		
Improper entry	0	2

Reviewer's Comment:

Examples of personal reasons for discontinuation should be stated in future protocols since only one patient should have been discontinued as personal. Patient should have been included under adverse events for nausea. All others listed under personal reasons should have been classified as terminated due to lack of efficacy.

8.1.1.4.2 Efficacy Endpoint Outcomes

Total Inflammatory Lesions

Analysis of Variance (Baseline Count and % Change from Baseline)

	<u>Baseline</u>	<u>% Change from Baseline</u> <u>Week 12</u>	<u>p-value</u>
Azelaic Acid Cream			
N	138	121	
Mean	21.99	-30.98	0.27
Vehicle Cream			
N	135	120	
Mean	23.24	-20.59	

Subgroup 1 (Invest 1966, 1938, 1967, 1900)

	<u>Baseline</u>	<u>% Change from Baseline</u> <u>Week 12</u>	<u>p-value</u>
Azelaic Acid Cream			
N	91	78	
Mean	20.37	-46.57	0.003
Vehicle Cream			
N	88	81	
Mean	21.90	-17.70	

Subgroup 2 (Invest 1558 and 1275)

	<u>Baseline</u>	<u>% Change from Baseline</u> <u>Week 12</u>	<u>p-value</u>
Azelaic Acid Cream			
N	47	43	
Mean	25.11	-2.70	0.057
Vehicle Cream			
N	47	39	
Mean	25.77	-26.61	

Mean Inflammatory Lesion Count by Investigator:

<u>Investigator Number</u>	<u>Group</u>	<u>Baseline</u>	<u>Week 12</u>
Jorizzo (1275)	Azelaic acid cream	28.7	34.8
	Vehicle cream	30.4	29.2
Shmunes (1558)	Azelaic acid cream	21.5	16.8
	Vehicle cream	24.2	14.4
Lucky (1900)	Azelaic acid cream	23.1	17.1
	Vehicle cream	26.3	26.5
Elson (1938)	Azelaic acid cream	21.0	8.0
	Vehicle cream	21.0	9.2
Moy (1966)	Azelaic acid cream	20.1	7.5
	Vehicle cream	22.3	14.4
Jones (1967)	Azelaic acid cream	16.5	7.3
	Vehicle cream	17.1	14.3

Total Non-inflammatory Lesions**Analysis of Variance (Baseline Count and % Change from Baseline)**

	<u>Baseline</u>	<u>% Change from Baseline</u> <u>Week 12</u>	<u>p-value</u>
Azelaic Acid Cream			
N	138	121	
Mean	65.14	-36.56	
			0.0008
Vehicle Cream			
N	135	120	
Mean	66.79	-13.90	

Mean Non-inflammatory Lesion Count by Investigator:

<u>Investigator Number</u>	<u>Group</u>	<u>Baseline</u>	<u>Week 12</u>
Jorizzo (1275)	Azelaic acid cream	129.0	82.1
	Vehicle cream	122.0	89.2
Shmunes (1558)	Azelaic acid cream	61.8	36.7
	Vehicle cream	56.2	33.7
Lucky (1900)	Azelaic acid cream	40.7	38.1
	Vehicle cream	39.1	42.5
Elson (1938)	Azelaic acid cream	53.2	37.7
	Vehicle cream	57.6	49.8
Moy (1966)	Azelaic acid cream	52.4	15.2
	Vehicle cream	56.7	40.0
Jones (1967)	Azelaic acid cream	60.5	39.0
	Vehicle cream	62.0	50.8

Total Lesions**Analysis of Variance (Baseline Count and % Change from Baseline)**

	<u>Baseline</u>	<u>% Change from Baseline</u> <u>Week 12</u>	<u>p-value</u>
Azelaic Acid Cream			
N	138	121	
Mean	87.13	-36.21	0.0028
Vehicle Cream			
N	135	120	
Mean	90.04	-20.30	

Global Evaluation of Response to Treatment

Treatment success rates (the percentage of subjects with a good or excellent global response or complete clearing of acne) were significantly higher for azelaic acid than for vehicle at weeks 8 and 12.

Azelaic Acid Cream		Week 4	Week 8	Week 12
	Complete clearing	0	0	0
	Excellent response	4	5	27
	Good response	19	30	28
	Fair response	39	33	19
	Poor response	36	31	24
	Condition unchanged	44	32	26
	Total	142	131	124
Vehicle Cream		Week 4	Week 8	Week 12
	Complete clearing	0	0	0
	Excellent response	3	3	12
	Good response	14	17	20
	Fair response	32	34	32
	Poor response	49	41	22
	Condition unchanged	42	36	38
	Total	140	131	124

Between group CMH p-value	0.26	0.08	0.01
Azelaic Acid Treatment Success Rate	16%	27%	44%
Vehicle Treatment Success Rate	12%	15%	26%
Fisher's Exact p-value	0.39	0.03	0.003

The LOCF analysis confirmed the significant difference in favor of azelaic acid ($p = 0.03$).

Reviewer's comments:

There were no instances of complete healing and it would have been encouraging clinically to expect a greater percentage of excellent responders.

The statistical review is pending.

Safety Variables

Data collected for the evaluation of safety of azelaic acid included adverse experience reports, laboratory results (hematology, blood chemistry, and urinalysis), and azelaic acid plasma level results.

Adverse Events:

Adverse Experiences (Treatment Related)

Azelaic Acid Group

The most common treatment-related adverse experiences were pruritus, burning, stinging, tingling, and dermatitis. Five patients were terminated from the study because of treatment-related adverse experiences: 3 patients because of dermatitis; 1 patient because of severe stinging, burning, and rash; and 1 patient because of severe burning and pruritus.

Adverse Experience	Mild	Moderate	Severe
Pruritus	5	3	1
Burning	1	3	2
Stinging	1	1	1
Tingling	3	0	0
Dermatitis	1	1	1
Contact Dermatitis	1	0	0
Dryness	1	0	0

Vehicle Cream Group

The most common treatment-related adverse experiences were burning and pruritus. Two patients treated with vehicle were terminated from the study because of treatment-related adverse experiences: 1 because of moderate dermatitis and 1 patient because of severe dryness, peeling, and burning.

Adverse Experience	Mild	Moderate	Severe
Pruritus	2	0	0
Burning	2	0	1
Peeling	0	0	1
Contact Dermatitis	0	1	0
Dryness	0	0	1

Adverse Events Probably or Possibly Related to Study Treatment

Azelaic Acid Group	14%	(21/151)
Vehicle Cream Group	4%	(6/149)

The incidence of pruritus of any severity grade was approximately:

- 6% among patients treated with azelaic acid
- 1% among patients treated with vehicle cream

The incidence of increased pruritus (mostly mild):

- 39% among patients treated with azelaic acid
- 11% among patients treated with vehicle cream ($p < 0.001$)

The incidence of burning was:

- 4% for azelaic acid
- 2% for vehicle cream

The incidence of increased burning (mostly mild):

- 33% for azelaic acid
- 12% for vehicle cream

All adverse experiences by age and sex cross-tabulated with race. Within the vehicle group, female patients had a significantly higher incidence of adverse experiences than male subjects ($p=0.014$).

Adverse Events Summary

Event	Azelaic Acid (N = 151)		Vehicle (N = 149)	
	N	%	N	%
Pruritus	9	(5.96%)	2	(1.34%)
Pharyngitis	9	(5.96%)	13	(8.72%)
Burning Skin	6	(3.97%)	3	(2.01%)
Headache	5	(3.31%)	3	(2.01%)
Dermatitis**	4	(2.65%)	1	(0.67%)
Flu Synd	4	(2.65%)	2	(1.34%)
Rhinitis	4	(2.65%)	2	(1.34%)
Stinging Skin	3	(1.99%)		
Tingling	3	(1.99%)		
Cough Inc	3	(1.99%)	2	(1.34%)
Fever	0		2	(1.34%)
Pain Back	0		2	(1.34%)
Bone Fract Spont	0		2	(1.34%)
Erythema Sun-Induced	2	(1.32%)		
Dermatitis Exfol	0		1	(0.67%)
Skin Dry	1	(0.66%)	1	(0.67%)
Urticaria	0		1	(0.67%)
Asthma	1	(0.66%)		
Bronchitis	1	(0.66%)		
Conjunctivitis	1	(0.66%)		
Diarrhea	1	(0.66%)		
Dysmenorrhea	1	(0.66%)	2	(1.34%)
Edema Peripheal	1	(0.66%)		
Blepharitis	0		1	(0.67%)
Burns Eye	0		1	(0.67%)
Infection Sinus	1	(0.66%)	1	(0.67%)
Inflammation	1	(0.66%)		
Myalgia	1	(0.66%)	1	(0.67%)
Nar Disorder	1	(0.66%)		
Pain Chest	0		1	(0.67%)
Reaction Uneval***	0		1	(0.67%)
Pain Abdo	1	(0.66%)	1	(0.67%)

NDA 20-428 2 of 3

	Azelaic Acid (N=151)		Vehicle (N=149)	
Stomatitis	1	(0.66%)	1	(0.67%)
Tenosynovitis	1	(0.66%)		
Tooth Dis	1	(0.66%)	2	(1.34%)
Abscess Periodont	0		1	(0.67%)
Depression	0		1	(0.67%)
Ulcer Mouth	1	(0.66%)		
Asthenia	0		1	(0.67%)
Vomit	1	(0.66%)		

- * Subject may have had more than one experience. For each Subject, only the maximum severity of each adverse experience is listed.
- ** Includes contact dermatitis and rash.
- *** A request has been made to remove the "Not Applicable" and "Reaction Uneval" from this table and any other, replacing it with the appropriate information.

Reviewer's comment:

Azelaic acid has been patented for the treatment of hyperpigmentary dermatoses (#4,292,326). It is postulated 'to be useful for normalizing the color of skin affected by non-cancerous or non-precancerous hyperpigmentation'. There have been pilot studies and clinical trials but no well controlled clinical trials conducted for efficacy of "normalization" of pigmentation (hypopigmentation). Since hypopigmentation is a known possible side effect of this chemical, data should have been collected with this possibility in mind.

"Change in pigmentation" was reported under local side effect in study AZEL-926-SCAG/7234 but was not specified as hypo nor hyperpigmentation. In study AZEL-926/SCAG, "white spots" were reported in two patients (n=151).

Normalization of pigment would be viewed as a desirable event, however, hypopigmentation to a deeply pigmented patient would be considered disfiguring.

It is the opinion of this reviewer that data should have been specifically collected via the case report forms. This side effect may have been subtle in Caucasian patients, consequently it may not have been reported. Therefore, it is recommended that a Phase 4 commitment to investigate hypopigmentation as a possible adverse event in darker pigmented patients should be obtained from the sponsor.

Concentration of Azelaic Acid in Plasma Samples:

Plasma samples from 56 patients treated with azelaic acid were assayed for concentrations of azelaic acid and its metabolite pimelic acid.

mean plasma concentration at baseline $83.8 \pm 15.5\text{ng/mL}$

mean plasma concentration at 12 weeks $89.6 \pm 36.5\text{ng/mL}$

Patients in each treatment group had "shifts" in hematology, blood chemistry, and urinalysis values but none of these changes were judged to be clinically significant by the investigators.

Reviewer's Comments:

There were no clinically significant "shifts" in hematology, blood chemistry, or urinalysis values found.

The estimated daily systemic load from percutaneous application of a 20% cream is within the normal fluctuations of dietary exposure.

Conclusion:

The results of study AZEL220-8466 demonstrated that azelaic acid 20% cream applied twice daily is safe and significantly more effective than its vehicle in the treatment of mild to moderate acne vulgaris. The statistical review is pending.

8.1.1.4**Results**

Of the 299 patients enrolled into the study:

246	(82%) completed the study
50	(17%) were discontinued
2	(1%) were terminated due to adverse events
1	(1%) were disqualified due to improper enrollment

The completion rate:

85%	for patients in the azelaic acid group
80%	for patients in the vehicle group.

A total of 272 patients were judged to be evaluable and were included in the preferred analysis.

Evaluable patients:

140	(evaluable rate, 93%) - azelaic acid group
132	(evaluable rate, 89%) - vehicle group

8.1.1.4.1**Population enrolled/analyzed**

The 272 evaluable patients (151 males and 121 females) ranged in age from _____ years (mean age, 18 years), were included in the preferred analysis. Ninety-four percent of the evaluable patients were Caucasian, 3% were Black, 2% Hispanic, and 1% were Oriental or Polynesian.

Tabulation of Screened, Enrolled, Eligible, and Evaluable Subjects*
By Investigator for AZEL-221-8466

	<u>Treatment Group</u>	<u>Number Enrolled</u>	<u>Number Eligible</u>	<u>Number Evaluable</u>
Investigator 0051	Azelaic Acid Cream	25	25	24
	Vehicle Cream	25	24	24
Investigator 1962	Azelaic Acid Cream	30	30	30
	Vehicle Cream	30	30	29
Investigator 1963	Azelaic Acid Cream	25	25	20
	Vehicle Cream	25	25	21
Investigator 1964	Azelaic Acid Cream	30	30	30
	Vehicle Cream	29	29	27
Investigator 1965	Azelaic Acid Cream	15	15	13
	Vehicle Cream	15	15	12
Investigator 1970	Azelaic Acid Cream	25	25	23
	Vehicle Cream	25	25	19

* Screened, enrolled, eligible, and evaluable are defined as follows:

Screened: any potential subject considered for the study.

Enrolled: any subject who signed the subject consent form.

Eligible: any enrolled subject who was not disqualified.

Evaluable: any eligible subject with at least one evaluable follow-up visit.

Protocol Deviations

There were several categories of protocol deviations of note. They are as follows:

1. The following patient was enrolled, but was not eligible for study inclusion (preferred analysis):

<u>Treatment Group</u>	<u>Investigator Number</u>	<u>Patient Number</u>	<u>Reason</u>
Vehicle cream	0051		Underage

2. The following patients were considered to be not evaluable (eligible patients who did not have at least one evaluable follow-up visit) and were not used in any analyses.

<u>Treatment Group</u>	<u>Investigator Number</u>	<u>Patient Number</u>
Azelaic acid cream	0051	
		1963
		1965
		1970
Vehicle cream	0051	
		1962
		1963
		1964
		1965
		1970

3. The following patients were not ITT evaluable since they did not have at least one follow-up visit data for lesion counts.

<u>Treatment Group</u>	<u>Investigator Number</u>	<u>Patient Number</u>
Azelaic acid cream		1963
		1965
		1970
Vehicle cream	0051	
		1963
		1964
		1965
		1970

Reviewer's comments:

1. *The following patients should have been listed as protocol deviations in the azelaic acid group due to pregnancy: The pregnancy outcome results of these patients need to be submitted.*
2. *All patients randomized to treatment should have been included in the classical intent-to-treat analysis.*

Demographic Characteristics of all patients enrolled

	<u>Azelaic acid cream</u>	<u>Vehicle cream</u>
Number of patients	140	132
Gender		
Male	68 (49%)	83 (63%)
Female	72 (51%)	49 (37%)
Age (yr)		
Number	140	132
Mean	18.4	18.4
SD	5.7	5.3
Range		
Race		
Caucasian	132 (94%)	124 (94%)
Black	3 (2%)	3 (3%)
Oriental	2 (1%)	1 (1%)
Hispanic	3 (2%)	3 (1%)

Reviewer's comment:

An attempt to recruit more pigmented patients should have been made in order to assess hypopigmentation as a possible adverse event.

Reasons For Dropouts

	<u>Azelaic acid cream</u>	<u>Vehicle cream</u>
<u>Terminated</u>		
Adverse Event (treatment related)	1	0
Lack of Efficacy	0	1
<u>Discontinued</u>		
Missed Visits	9	6
Concomitant antibiotics	7	9
Pregnancy	2	0
Personal Reasons	2	2
Noncompliance	1	0
Unable to Continue	0	7
Concomitant Steroid Therapy	0	1
<u>Disqualified</u>		
Improper Entry	0	1

Reviewer's comments:

Lack of efficacy should have been listed as the reason for exit for the following patients:

<i>Azelaic acid cream</i>	<i>Vehicle cream</i>
1963	1963-
1963	1963-
1963	1965-
1963	1965-
1965	1970

8.1.1.4.2. Efficacy Endpoint Outcomes

Total Inflammatory Lesions

Analysis of Variance (Baseline Count and % Change from Baseline)

	<u>Baseline</u>	<u>% Change from Baseline</u> <u>Week 12</u>	<u>p-value</u>
Azelaic Acid Cream			
N	140	126	
Mean	25.72	-33.82	< .0001
Vehicle Cream			
N	132	118	
Mean	25.81	-23.41	< .0001
AOV p-values			
Group	0.8020	0.1419	
Invest.	<0.0001	<0.0001	
Group*Invest.	0.0325	0.8286	

Total Inflammatory Lesions

Analysis of Variance (excluding Investigator 1963)

	<u>Baseline</u>	<u>% Change from Baseline</u> <u>Week 12</u>	<u>p-value</u>
Azelaic Acid Cream			
N	120	110	
Mean	26.07	-30.16	< 0.0001
Vehicle Cream			
N	111	99	
Mean	24.36	-19.40	.0001
AOV p-value			
Group	0.1355	0.2633	
Invest.	<0.0001	<0.0001	
Group*Invest.	0.3361	0.7527	

There was a significant treatment-by-investigator interaction at baseline for total inflammatory lesions. Categorized baseline and percent change from baseline were therefore analyzed in the subgroups of Investigator 1963 and the remaining five investigators.

Azelaic acid cream was associated with a significantly larger reduction of total inflammatory lesions than was vehicle cream at weeks 8, 12, and in the LOCF analysis for the subgroup of five investigators (0051, 1963, 1964, 1965, and 1970). However, there was no significant differences between treatment groups in the reduction of total inflammatory lesions at any week for Investigator 1963. Note that there were no significant differences between-group differences for any of the subgroups.

Total Non-Inflammatory Lesions

Analysis of Variance (Baseline Count and % Change from Baseline)

	<u>Baseline</u>	<u>% Change from Baseline</u> <u>Week 12</u>	<u>p-value</u>
Azelaic acid cream			
N	140	126	
Mean	48.81	-24.39	
			0.5879
Vehicle cream			
N	132	118	
Mean	46.23	-20.34	

There were no significant differences between treatment groups in the reduction of total non-inflammatory lesions at any week or in the LOCF analysis, nor at baseline, nor were there any significant group-by-investigator interactions at any week.

Total Lesions

Analysis of Variance (Baseline Count and % Change from Baseline)

	<u>Baseline</u>	<u>% Change from Baseline</u> <u>Week 12</u>	<u>p-value</u>
Azelaic acid cream			
N	140	126	
Mean	74.54	-32.02	
			0.1147
Vehicle cream			
N	132	126	
Mean	72.04	-23.86	

Azelaic acid cream was associated with a trend to a larger reduction of total lesions (inflammatory + non-inflammatory) than was vehicle cream at weeks 4, 8, and 12 and in the LOCF analysis. Note that there was no significant between-group difference at baseline or group-by-investigator interaction at any week.

Mean Total Inflammatory Lesion Count by Investigator:

<u>Investigator Number</u>	<u>Group</u>	<u>Baseline</u>	<u>Week 12</u>
Kligman (0051)	Azelaic acid cream	21.8	11.4
	Vehicle cream	24.4	16.0
Berger (1962)	Azelaic acid cream	23.5	20.3
	Vehicle cream	20.7	21.6
Merchant (1963)	Azelaic acid cream	24.1	8.9
	Vehicle cream	33.1	18.2
Swinyer (1964)	Azelaic acid cream	29.7	13.8
	Vehicle cream	29.0	16.7
Williams (1965)	Azelaic acid cream	38.2	27.0
	Vehicle cream	30.1	22.8
Whiting (1970)	Azelaic acid cream	21.2	20.6
	Vehicle cream	17.2	17.9

Global Evaluation of Response to Treatment

Azelaic acid cream was associated with a significantly better global evaluation of response to treatment than was vehicle cream at weeks 4, 12 and in the LOCF analysis, and with significantly better treatment success rate than was vehicle cream at week 12 and in the LOCF analysis.

		Treatment Success Rate Intent-to-Treat Analysis		
		<u>Week 4</u>	<u>Week 8</u>	<u>Week 12*</u>
Azelaic acid cream	Completely cleared	0	0	2
	Excellent response	2	8	15
	Good response	12	22	37
	Fair response	33	24	20
	Poor response	40	43	30
	Condition unchanged	54	40	23
	Total	141	137	127
Vehicle cream	Completely cleared	0	0	0
	Excellent response	0	2	5
	Good response	0	21	29
	Fair response	25	23	21
	Poor response	30	30	29
	Condition unchanged	64	49	35
	Total	135	125	119
Between group CMH p-value		0.032	0.098	0.001
Azelaic acid cream	Treatment Success Rate	10%	22%	43%
Vehicle cream	Treatment Success Rate	6%	18%	29%
Fisher's Exact p-value		0.269	0.539	0.024

Reviewer's comments: *The statistical review is pending.*

Safety VariablesAdverse Experiences (Treatment Related)

Azelaic acid cream was associated with a significantly higher incidence of burning and pruritus than was the vehicle cream. One patient was terminated due to burning.

Vehicle cream was associated with a significantly higher incidence of increase in symptoms of oiliness. There was a significant difference in the adverse reported by age range in the vehicle cream group. There were no significant differences between treatment groups in the overall incidence rates of adverse experiences.

Summary of Adverse Experiences

Event*	Azelaic Acid Cream		Vehicle	
	N	%	N	%
Pharyngitis	10	(6.67%)	7	(4.70%)
Burning skin	7	(4.67%)	1	(0.67%)
Pruritus	5	(3.33%)	1	(0.67%)
Rhinitis	5	(3.33%)		
Headache	4	(2.67%)	8	(5.37%)
Erythema	2	(1.33%)	1	(0.67%)
Pregnancy	2	(1.33%)		
Ineffective			2	(1.33%)
Seborrhea			2	(1.34%)
Skin dry	2	(1.33%)	1	(0.67%)
Dermatitis exfol	1	(0.67%)		
Flu synd	2	(1.33%)		
Injury accid	2	(1.33%)	2	(1.34%)
Bronchitis	1	(0.67%)		
Erythema sun-induced	1	(0.67%)		
Irritation skin	1	(0.67%)		
Dermatitis**			2	(1.33%)
Conjunctivitis	1	(0.67%)	1	(0.67%)
Depression	1	(0.67%)		
Edema eye	1	(0.67%)		
Fever	1	(0.67%)	1	(0.67%)
Infection	1	(0.67%)		
Infection urin tract	1	(0.67%)		
Insomnia	1	(0.67%)		
Laceration skin	1	(0.67%)		
Myalgia	2	(1.33%)	1	(0.67%)
Otitis	1	(0.67%)	1	(0.67%)
Pain***			2	(1.33%)

Sinusitis	1	(0.67%)	1	(0.67%)
Skin dry	1	(0.67%)		
Diarrhea			1	(0.67%)
Flu synd			1	(0.67%)
Bleeding mole			1	(0.67%)
Dysmenorrhea			1	(0.67%)
Dizziness			1	(0.67%)
Dypepsia			1	(0.67%)
Urethritis			1	(0.67%)
Ulcer stomach			1	(0.67%)
Rhinitis			1	(0.67%)
UG infection			1	(0.67%)
Contact dermatitis (Poison Ivy)			1	(0.67%)
Cough inc			1	(0.67%)
Bone fract			1	(0.67%)
Abscess periodont			1	(0.67%)

* Subject may have had more than one adverse experience. For each subject, only the maximum severity of each adverse experience is listed.

** Includes eczema and forearm rash

*** Includes abdo and ear pain

Note: One report of BURNING SKIN(SKIN/GEN) was reported but is not listed in this table (investigator was unable to determine the reaction severity).

Reviewer's comments:

1. *Pregnancy outcomes should be reported.*
2. *The terms "not applicable" under body part and "reaction unevaluable" under reaction term for adverse experience tables are unacceptable in support of an NDA submission.*

Conclusion: *The results of study AZEL-221-8466 demonstrated that azelaic acid 20% cream applied twice daily is safe and significantly more effective than its vehicle in the treatment of mild to moderate acne.*

The statistical review is pending.

- Study AZEL-907-SCAG/6499**
- Study Title: Clinical and Laboratory Investigations of the Effect of Azelaic Acid in the Treatment of Acne
- Study Sponsor: Schering AG
- Dates of Study: September 1983 to June 1984
- Study Objective: The objective of this study was to compare the efficacy of azelaic acid 20% cream to that of benzoyl peroxide 5% gel in the treatment of acne.
- Study Design: Randomized: double-blind; active control
- Study Population: Forty male subjects with physiological acne (acne minor) were enrolled and completed this study at one investigational site. Data for all subjects, age 18 to 22 years, were included in the statistical evaluation.
- Investigator: Dr. W. J. Cunliffe
Consultant Dermatologist
Leeds General Infirmary
Leeds, LS1 3EX
England, United Kingdom
- Study Formulations: Azelaic acid 20% cream (SHC 441DA)
Benzoyl peroxide 5% gel (Pannogel-5, Pannoc Chemie)
- Study Methods: At the preliminary evaluation, lesions were counted and classified as noninflamed lesions, small inflamed lesions, deep pustules, nodules, and macules after visual inspection and palpation of the skin. Severity was graded on a scale of 0 (no acne) to 10 (the most severe acne). Two balanced groups were formed based on the number of lesions and severity grade. Treatment was randomly assigned to each group.
- Patients were instructed to apply study medications twice daily for a period of 6 months and returned monthly or bi-monthly for clinical evaluations which included lesion counts and severity grading.
- Free fatty acid concentration was determined at baseline and at each clinical evaluation.
- Because the data were not normally distributed, nonparametric tests were used for hypothesis testing. Differences between groups were

compared using the Mann-Whitney U-test, and within group comparisons to ~~DESIMYPERGE~~ performed using the Wilcoxon matched pair signed rank test. Changes from baseline and differences between groups in the number of lesions and in the severity grade were the primary criteria of efficacy. Changes from baseline in free fatty acid concentrations and differences between groups were of secondary importance and were used to assist in defining the mechanism of action of the azelaic acid cream.

Patients were evaluated at each clinic visit for the occurrence of adverse experiences or local irritation. No other clinical or laboratory evaluation of safety were performed.

Results:

The median number of lesions was significantly reduced from baseline at month one in both treatment groups; however, the difference between groups was not significant. The maximal improvement for both number of lesions and severity grade in each treatment group was observed at month four. Benzoyl peroxide consistently produced a greater reduction in facial severity grade and in the median number of small inflammatory lesions, non-inflammatory lesions, and total lesion count than did azelaic acid. With the exception of macules, these differences in favor of benzoyl peroxide were statistically significant from month 2 to month 5 ($p < 0.05$).

Conclusion:

Schering AG concluded that azelaic acid was effective in treating physiological acne (acne minor). In this small pilot study, benzoyl peroxide was significantly superior to azelaic acid for most comparisons. Free fatty acid concentration was significantly lower at each follow-up visit in the benzoyl peroxide group than in the azelaic acid group. These results suggest a need for further comparisons between azelaic acid and benzoyl peroxide as a treatment for acne. Adverse events were relatively minor. Among patients treated with azelaic acid, approximately 5% reported erythema, and 7% reported scaling.

Reviewer's comment:

1. *The investigator is qualified.*
2. *This study does not support the label claim of "demonstrated efficacy comparable to benzoyl peroxide".*

- Study AZEL-921-SCAG/7232****
- Study Title: A Multicenter, Single-Blind Comparison of Topical Azelaic Acid Cream with Topical Benzoyl Peroxide 5% in the Treatment of Acne
- Study Sponsor: Schering AG
- Dates of Study: October 1983 to July 1985
- Study Objective: The objective of this study was to compare the clinical efficacy and safety of azelaic acid 20% cream to that of benzoyl peroxide 5% gel in the treatment of acne.
- Study Design: Single-blind, randomized, parallel group, active control
- Study Population: Three hundred and forty-one patients with papulo-pustular acne were enrolled into the study. The study was conducted at seventeen investigational sites. Data for 309 patients, 224 males and 85 females, age 13 to 48 years, were included in the statistical analysis.
- Investigators: Seventeen European Investigational Sites
- Study Formulations: Azelaic acid 20% cream (SHC 441DA)
Benzoyl peroxide 5% gel (Pan Oxyl® 5, Stiefel Laboratories)
- Results: Both treatments led to significant and clinically relevant improvements. At endpoint, good to excellent results were achieved in 51.3% of patients in the azelaic acid group and in 68.8% of patients in the benzoyl peroxide group. Benzoyl peroxide had a more rapid initial effect, leading to better therapeutic results during the early phase of treatment.
- Conclusion: Schering AG concluded that azelaic acid was effective in treating papulopustular acne and was generally well tolerated. In contrast to the more protracted onset of action of azelaic acid, benzoyl peroxide had a more rapid initial effect, leading to better therapeutic results during the early phase of treatment.

Reviewer's comments:

1. *Double-blinded studies are preferred in support of labeling claims of NDA submissions.*
2. *Investigator qualifications could not adequately be assessed since curricular vitae are available for only six of the seventeen investigators.*

Regulatory Action:

Labeling claim of "demonstrated efficacy comparable to 5% benzoyl peroxide" should be deleted from the label unless supported by well controlled, double-blinded, randomized clinical trials.

- Study AZEL-920-SCAG/7234**
- Study Title: A Multicenter, Single-Blind Comparison of Topical Azelaic Acid Cream with Topical Tretinoin (Vitamin A Acid) in the Treatment of Acne
- Study Sponsor: Schering AG
- Dates of Study: October 1983 to July 1985
- Study Objective: The objective of this study was to compare the clinical efficacy and safety of azelaic acid 20% cream to that of topical tretinoin in the treatment of acne
- Study Design: Single-blind, randomized, parallel group, active control
- Study Population: Three hundred and thirty-seven patients with comedonal acne were enrolled into the study. The study was conducted at 36 investigational sites. Data for 289 patients, 137 males and 152 females, age 11 to 47 years, were included in the statistical analysis
- Investigators: Thirty-six European Investigational Sites
- Study Formulation: Azelaic acid 20% cream (SHC 441DA)
Tretinoin 0.05% cream (Ainol[®], Roche)
- Results: Both treatments led to significant and clinically relevant improvements.
- There were no statistically significant differences between treatment groups for any type of lesion count. At the end of the second month, the proportion of patients with a good or excellent overall rating was significantly greater for tretinoin (47.2%) than for azelaic acid (30.4%). No other differences between treatment groups were statistically significant.

Conclusion: Schering AG concluded that azelaic acid was effective in treating comedonal acne and was generally well tolerated. There were no statistically significant differences between azelaic acid and tretinoin cream in the reduction of lesion counts.

Reviewer's comments:

- 1. Double-blinded studies are preferred in support of labeling claims of NDA submissions.*
- 2. Investigator qualifications could not adequately be assessed since curriculum vitae are available for only six of the thirty-six investigators.*

Study Title: **Study AZEL-909-SCAG/6499**
Clinical and Laboratory Investigation of the Effect of Azelaic Acid in the Treatment of Acne

Study Sponsor: Schering AG

Dates of Study: September 1983 to June 1984

Study Objective: The objective of this study was to compare the clinical efficacy and safety of azelaic acid 20% cream to that of topical tretinoin in the treatment of acne.

Study Design: Double-blind, randomized, parallel group, active control

Study Population: Forty-three patients were enrolled into the study. Data for 42 male patients, age 15 to 23 years, were included in the statistical analysis.

Investigators: Dr. W. J. Cunliffe
Consultant Dermatologist
Leeds General Infirmary
Leeds, LS1 3EX
England, United Kingdom

Study Formulation: Azelaic acid 20% cream (SHC 441DA)
Tretinoin 0.05% cream (Airo1[®], Roche)

Results: Compliance with the treatment regimens was poor in the study.

Conclusion: Schering AG concluded that poor compliance coupled with the small number of patients originally entered into the study suggest the need for further comparison.

Reviewer's comments:

1. *The investigator is qualified.*
2. *This study cannot be used to support labeling claims.*

Recommended Action:

Labeling claim of *should be deleted*
from the label unless supported by well controlled, double-blinded, randomized clinical trials.

- Study AZEL-925-SCAG/8943**
- Study Title: A Multicenter, Controlled, Double-Blind Comparison of Topical Azelaic with Topical Erythromycin in the Treatment of Papulo-Pustular Acne
- Study Sponsor: Schering AG
- Dates of Study: November 1988 to July 1989
- Study Objective: The objective of this study was to compare the clinical efficacy of azelaic acid 20% cream with that of a topical antibiotic (erythromycin) in the treatment of mild-moderate inflammatory acne.
- Study Design: Double-blind, randomized, parallel group, active control
- Study Population: Three hundred and fifteen patients with mild to moderate papulo-pustular acne were enrolled into the study. The study was conducted at 17 investigational sites. Data for 306 patients, 126 males and 180 females, age 12 to 43 years, were included in the statistical analysis.
- Investigators: Seventeen European Investigational Sites
- Study Formulation: Azelaic acid 20% cream (SHC 441DA)
Erythromycin 2% ointment (Akne Mycin 2000®, Hermal)
- Results: Both treatments were effective and produced clinically significant reductions in the lesion counts over a similar time course. There were no statistically significant differences between treatments.
- Median reduction in total lesion count at month 5 was 74.5% in the azelaic acid group and 69.5% in the erythromycin group. At endpoint, the median reduction was approximately 67% in each treatment group.
- Investigator and patient overall ratings of improvement were quite similar and resulted in a small numerical advantage for azelaic acid in each instance. In the azelaic acid group, overall improvement in the physician and patient ratings for azelaic acid was good or excellent (71.4% for azelaic acid vs. 66.7% for erythromycin and 69.8% vs. 66.7% respectively).
- Local adverse events, including pruritus, erythema, and burning, were more frequently observed ($p < 0.05$) in the azelaic acid group (26.6%) than in the erythromycin group (11.2%).

Conclusion: Schering AG concluded that azelaic acid was effective in treating papulopustular acne and was generally well tolerated.

Reviewer's comments: *Based on the results of study AZEL-925-SCAG/8943, the label should be modified with the following or similiar statement:*

In an active-control study, topical AZELEX™ demonstrated efficacy comparable to erythromycin ointment. However, local adverse events including pruritus, erythēma, and burning were more frequently observed in the azelaic acid group (26.6%) than in the erythromycin group (11.2%).

9 Overview of Efficacy

The following data is based on the data set utilized by the statistical reviews.

Summary of p-values Modified Intent-to-Treat Analysis

	Inflammatory Lesions*	Non-Inflammatory Lesions*	Total Lesions*	Global**
AZEL-220-8466***	0.0132	0.0003	0.0001	0.01
AZEL-221-8466	0.0126	0.3872	0.0400	0.001

* From an ANCOVA of log response with log baseline as a covariate, treatment group, investigator, and interaction as factors.

** From a CMH test using modified ridit scores, stratifying an investigator.

*** Excluding Investigator 1275

10 Overview of Safety

10.1 Significant/Potentially Significant Events

One spontaneous post-marketing report of asthma was designated as treatment related by the Danish Council. Schering AG designated the event as non-assessable.

Reviewer's comment:

One spontaneous post-marketing report of asthma was designated as treatment related by the Danish Council. Schering AG designated the event as non-assessable, however, the event was listed as reexposure positive. In U.S. clinical trial AZEL 220-8466, patient (azelaic acid control group) discontinued at visit #3 for exacerbation of asthma which necessitated the use of systemic prednisone and antibiotics. This adverse event was designated as unlikely related to the study medication. Since there was no known re-challenge with this patient as with the Danish Council report, the possibility of exacerbation of asthma should be addressed in the label.

10.1.1 Deaths

No death was reported in any U.S. or non-U.S. study.

10.1.2 Other Significant/ Potentially Significant Events

Pregnancy outcome results are pending for patients 1970-205 and 1970-221 in U.S. trial AZEL-221-8466.

10.2.3 Special Studies

1. Cumulative Irritation Study Number Azel-101-8466

Twenty-One Day Cumulative Irritation Study of Azelaic Acid 20% Cream, Azelaic Acid Vehicle Cream, Two AGN 190168 0.1% Gels, Two AGN 190168 0.05% Gels, and Two AGN 1909168 Vehicle Gels in Healthy Subjects (AZEL-101-8466)

Investigator: Robert W. Shanahan, Ph.D. (ID#1685)
Essex Testing Clinic, Inc.
799 Bloomfield Ave.
Verona, NJ

Consulting Dermatologist: John A. Erriane, M.D. of Jersey City, NJ

Study Formulations:

Azelaic acid 20% cream (8466X)
Azelaic acid vehicle cream (8465X)
AGN 190168 0.1% gel (7997X)
AGN 190168 0.05% gel (8225X)
AGN 190168 vehicle gel (8006X)
AGN 190168 0.1% gel (8606X)
AGN 190168 0.05% gel (8607X)
AGN 190168 vehicle gel (8608X)
Retin-A™ 0.05% cream (Ortho Pharm. Corp.) (8174X)
Retin-A™ 0.1% cream (8175X)
Benzac™ 5 gel (Qwen/Galderma) (8556X)
Sodium lauryl sulfate (0.5%) in water (7967)

Study Objective:

The objective of this study was to determine the cumulative irritation potential of azelaic acid 20% cream and to concentrations (0.1% and 0.05%) of two different AGN 190168 gel formulations, in comparison with that of azelaic acid vehicle cream, Two AGN 190168 vehicle gel formulation, Retin-A™ 0.1 and 0.05% creams, Benzac™ 5 gel, and a standard irritant (sodium lauryl sulfate 0.5% solution) when applied topically to small areas of the skin in healthy subjects.

Study Design:

The study is an investigator-masked, randomized-block of 30 healthy Caucasian subjects, enrolled at one investigational center. Twenty-nine subjects completed the study and were included in the evaluation of cumulative irritation; the participation of one subject was terminated after only one day because of severe headache. The 29 subjects evaluated included 24 females and 5 males, ranging in age from years with a mean age of 41.8 years.

Study Methods:

Subjects meeting the inclusion criteria provided written informed consent and were enrolled in the study. Study formulations were applied to patches, which were affixed to the infrascapular area of each subjects back with hypoallergenic tape (semioclusion). The patches were removed after 24 hours, and the severity of the reactions at each site was evaluated on a six point scale. This sequence of events was repeated for 21 days (excluding Sundays), each formulation being applied to the same site each day. The cumulative irritation scores were tabulated, and based on the investigator provided an interpretation of the potential of each formulation to cause dermal irritation.

Results:

The 21-day mean cumulative scores for each test medication are shown below. The scores are presented in descending order.

<u>Study Formulation (formulation #)</u>	<u>Mean Cumulative Irritation Score (n=29)</u>
AGN 190168 0.1% gel (7997X)	38.34
AGN 190168 0.1% gel (8606X)	37.14
Retin-A 0.1% cream (8175X)	34.29
AGN 190168 0.05% gel (8607X)	34.14
AGN 190168 0.05% gel (8225X)	33.24
Benzac™ 5 gel (8556X)	29.53
Retin-A™ 0.05 cream (8174X)	26.19
Azelaic acid 20% cream (8466X)	20.53
Sodium lauryl sulfate 0.5% solution (7967X)	3.95
Azelaic acid vehicle cream (8465X)	2.43
AGN 190168 vehicle gel (8608X)	2.41
AGN 190168 vehicle gel (8006X)	2.16

No treatment-related adverse experiences were reported. Eleven subjects reported adverse events that were judged by the investigator to have a relationship to the study medications of none, unlikely, or unknown.

The reported adverse events were as follows:

<u>Event</u>	<u>Number</u>
Headaches*	5
Mild Chills	2
Myalgia**	2
UTI	1
Facial Rash	1

* Subject was terminated from the study at Visit 2 due to a severe headache.

** Includes pulled muscles and mildly sore muscles

Statistical Analysis:

Statistical analysis of mean 21-day cumulative irritation scores demonstrated that azelaic acid 20% cream was significantly less irritating ($P < 0.01$) than the AGN 190168 0.1% and 0.05% gel formulations, Retin-A 0.05% and .1% creams, Benzac™ 5 gel, but significantly more irritating than its vehicle formulation, AGN 190168 vehicle formulations, and sodium lauryl sulfate (0.5%) in water.

Sponsor's Conclusion:

On the basis of the cumulative irritation scores observed under semi-occlusive patch test conditions, azelaic acid 20% cream is less irritating than the marketed acne products (Retin-A™ 0.05% and 0.1% creams, and Benzac™ 5 gel) included in this study.

Reviewer's comments:

1. *Comparing the irritation potential of Azelaic acid cream against the irritating potential of a non-approved medication (e.g., AGN 190168 0.1%, 0.05% gel) is not useful information in support of this NDA.*
2. *A relatively non-irritating standard control should have been included.*

2. Sensitization Potential Study Number Azel-102-8466

Study Objective: To determine the contact sensitization potential of Azelaic Acid 20% Cream in comparison with that of its vehicle cream, and AGN 190168 0.1% Gel, AGN 190168 0.05% Gel, two AGN 1909168 vehicle gels and Retin-A™ 0.1% Cream in Healthy Subjects (AZEL-102-8466.)

Investigator: Robert W. Shanahan, Ph.D. (ID#1685)
Essex Testing Clinic, Inc.
799 Bloomfield Ave.
Verona, NJ

Consulting Dermatologist: John A. Erriane, M.D. of Jersey City, NJ

Study Formulations: Azelaic acid 20% cream (8466X)
Azelaic acid vehicle cream (8465X)
AGN 190168 0.1% gel (7997X)
AGN 190168 0.05% gel (8225X)
AGN 190168 vehicle gel (8006X)
AGN 190168 0.1% gel (8606X)
AGN 190168 0.05% gel (8607X)
AGN 190168 vehicle gel (8608X)
Retin-A™ 0.1% cream (8175X)

Study Design: Investigator-masked, randomized-block study.

Study Population: Two hundred three healthy subjects were enrolled into this study at one investigational center. One hundred eighty-one subjects (151 females and 30 males) completed the study. Evaluated subjects ranged in age from _____ years and had a mean age of 42.5 years; 176 of the subjects were Caucasian, three were Hispanic, and two were Asian.

Study Method: Study formulations were applied to semi-occlusive patches that were affixed on the backs of subjects. Subjects removed the patches at home, 24 hours after application. Induction patches were applied over a three-week period. Skin reactions were evaluated on a six-point scale 48 hours after each patch application. After a two-week "rest" period, challenge patches were applied to sites previously unexposed. Patches were removed after 24 hours. Forty-eight hours after application, test sites were examined for any dermal response. A second evaluation was made 48 hours later (96 hours after application). Subjects who had skin reactions to the challenge patches were rechallenged (conducted under a supplemental protocol, AZEL-102-8466S).

Results:

Five subjects were terminated from the study because of adverse events as follows:

<u>Event</u>	<u>Number</u>
URI	2
Fracture	1
Intestinal Virus	1
Rash (tape reaction)	1

Azelaic acid 20% cream and its vehicle induced skin reactions in four subjects. Two of the four returned for rechallenge [negative on rechallenge] and two were unwilling or unable to return, and their data are not included in the conclusions drawn from this study.

Sponsor's Conclusion:

Based on the investigator's judgement and experience, azelaic acid 20% cream does not appear to have contact sensitization potential.

Reviewer's comment:

1. *During both the induction and challenge phases, the patch should be left in place for 48 hours instead of 24 hours.*
2. *Subject who had moderate erythema with edema (2e) at 48 hour challenge site, but did not return for rechallenge should be counted as a contact sensitization.*

3. Phototoxicity Study AZEL-103-8466

Study Objective: To determine the phototoxicity potential of Azelaic acid cream 20%, Azelaic acid vehicle cream, AGN 190168 0.1% gel, AGN 190168 0.05% gel, AGN 190168 vehicle gel, and Retin-A™ 0.0% Cream in healthy subjects.

Study Design: Investigator- masked, randomized-block

Investigator: Robert W. Shanahan, Ph.D. (ID#1685)
Essex Testing Clinic, Inc.
799 Bloomfield Ave.
Verona, NJ

Consulting Dermatologist: John A. Erriane, M.D. of Jersey City , NJ

Study Population and Methods:

Ten healthy, Caucasian, female subjects meeting the inclusion criteria, ranging in age from were enrolled into this study at one investigational center. All subjects completed the study.

Study formulations were applied under semi-occlusive patches to 2cm x 2cm test sites on the inner aspects of the forearm of each subject. Approximately 24 hours after application, subjects returned to the clinic and all patches were removed. After excess test material was wiped off, designed test sites were subjected to non-erythrogenic ultraviolet radiation (UV-A) at a distance of cm from the source (the UV-A dose was approximately Joules/cm² during a minute exposure period). One forearm was irradiated, and the other forearm was used as the non-irradiated control. The non-irradiated (control) test sites were protected from exposure to the UV light. Subjects returned 24 hours later (48 hours after application) to have the test sites evaluated on the six-point scale. Dermal responses were tabulated, and the investigator provided an interpretation of the phototoxicity potential of the test materials.

Results:

There were no skin reactions to the study formulations, nor any evidence of phototoxicity. No treatment-related adverse events were reported.

Sponsor's Conclusion:

Based on the investigator's judgement and experience, azelaic acid 20% cream dose not appear to be a phototoxic agent.

Reviewer's comments:

This protocol did not follow the more customary protocol for phototoxicity testing encountered by the division. Justification for the use of protocol Azel-103-8466 is needed. The following protocol has been recommended by the agency:

This test entails the response of the skin to exposure of the test material and an ultraviolet light source (usually a xenon arc solar simulator). Both the test material and its vehicle are tested.

- 1. The test material is applied to sites on the back along with a duplicate site (opposite side of the back) for each material*
- 2. The materials are covered with patches (occluded)*
- 3. Six hours later the patches from one side of the back are removed and exposed to UV light (UV-A dose: joules/cm² for skin types I-IV)*
- 4. Readings were taken immediately and at 24, 48, and 72 hours after exposure to light.*

4. Phototoxicity Study AZEL-902-SCAG*/7396**

Study Objective: To evaluate the phototoxic potential of azelaic acid 20% cream in healthy volunteers. Twelve normal, healthy subjects were enrolled and completed this study at one investigational site. Data for six males and six females, ages 19 to 57 years, were included in the statistical analysis.

Study Sponsor: Schering AG

Dates of Study: December 2 to December 5, 1986

Study Design: Single-blind

Investigator: Dr. med. A. Kecskés
Main Dept. of Human Pharmacology
Schering Akiengesellschaft
Müllerstraße 170-178
D-1000 Berlin 65, Germany

Reviewer's comments:

This investigator's qualifications are unknown. A CV was requested.

Study Formulation: Azelaic acid 20% cream (SHC 441F***)

Study Methods: The phototoxicity test according to Kaidbey and Kligman was followed.

Results: Erythema scores were 0 for all subjects immediately after irradiation and 24, 48, and 72 hours later.

Sponsor's Conclusions: Schering AG concluded that azelaic acid 20% cream was not phototoxic under the conditions of the study.

* Allergan Herbert assigned study number.

** Schering AG assigned report number.

*** Schering assigned formulation number. SHC 441F is equivalent to Allergan Herbert formulation number 8466X.

Reviewer's comments:

The phototoxicity test according to Kaidbey and Kligman is the protocol generally followed by the division.

5. Photoallergy

Study Protocol # Azel-104-8466

Study Objective:

To determine the photoallergic potential of (1) azelaic acid 20% cream in comparison with that of its vehicle cream, and (2) AGN 19168 0.1% and 0.05% gel formulations in comparison with their vehicle gels and Retin-A™ 0.1% cream.

Study Design:

Investigator-masked, randomized-block

Study Population:

Twenty-eight healthy, Caucasian subjects were enrolled into this study at one investigational center. Twenty-two subjects (19 females and 3 males) ranging in age from 20 to 64 years (mean age of 44 years) completed the study, and their data were included in the evaluation of photoallergy.

Investigator:

Robert W. Shanahan, Ph.D. (ID#1685)
Essex Testing Clinic, Inc.
799 Bloomfield Ave.
Verona, NJ

Consulting Dermatologist:

John A. Erriane, M.D. of Jersey City, NJ

Study Method:

Subjects meeting the inclusion criteria provided written informed consent and were enrolled into the study. Study formulations were applied under semi-occlusive patches to 2 cm x 2 cm test sites on the inner aspects of the forearms of each subject. Approximately 24 hours after application, subjects returned to the clinic and all patches were removed. After excess test material was wiped off, designed test sites were subjected to nonerythrogenic ultraviolet radiation (UV-A) at a distance of cm from the source (the UV-A dose was approximately Joules/cm² during a minute exposure to the UV light. Subjects returned 24 hours later (48 hours after application) to have the test sites evaluated on a six-point scale.

The remainder of the induction phase, rest period, and challenge phase of the protocol was standard except as noted in the reviewer comments.

Results:

The study formulations did not produce any photoallergic reactions. Two subjects had adverse experiences judged by the investigator to be possibly treatment related. One subject experienced moderate erosion of the skin on the tip of a finger and was terminated from the study. The other subject, who completed the study, experienced mild pruritus, dryness, and erythema, also on a finger. The investigator speculated that both subjects may have scratched underneath one of the semi-occlusive patches, thus exposing their fingers to the study formulations.

Sponsor's Conclusion:

Based on the investigator's judgement and experience, azelaic acid 20% cream does not appear to induce photoallergy.

Reviewer's comments:

This protocol did not follow the more customary protocol for photoallergy testing recommended by the division.

1. *Justification for the following is needed:*
 - *not determining the individual minimal erythema dose (MED)*
 - *the use of semi-occlusive patches instead of occlusive patches*
 - *irradiating the test sites with a non-erythrogenic ultraviolet radiation (UV-A) instead of 3 times the MED*

2. *The relationship between the moderate erosion of the finger tip skin of subject and Azelaic acid is needed.*

6. Photoallergy Study AZEL-903-SCAG/7396

Study Objective: To evaluate the photoallergenic potential of azelaic acid 20% cream in healthy volunteers.

Study Sponsor: Schering AG

Dates of Study: November 15, 1986 to December 15, 1986

Study Design: Single-blind; modified Draize test

Study Population: Fifty healthy subjects were enrolled and completed this study at one investigational site. Data for the subjects, 26 females and 24 males, age years (mean age 35 years), were included in the statistical evaluation.

Investigator: Dr. med. A. Kecskés
Main Dept. of Human Pharmacology
Schering Aktiengesellschaft
Müllerstraße 170-178
D-1000 Berlin 65, Germany

Study Formulation: Azelaic acid 20% cream (SHC 441F)

Study Method: The standard protocol was followed except the induction phase use of 2 MEDs instead of 3 MEDs.

Results: Erythema scores were 0 for all subjects immediately after irradiation and 24, 48, and 72 hours later.

Conclusion: Schering AG concluded that azelaic acid 20% cream was not photoallergenic under the conditions of the study.

Reviewer's comments:

1. *This protocol generally followed the procedure acceptable to the Division except for the use of an exposure dose of the two times the MED during the induction phase instead of three times the MED.*
2. *Justification is needed regarding the exposure of twice the MED during the induction phase instead of three times the MED.*
3. *A CV is not available for this investigator.*

10.2.4 Drug-Demographic Interactions

No special investigations of azelaic acid in elderly patients or patients with impaired hepatic or renal function were conducted in view of the normally young age of acne patients and the low systemic burden after topical application of azelaic acid, a normal dietary constituent.

The distribution of the most common drug-related adverse events, burning skin and pruritus were age and sex tabulated with race respectively. In the azelaic acid group, the incidences of drug-related adverse events tended to be higher in patients over 20 years of age. The incidence of burning skin was twofold higher in Caucasian females than males (6% vs. 3%). The incidence of pruritus was also slightly higher in patients >20 years of age (9% vs. 4%).

Gender and race did not appear to influence the incidences of pruritus in any of the treatment groups, however, the results of these analyses should be interpreted with caution because of the small number of patients in each age and gender-by-race stratum.

10.2.5 Drug-Disease Interactions

Because azelaic acid is a topical drug with predominately local effects, no special analyses were performed to evaluate drug-disease interactions.

Claims of allergic sensitization associated with azelaic acid were made more frequently in patients with melasma studies; an allergenic reaction was claimed in 22 (4.7%) out of 472 patients with melasma treated with azelaic acid. Patients in the melasma studies were using a sunscreen cream (Contralum Ultra™) concomitantly throughout treatment that could have contributed to the claimed allergic sensitization.

10.2.6 Drug-Drug Interactions

Because azelaic acid is a topical drug with predominately local side effects, no special analyses were performed to evaluate drug-drug interactions. Patients were prohibited from concomitant use of other anti-acne medications, either systemic or topical during the clinical trials. In addition, in the pivotal trials, there was also a "wash-out period" immediately preceding study entry. Interactions of azelaic acid with other topical medications for acne are not known, but an incompatibly appears unlikely since azelaic acid chemically is a rather inert substance. Potentiation or reduction in the activity of other systemic drugs has not been reported and appears unlikely in view of the low systemic absorption of azelaic acid. Since 1989, when azelaic acid (Skinoren™) was first marketed in Europe, there have been no spontaneous reports of drug interactions.

Reviewer's comments:

Patients were restricted from concomitant use of other acne medications during the clinical trial, however, in a clinical setting many acne patients are concomitantly treated with other medications both systemic and topical. There were two spontaneous reports of "burning sensation" in which the patients were also on other acne preparations (benzoyl peroxide), however, there was no way of assessing the connection with Skinoren™. This symptom of irritation was also observed in the clinical program, therefore there is the possibility of potentiation of irritation with the use of concomitant irritants.

10.2.7 Withdrawal Phenomena

Discontinuation of azelaic acid 20% cream was not associated with any known, relevant withdrawal effects; notably, to date, there have been no reports of acne flare-up following discontinuation of azelaic acid 20% cream.

11. Labeling Review

Wording to be deleted are shown by ~~strikeout lines~~.

Wording to be added are shown by shading.

LABELING

PACKAGE INSERT DRAFT No.14

1994

AZELEX™

(azelaic acid) 20% Cream

ALLERGAN Herbert

For Dermatologic Use Only**Not for Ophthalmic Use**

DESCRIPTION: AZELEX™ (azelaic acid) 20% Cream contains azelaic acid, a naturally occurring saturated dicarboxylic acid found in cereal grains.

Structural Formula: $\text{HOOC}-(\text{CH}_2)_7-\text{COOH}$

Chemical Name: 1,7-heptanedicarboxylic acid.

Empirical Formula: $\text{C}_9\text{H}_{16}\text{O}_4$

Molecular Weight: 188.22

Active Ingredient: Each gram of AZELEX Cream contains azelaic acid .0.2 gm (20% w/w).

Inactive Ingredients: cetearyl octanoate, glycerol, glyceryl stearate and cetearyl alcohol and cetyl palmitate and cocoglycerides, PEG-5 glyceryl stearate, propylene glycol and purified water. Benzoic acid is present as a preservative.

CLINICAL PHARMACOLOGY:

The following *in vitro* data are available, but their clinical significance is unknown. Azelaic acid has been shown to possess bacteriostatic and/or bactericidal activity against a variety of aerobic microorganisms which includes various species of *Staphylococcus*, including *S. epidermidis*, as well as *Proteus*, *Escherichia*, *Pseudomonas*, *Pityrosporum ovale*, *Candida*, and the anaerobe *Propionibacterium acnes*.

Reviewer's Comments: Subject to Microbiology Review.

In vehicle-controlled clinical studies, AZELEX™ Cream demonstrated efficacy in the treatment of patients with acne vulgaris. In an active-controlled study, topical AZELEX™ demonstrated efficacy comparable to topical 2% erythromycin ointment. However, local adverse events including pruritus, erythema, and burning were more frequently observed in the azelaic acid group (26.6%) than in the erythromycin group (11.2%).

Pharmacokinetics:

Following a single application of AZELEX Cream 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). After a single topical application of AZELEX™ in humans, bacteriostatic concentrations are achieved in the follicles. Negligible cutaneous metabolism occurs after topical application. Only 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 and 12 hours after oral and topical dosing respectively, indicating percutaneous absorption rate-limited kinetics. Humans are constantly exposed to azelaic acid via dietary and endogenous sources. Azelaic acid is a natural constituent in whole grain cereals and can be formed from longer chain dicarboxylic acids, metabolism of oleic acid, and β -oxidation of monocarboxylic acids.

Endogenous plasma concentration (ng/mL) and daily urinary excretion of azelaic acid (4 to 28 mg) are highly dependent on dietary intake. After topical treatment with AZELEX in humans, plasma concentration and urinary excretion of azelaic acid are well within normal fluctuations of the baseline dietary levels.

INDICATIONS AND USAGE:

AZELEX™ Cream is indicated for the topical treatment of mild to moderate inflammatory acne vulgaris.

CONTRAINDICATIONS:

AZELEX™ Cream is contraindicated in those individuals who have shown hypersensitivity to any of its components.

WARNINGS:

1. There have been reports of hypopigmentation after use of AZELEX Cream. The frequency of this adverse event is not known. AZELEX Cream has not been well studied in people of color. The use of this product requires frequent monitoring for any signs of hypopigmentation.
2. AZELEX™ Cream is for Dermatologic use only and not for ophthalmic use.

PRECAUTIONS:

General: If sensitivity or severe irritation develop with the use of AZELEX, treatment should be discontinued and appropriate therapy instituted.

Information for patients: The patient should be told:

1. To carefully observe for any changes in pigmentation. Azelex treatment should be discontinued at the first sign of any change in skin color.
2. To use AZELEX™ Cream for the full prescribed treatment period
3. To avoid the use of occlusive dressings or wrappings.
4. To keep AZELEX™ away from the mouth, eyes and other mucous membranes. If it does come in contact with the eyes, they should wash their eyes with large amounts of cool water and consult a physician if eye irritation persists.
5. Due in part to the low pH of azelaic acid, temporary skin irritation may occur when AZELEX Cream is applied to broken or inflamed skin, usually at the start of treatment. However, this irritation commonly subsides if treatment is continued. If the skin irritation continues, AZELEX should be applied only once-a-day, or the treatment should be temporarily stopped, until the irritation has subsided. If troublesome irritation persists, use should be discontinued, and the patient should consult a physician. (See ADVERSE REACTIONS).

Carcinogenesis, mutagenesis impairment of fertility:

battery of *in vitro* and animal studies performed to assess mutagenic activity did not demonstrate any mutagenic effect. Animal studies have shown no ill effects related to fertility.

Pregnancy:**Pregnancy Category B.**

Embryotoxic effects were observed in Segment I and Segment II oral studies with rats receiving 2500 mg/kg/day. 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.

Teratogenic Effects:**Nursing Mothers:**

Equilibrium dialysis was used to assess human milk partitioning *in vitro*. At a concentration of 25 ug/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.

Pediatric Use: Safety and effectiveness in children under 12 years of age have not been established.

ADVERSE REACTIONS:

During U.S. clinical trials with AZELEX™ Cream, adverse reactions were generally mild and transient in nature. The most common adverse reactions occurring in approximately 1-5% of patients were pruritus burning stinging and tingling

Other adverse reactions such as exacerbation of asthma, erythema, dryness, rash, peeling, irritation, dermatitis, and contact dermatitis were reported in less than 1% of subjects.

The following additional adverse experiences have been reported with other azelaic acid formulations: shock (tachycardia hypotension), extrasystoles, vitiloid depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris) and recurrent exacerbation of herpes labialis.

DOSAGE AND ADMINISTRATION:

After the skin is thoroughly washed and patted dry, a thin film of AZELEX™ Cream should be gently but thoroughly massaged into the affected areas twice daily, in the morning and evening. The hands should be washed following application. The duration of use of AZELEX™ can vary from person to person and depends on the severity of the acne. In general, an improvement of the condition becomes apparent within 12 weeks.

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

Revised February 1994

1994 Allergan, Inc

Printed in U.S.A.

Herbert Skin Care Division of ALLERGAN, INC.
Irvine, California 92715, U.S.A.

12. Conclusions

Clinical studies have found azelaic acid cream to be more effective in the treatment of mild to moderate acne vulgaris than its vehicle cream in two well-controlled clinical trials. There was no evidence of systemic toxicity found in patients participating in the efficacy trials. There is also supporting foreign data available. This product has been marketed since approval in Europe in 1989. Dermatologic side effects are mainly mild to moderate burning, pruritus, erythema and scaling. Hematology, blood chemistry, and urinalysis results showed no clinically significant drug effects, and plasma concentrations of azelaic acid showed no significant change from pre-to post-treatment.

13. Recommendations

From the clinical standpoint this drug is approvable (pending statistical review) with the following recommendations:

1. Labeling changes as noted in Section 11 should be made.
2. It is recommended that a "Phase 4" commitment to investigate hypopigmentation as a possible adverse event should be obtained from the sponsor.
3. Pregnancy outcome results for patient: _____ from study AZEL-221-8466, who were exposed to the active drug need to be reported.

Recommendations

20-428
 AZELEX 20% (NDA ~~20-482~~) as submitted is recommended for approval provided the labeling is revised as identified in this review.

cc:

~~HFD-540~~

HFD-340

HFD-540/CSO/Chapman

HFD-540/CHEM/Mokhtari-Rejali

HFD-520/MICRO/King

HFD-540/PHARM/Mainigi

HFD-540/MO/Vaughan

1/12/95

025
Brenda Vaughan, M.D.
 Brenda Vaughan, M.D.
 Medical Officer, Dermatology

Jan 11/195

AUG 10 1995

Medical Officer's Review 20-428
Amendment

NDA 20-428
M.O. Review #2

Submission Date: 08/03/95
Review Date: 08/04/95

Drug Name:

Generic Name:

Azelaic acid cream

Proposed Trade Name:

AZELEX™ 20% Cream

Chemical Name:

1;7-heptanedicarboxylic acid

Sponsor:

Allergan Herbert Division of Allergan Inc
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92713-9534

Pharmacologic Category:

Topical anti-acne (antimicrobial)

Proposed Indication:

Acne Vulgaris

Dosage Form

and Route of Administration:

Cream, topical

NDA Drug Classification:

1 S

Related Drugs:

None

Related Reviews:

IND
DMF
DMF

Materials Reviewed:

Volumes 1 and 2

Chemistry/Manufacturing Controls: See Chemistry Review

Animal Pharmacology/Toxicology: See Pharm/Tox Review

Labeling Review

Reviewer's comments:

*The following is the labeling submitted by the company.
Reviewer recommended deletions are noted by ~~strikeout lines~~
and additions by shading within the review.*

AZELEX™ LABELING
PACKAGE INSERT REPROPOSAL Draft No. 16

August 4, 1995

AZELEX™
(azelaic acid cream) 20%

ALLERGAN Herbert

For Dermatologic Use Only
Not for Ophthalmic Use

DESCRIPTION:

AZELEX™ (azelaic acid cream) 20% contains azelaic acid, a naturally occurring saturated dicarboxylic acid found in cereal grains.

Structural Formula: $\text{HOOC}-(\text{CH}_2)_7-\text{COOH}$
Chemical Name: 1,7-heptanedicarboxylic acid
Empirical Formula: $\text{C}_9\text{H}_{16}\text{O}_4$
Molecular Weight: 188.22

Active Ingredient: Each gram of AZELEX™ contains azelaic acid.....0.2 gm (20% w/w).

Inactive Ingredients: cetearyl octanoate, glycerol, glyceryl stearate and cetearyl alcohol and cetyl palmitate and cocoglycerides, PEG-5 glyceryl stearate, propylene glycol and purified water. Benzoic acid is present as a preservative.

CLINICAL PHARMACOLOGY:

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 anti-comedonal effect of azelaic acid may also contribute to its clinical activity. Electron microscopic and immunohisto-chemical 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.

In vehicle-controlled clinical studies, AZELEX™ demonstrated efficacy in the treatment of patients with acne vulgaris.

Pharmacokinetics: 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 and 12 hours after oral and topical dosing respectively, indicating percutaneous absorption rate-limited kinetics.

Humans are constantly exposed to azelaic acid via dietary and endogenous sources. Azelaic acid is a natural constituent in whole grain cereals and can be formed 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 of azelaic acid (4 to 28 mg) are highly dependent on dietary intake. After topical treatment with AZELEX™ in humans, plasma concentration and urinary excretion of azelaic acid are well within normal fluctuations of the baseline dietary levels.

INDICATIONS AND USAGE:

AZELEX™ is indicated for the topical treatment of mild to moderate inflammatory acne vulgaris.

CONTRAINDICATIONS:

AZELEX™ is contraindicated in those individuals who have shown hypersensitivity to any of its components.

WARNINGS:

AZELEX™ is for dermatologic use only and not for ophthalmic use.

There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexions, these patients should be monitored for early signs of hypopigmentation.

PRECAUTIONS:

General: If sensitivity or severe irritation develop with the use of AZELEX™, treatment should be discontinued and appropriate therapy instituted.

Information for patients:

Patients should be told:

1. To use AZELEX™ for the full prescribed treatment period.
2. To avoid the use of occlusive dressings or wrappings.
3. To keep AZELEX™ away from the mouth, eyes and other mucous membranes. If it does come in contact with the eyes, they should wash their eyes with large amounts of water and consult a physician if eye irritation persists.
4. Patients with dark complexions should consult their physician if an abnormal change in skin color is noticed.
5. Due in part to the low pH of azelaic acid, temporary skin irritation (pruritus, burning, or stinging) may occur when AZELEX™ is applied to broken or inflamed skin, usually at the start of treatment. However, this irritation commonly subsides if treatment is continued. If it continues, AZELEX™ should be applied only once-a-day, or the treatment should be stopped until these effects have subsided. If troublesome irritation persists, use should be discontinued, and patients should consult their physician. (See ADVERSE REACTIONS).

Carcinogenesis, mutagenesis, impairment of fertility: A battery of *in vitro* and animal studies performed to assess mutagenic activity did not demonstrate any mutagenic effect. Animal studies have shown no ill effects related to fertility.

Pregnancy: Teratogenic Effects: Pregnancy Category B.

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.

Nursing Mothers:

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.

Pediatric Use:

Safety and effectiveness in pediatric patients under 12 years of age have not been established.

ADVERSE REACTIONS:

During U.S. clinical trials with AZELEX™, adverse reactions were generally mild and transient in nature. The most common adverse reactions occurring in approximately 1-5% of patients were pruritus, burning, stinging and tingling. Other adverse reactions such as erythema, dryness, rash, peeling, irritation, dermatitis, and contact dermatitis were reported in less than 1% of subjects. There is the potential for experiencing allergic reactions with use of AZELEX™.

In patients using azelaic acid formulations, the following additional adverse experiences have been reported rarely: worsening of asthma, vitiligo depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris), and recurrent exacerbation of herpes labialis.

DOSAGE AND ADMINISTRATION:

After the skin is thoroughly washed and patted dry, a thin film of AZELEX™ should be gently but thoroughly massaged into the affected areas twice daily, in the morning and evening. The hands should be washed following application. The duration of use of AZELEX™ can vary from person to person and depends on the severity of the acne. Improvement of the condition occurs in the majority of patients with inflammatory lesions within four weeks.

HOW SUPPLIED:

AZELEX™ is supplied in collapsible tubes in a 30 gm size:
30 g - NDC 0023-XXXX-XX

Note: Protect from freezing. Store below 30° C (86° F).

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

1995

ALLERGAN Herbert
Skin Care Division of ALLERGAN, INC.
Irvine, California 92715, U.S.A.

©1995 Allergan, Inc.
Printed in U.S.A.
(PM#)(cc code)

Recommendations:

NDA 20-428, Azelex is recommended for approval.

Brenda Vaughan, MD 2/4/95
Brenda Vaughan, M.D.
Medical Officer, Dermatology

- cc: HFD-540
 - HFD-340
 - HFD-540/Derm File
 - HFD-540/CSO/Chapman
 - HFD-540/CHEM/Mokhtari-Rejali
 - HFD-540/MICRO/King
 - HFD-540/PHARM/Mainigi
 - HFD-540/MO/Vaughan
 - HFD-540/SMO/Chambers *INC 5/4/95*
- 92 8/10/95*

Medical Officer's Review
Amendment

NDA 20-428
M.O. Review #3

Submission Date: 3/09/95
Initial Review Date: 5/30/95
Addendum Review Date: 9/8/95

Drug Name:

Generic Name:
Proposed Trade Name:
Chemical Name:

Azelaic acid
AZELEX™ 20% Cream
1,7-heptanedicarboxylic acid

Sponsor:

Allergan Herbert Division of Allergan Inc
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92713-9534

Pharmacologic Category:

Topical anti-acne (antimicrobial)

Proposed Indication:

Acne Vulgaris

Dosage Form

and Route of Administration:

Cream, topical

NDA Drug Classification:

1 S

Related Drugs:

None

Related Reviews:

IND
DMF
DMF

Materials Reviewed:

Volumes 1 and 2

Chemistry/Manufacturing Controls: See Chemistry Review

Animal Pharmacology/Toxicology: See Pharm/Tox Review

Submitted: Response to Approvable letter

Safety Update:

Applicant's Response:

Currently, Allergan has no new safety information regarding AZELEX™ from clinical studies, animal studies, or other sources which would reasonably affect the statement of contraindications, warnings, precautions, and adverse events in the draft labeling. No death or serious adverse event was reported for any U.S. or non-U.S. study involving AZELEX™. Medical narratives of patients terminated due to lack of efficacy or adverse event(s) were provided in the NDA. Allergan has no new information concerning such patients.

Reviewer's comment: *Acceptable. No additional changes to labeling are indicated.*

Brenda Vaughan, M.D. 9/8/95
Brenda Vaughan, M.D.
Medical Officer, Dermatology

- cc: HFD-540
- HFD-340
- HFD-540/Derm File
- HFD-540/CSO/Chapman
- HFD-540/CHEM/Mokhtari-Rejali
- HFD-540/MICRO/King
- HFD-540/PHARM/Mainigi
- HFD-540/MO/Vaughan
- HFD-540/SMO/Chambers *mac 9/8/95*
-AMK 9/18/95

AZELEX™
(azelaic acid cream) 20%

ALLERGAN Herbert

For Dermatologic Use Only
Not for Ophthalmic Use

DESCRIPTION:

AZELEX™ (azelaic acid cream) 20% contains azelaic acid, a naturally occurring saturated dicarboxylic acid found in cereal grains.

Structural Formula: $\text{HOOC}-(\text{CH}_2)_7-\text{COOH}$
Chemical Name: 1,7-heptanedicarboxylic acid
Empirical Formula: $\text{C}_9\text{H}_{16}\text{O}_4$
Molecular Weight: 188.22

Active Ingredient: Each gram of AZELEX™ contains azelaic acid.....0.2 gm (20% w/w).

Inactive Ingredients: cetearyl octanoate, glycerol, glyceryl stearate and cetearyl alcohol and cetyl palmitate and cocoglycerides, PEG-5 glyceryl stearate, propylene glycol and purified water. Benzoic acid is present as a preservative.

CLINICAL PHARMACOLOGY:

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 anti-comedonal effect of azelaic acid may also contribute to its clinical activity. Electron microscopic and immunohisto-chemical 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.

In vehicle-controlled clinical studies, AZELEX™ demonstrated efficacy in the treatment of patients with acne vulgaris

Pharmacokinetics: 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 and 12 hours after oral and topical dosing respectively, indicating percutaneous absorption rate-limited kinetics.

Humans are constantly exposed to azelaic acid via dietary and endogenous sources. Azelaic acid is a natural constituent in whole grain cereals and can be formed 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 of azelaic acid (4 to 28 mg) are highly dependent on dietary intake. After topical treatment with AZELEX™ in humans, plasma concentration and urinary excretion of azelaic acid are well within normal fluctuations of the baseline dietary levels.

INDICATIONS AND USAGE:

AZELEX™ is indicated for the topical treatment of mild to moderate inflammatory acne vulgaris.

CONTRAINDICATIONS:

AZELEX™ is contraindicated in those individuals who have shown hypersensitivity to any of its components.

WARNINGS:

AZELEX™ is for dermatologic use only and not for ophthalmic use.

There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexions, these patients should be monitored for early signs of hypopigmentation.

PRECAUTIONS:

General: If sensitivity or severe irritation develop with the use of AZELEX™, treatment should be discontinued and appropriate therapy instituted.

4

Information for patients: Patients should be told:

1. To use AZELEX™ for the full prescribed treatment period.
2. To avoid the use of occlusive dressings or wrappings.
3. To keep AZELEX™ away from the mouth, eyes and other mucous membranes. If it does come in contact with the eyes, they should wash their eyes with large amounts of water and consult a physician if eye irritation persists.
4. Patients with dark complexions should consult their physician if an abnormal change in skin color is noticed.
5. Due in part to the low pH of azelaic acid, temporary skin irritation (pruritus, burning, or stinging) may occur when AZELEX™ is applied to broken or inflamed skin, usually at the start of treatment. However, this irritation commonly subsides if treatment is continued. If it continues, AZELEX™ should be applied only once-a-day, or the treatment should be stopped until these effects have subsided. If troublesome irritation persists, use should be discontinued, and patients should consult their physician. (See ADVERSE REACTIONS).

Carcinogenesis, mutagenesis, impairment of fertility: Azelaic acid is a human dietary component of a simple molecular structure which does not suggest carcinogenic potential, and it does not belong to a class of drugs for which there is concern about carcinogenicity. Therefore, animal studies to evaluate carcinogenic potential with Azelex™ Cream were not deemed necessary. 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. Animal studies have shown no adverse effects on fertility.

Pregnancy: Teratogenic Effects: Pregnancy Category B.

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.

Nursing Mothers:

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.

Pediatric Use:

Safety and effectiveness in pediatric patients under 12 years of age have not been established.

ADVERSE REACTIONS:

During U.S. clinical trials with AZELEX™, adverse reactions were generally mild and transient in nature. The most common adverse reactions occurring in approximately 1-5% of patients were pruritus, burning, stinging and tingling. Other adverse reactions such as erythema, dryness, rash, peeling, irritation, dermatitis, and contact dermatitis were reported in less than 1% of subjects. There is the potential for experiencing allergic reactions with use of AZELEX™.

In patients using azelaic acid formulations, the following additional adverse experiences have been reported rarely: worsening of asthma, vitiligo depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris), and exacerbation of recurrent herpes labialis.

DOSAGE AND ADMINISTRATION:

After the skin is thoroughly washed and patted dry, a thin film of AZELEX™ should be gently but thoroughly massaged into the affected areas twice daily, in the morning and evening. The hands should be washed following application. The duration of use of AZELEX™ can vary from person to person and depends on the severity of the acne. Improvement of the condition occurs in the majority of patients with inflammatory lesions within four weeks.

HOW SUPPLIED:

AZELEX™ is supplied in collapsible tubes in a 30 gm size:
30 g - NDC 0023-8694-30

Note: Protect from freezing. Store between 15°- 30° C (59°- 86° F).

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

August 1995

ALLERGAN Herbert
Skin Care Division of **ALLERGAN, INC.**
Irvine, California 92715, U.S.A

©1995 Allergan, Inc.
Printed in U.S.A.
(PM#)(copy code)

Recommendations:

NDA 20-428, Azelex is recommended for approval.

Brenda Vaughan, M.D. 9/6/95
Brenda Vaughan, M.D.
Medical Officer, Dermatology

cc: HFD-540
HFD-340
HFD-540/Derm File
HFD-540/CSO/Chapman
HFD-540/CHEM/Mokhtari-Rejali
HFD-540/MICRO/King
HFD-540/PHARM/Mainigi
HFD-540/MO/Vaughan
HFD-540/SMO/Chambers *MAC 9/6/95*

JW 9/6/95

AUG 24 1995

**Medical Officer's Review
Amendment**

**NDA 20-428
M.O. Review #1**

**Submission Date: 3/09/95
Review Date: 5/30/95**

Drug Name:

Generic Name:

Azelaic acid

Proposed Trade Name:

AZELEX™ 20% Cream

Chemical Name:

1,7-heptanedicarboxylic acid

Sponsor:

Allergan Herbert Division of Allergan Inc
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92713-9534

Pharmacologic Category:

Topical anti-acne (antimicrobial)

Proposed Indication:

Acne Vulgaris

Dosage Form

and Route of Administration:

Cream, topical

NDA Drug Classification:

1 S

Related Drugs:

None

Related Reviews:

IND
DMF
DMF

Materials Reviewed:

Volumes 1 and 2

Chemistry/Manufacturing Controls: See Chemistry Review

Animal Pharmacology/Toxicology: See Pharm/Tox Review

Submitted: Response to Approvable letter

1. Proposed Phase 4 Study
2. Follow-up of patients who became pregnant during therapy
3. Revised labeling

1. Phase 4 Study Commitment

Allergan commits to conducting a Phase 4 study to examine the incidence of hypopigmentation associated with AZELEX™ use. Further, to ensure that the study design fully addresses FDA concerns, Allergan commits to submitting the study protocol for FDA comment prior to initiating the study.

Reviewer's comment: *Acceptable*

2. Pregnancy Outcome Results for Patients 1970-205 and 1970-221 from Study AZEL-221-8466, Who Were Exposed to Active Drug

Patient _____ had no complications during pregnancy or delivery and now has a healthy two-year-old girl.

Patient _____, despite repeated attempts, could not be reached to provide additional information regarding her pregnancy. The investigator's office believes that the patient is reluctant to respond due to her marital status at the time of pregnancy.

Reviewer's comment: *Noted.*

3. Labeling Review

Reviewer's comments: *The following is the labeling submitted by the company. Reviewer recommended deletions are noted by ~~strikeout lines~~ and additions by shading within the review.*

AZELEX™ LABELING
PACKAGE INSERT REPROPOSAL Draft No. 15

March 8, 1995

NDA 20-428 3 of 3

AZELEX™
(azelaic acid cream) 20%

ALLERGAN Herbert

For Dermatologic Use Only
Not for Ophthalmic Use

DESCRIPTION:

AZELEX™ (azelaic acid cream) 20% contains azelaic acid, a naturally occurring saturated dicarboxylic acid found in cereal grains.

Structural Formula: $\text{HOOC}-(\text{CH}_2)_5-\text{COOH}$
Chemical Name: 1,7-heptanedicarboxylic acid
Empirical Formula: $\text{C}_7\text{H}_{12}\text{O}_4$
Molecular Weight: 188.22

Active Ingredient: Each gram of AZELEX™ contains azelaic acid.....0.2 gm (20% w/w).
Inactive Ingredients: cetearyl octanoate, glycerol, glyceryl stearate and cetearyl alcohol and cetyl palmitate and cocoglycerides, PEG-5 glyceryl stearate, propylene glycol and purified water. Benzoic acid is present as a preservative.

CLINICAL PHARMACOLOGY:

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 anti-comedonal effect of azelaic acid may also contribute to its clinical activity. Electron microscopic and immunohisto-chemical 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.

In vehicle-controlled clinical studies, AZELEX™ demonstrated efficacy in the treatment of patients with acne vulgaris. In active-controlled studies, topical AZELEX™ demonstrated efficacy comparable to topical 2% erythromycin ointment. The frequency of local adverse events was lower with erythromycin ointment than with azelaic acid cream.

Reviewer's comments: *Study AZEL-920-SCAG/7234, comparing azelaic acid 20% cream vs. tretinoin 0.05% cream was a single-blind, randomized, parallel group study with potentially biased conclusions. As stated in volume 1.55, page 167; the controlled trial was a single blind study, "since due to the yellow color of the tretinoin cream the investigator could distinguish between medications."*

Paragraph #2, p 4, should be modified to reflect the fact that this was a single blind trial. MK.

Pharmacokinetics: 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 and 12 hours after oral and topical dosing respectively, indicating percentage absorption rate-limited kinetics.

Humans are constantly exposed to azelaic acid via dietary and endogenous sources. Azelaic acid is a natural constituent in whole grain cereals and can be formed 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 of azelaic acid (4 to 28 mg) are highly dependent on dietary intake. After topical treatment with AZELEX™ in humans, plasma concentration and urinary excretion of azelaic acid are well within normal fluctuations of the baseline dietary levels.

INDICATIONS AND USAGE:

AZELEX™ is indicated for the topical treatment of mild to moderate inflammatory acne vulgaris.

CONTRAINDICATIONS:

AZELEX™ is contraindicated in those individuals who have shown hypersensitivity to any of its components.

WARNINGS:

AZELEX™ is for dermatologic use only and not for ophthalmic use.

There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexions, these patients may require monitoring for signs of hypopigmentation.

PRECAUTIONS:

General: If sensitivity or severe irritation develop with the use of AZELEX™, treatment should be discontinued and appropriate therapy instituted.

Information for patients: The patient should be told:

1. To use AZELEX™ for the full prescribed treatment period.
2. To avoid the use of occlusive dressings or wrappings.
3. To keep AZELEX™ away from the mouth, eyes and other mucous membranes. If it does come in contact with the eyes, they should wash their eyes with large amounts of cool water and consult a physician if eye irritation persists.
4. Patients with dark complexions should consult his/her physician if an abnormal change in skin color is noticed.
5. Due in part to the low pH of azelaic acid, temporary skin irritation (pruritus, burning, or stinging) may occur when AZELEX™ is applied to broken or inflamed skin, usually at the start of treatment. However, this irritation commonly subsides if treatment is continued. If it continues, AZELEX™ should be applied only once-a-day, or the treatment should be stopped until these effects have subsided. If troublesome irritation persists, use should be discontinued, and the patient should consult his/her physician. (See ADVERSE REACTIONS).

Carcinogenesis, mutagenesis, impairment of fertility: A battery of *in vitro* and animal studies performed to assess mutagenic activity did not demonstrate any mutagenic effect. Animal studies have shown no ill effects related to fertility.

Pregnancy: Teratogenic Effects: Pregnancy Category B :

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.

Nursing Mothers:

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 Azelac™ is administered to a nursing mother.

Pediatric Use:

Safety and effectiveness in pediatric patients under 12 years of age have not been established.

ADVERSE REACTIONS:

During U.S. clinical trials with AZELEX™, adverse reactions were generally mild and transient in nature. The most common adverse reactions occurring in approximately 1-5% of patients were pruritus, burning, stinging and tingling. Other adverse reactions such as erythema, dryness, rash, peeling, irritation, dermatitis, and contact dermatitis were reported in less than 1% of subjects.

There is the potential for experiencing allergic reactions with use of AZELEX™.

The following additional adverse experiences have been reported rarely in patients using azelaic acid formulations: allergic contact dermatitis, worsening of asthma, vitiligo depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris), and recurrent exacerbation of herpes labialis.

DOSAGE AND ADMINISTRATION:

After the skin is thoroughly washed and patted dry, a thin film of AZELEX™ should be gently but thoroughly massaged into the affected areas twice daily, in the morning and evening. The hands should be washed following application. The duration of use of AZELEX™ can vary from person to person and depends on the severity of the acne. Improvement of the condition occurs in the majority of patients with inflammatory lesions within four weeks.

HOW SUPPLIED:

AZELEX™ is supplied in collapsible tubes in a 30 gm size:
30 g - NDC 0023-XXXX-XX

Note: Protect from freezing. Store below 30° C (86° F).

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

1995

ALLERGAN Herbert
Skin Care Division of **ALLERGAN, INC.**
Irvine, California 92715, U.S.A.

©1995 Allergan, Inc.
Printed in U.S.A.
(PM#)(copy code)

Recommendations:

NDA 20-482, Azelex is recommended for approval with the labeling revisions identified in this review.

Brenda Vaughan, M.D. 7/25/95
Brenda Vaughan, M.D.
Medical Officer, Dermatology

cc:

~~_____~~

- HFD-340
- HFD-540/Derm File
- HFD-540/CSO/Chapman
- HFD-540/CHEM/Mokhtari-Rejali
- HFD-540/MICRO/King
- HFD-540/PHARM/Mainigi
- HFD-540/MO/Vaughan
- HFD-540/SMO/Chambers

MSK 7/25/95
Mainigi 8/24/95

Umicore

JUL 5 1994

1

Division of Anti-Infective Drug Products (HFD-520)
Microbiology and Drug Control Review Notes #1
Consult (HFD-540)

NDA # 20-428

DATE COMPLETED: 4 May, 1994

APPLICANT(NDA):

Allergan
Dupont Drive
P.O. Box 19534
Irvine, CA 92713-9534

CHEM/THER. TYPE:

Anti-acne preparation

SUBMISSION REVIEWED: Original NDA volumes 1.4-5, 1.30-31, 1.39-40, 1.45, and 1.67; draft package insert No. 14 (2/23/94)

PROVIDING FOR: clinical and microbiological studies

PRODUCT NAMES(S):

Proprietary: Azelex

Non-Proprietary/USAN: azelaic acid 20% cream

Compendia: azelaic acid

CHEMICAL NAME, STRUCTURAL FORMULAS, MOLECULAR FORMULA, MOL. WT.

1,7-heptanedicarboxylic acid; $\text{HOOC}-(\text{CH}_2)_7-\text{COOH}$;
 $\text{C}_9\text{H}_{16}\text{O}_4$; 188.22

DOSAGE FORMS(S) and STRENGTHS:

20% Cream

20% Cream

ROUTE(S) OF ADMINISTRATION:

Dermatological

PHARMACOLOGICAL CATEGORY:

Antiacne

INITIAL SUBMISSION:

Received by CDER: Filing date

Received by Reviewer: Filing date

Review Completed: 4 May, 1994

AMENDMENT(S)

Received by CDER: N/A

Received by Reviewer:

Review Completed:

RELATED DOCUMENTS: None provided

REMARK(S):

This submission provides the clinical and microbiological evidence designed to support the proposed claims for this product in the clinical and microbiological portions of the product package insert. The microbiological claims are included in the Clinical Pharmacology portion of the package insert. The package insert will need major revisions as noted below, based on the *clinical and microbiological data in the volumes of the submission referenced above*. Other microbiological data included in the submission relate to the preservatives effectiveness test required for the CMC portion of the submission; these data appear to confirm the adequacy of the preservatives effectiveness.

CONCLUSIONS and/or RECOMMENDATIONS:

The application is approvable, except for needed changes in the Microbial Limits Test and the **Clinical Pharmacology** section of the package insert.

- 1- The Microbial Limits Test standard should be reduced to 100 organisms per gram instead of 500 organisms per gram.

- 2- From the microbiological perspective, the first three paragraphs of the **Clinical Pharmacology:** section of the draft package insert should be deleted and the following paragraph should be substituted:

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

James R. King 6/30/94
 James R. King
 Microbiologist, HFD-520

cc: Orig. NDA # 20-428

HFD-473

HFD-635

HFD-502

HFD-520

HFD-520/Micro/King

HFD-540/MO/Vaughan

HFD-540/Pharm/Mainigi

HFD-540/Chem/DeCamp

HFD-540/CSO/Chapman

HFD-540/WILKIN

HFD-520/L :pDir/LGavrilovich

HFD-520/SMicro/ASheldon

7/30/94

Rev. JRK 6/30/94

cc 7/2/94

4

Table of Contents

INTRODUCTION

6

PRECLINICAL EFFICACY

6

In vitro

6

Mechanism(s) of Action.

6

Antimicrobial Spectrum of Activity

7

Mechanism(s) of Resistance Studies

7

In vivo

8

Pharmacokinetics/Bioavailability

(Human and animal)

8

Animal Prophylactic and Therapeutic Studies

8

CLINICAL EFFICACY

8

Clinical Microbiology

8

Package Insert

9

Isolates Approved

9

Interpretative Criteria Established

9

INTRODUCTION

6

PRECLINICAL EFFICACY

6

In vitro

6

Mechanism(s) of Action.

6

Antimicrobial Spectrum of Activity

	5
	7
Mechanism(s) of Resistance Studies	7
In vivo	8
Pharmacokinetics/Bioavailability <u>(Human and animal)</u>	8
Animal Prophylactic and Therapeutic Studies	8
CLINICAL EFFICACY	8
Clinical Microbiology	8
Package Insert	9
Isolates Approved	9
Interpretative Criteria Established	9

Microbiological Review Notes:

INTRODUCTION

The applicant proposes to market an azelaic acid cream for the treatment of acne. The proposed underlying rationale for the efficacy of azelaic acid is that the drug modifies the physiology of both the host and the resident flora of the skin structures to truncate the formation of acne lesions or to prevent their formation. The rationale is plausible, but it is somewhat flawed because there is no completely confirmed microbial etiology for acne, although there is a strong association with Propionibacterium acnes. Other organisms seem to be peripherally associated with acne, but their presence in lesions is not as predictable as for Propionibacterium acnes.

The microbial role in acne lesions is purported to be somewhat peripheral. The microbes, presumably Propionibacterium acnes, seem to produce free fatty acids which mimic the activity of a typical exotoxin. The free fatty acids seem to produce an irritation in a forming comedone, which then may become infected with another organism, typically reported as Staphylococcus epidermidis. The toxin may be free fatty acids generated in the comedone by the P. acnes as noted above. The inhibition of free fatty acid formation has been frequently used as a secondary clinical measure of the effectiveness of antiacne medication.

The clinical microbiological data discussed below should be considered in the context of these presumptions noted above.

PRECLINICAL EFFICACY

In vitro

Mechanism(s) of Action.

Evidence to establish the mechanism of action of the drug relies almost exclusively on a publication by Bohar, et al. (1988. Azelaic acid: its uptake and mode of action in Staphylococcus epidermidis NCTC 11047. Journal of Applied Bacteriology 64:497-504). Clearly, the authors observed inhibition of protein synthesis under extremely defined cultural conditions. The cultural conditions included a baffling pH of 5.6, a condition normally seen only after initiation of a strong inflammatory response involving a progression of phagocytic cells. Another baffling aspect of the study was the choice of the model organism as S. epidermidis when the organism most frequently associated with acne is Propionibacterium acnes although future

studies with P. acnes were proposed in the discussion in the article. The future studies were performed and reported in another publication (Bojar, et al., 1991. The in vitro antimicrobial effects of azelaic acid upon Propionibacterium acnes strain P37. Journal of Antimicrobial Chemotherapy 28:843-853). This study encompassed a broader range of testing conditions and corroborated the probable role of inhibition of protein synthesis in the mode of action of azelaic acid on the model organisms. The two studies cited here stem from Bojar's Ph.D. dissertation studies.

Antimicrobial Spectrum of Activity

Bojar's dissertation studies also contained studies to show activity of azelaic acid on other microorganisms. Clearly, activity was demonstrated for a number of microorganisms; however, these studies are not useful for consideration for in vitro labeling because the experiments were not conducted under standardized susceptibility testing protocols. Many of the experiments were actually growth kinetics experiments in the presence of the proposed inhibitor while growing under continuous flow culture systems. Similar studies or abstracts without data were submitted as follows: 1) Holland and Bojar. 1989. The effect of azelaic acid on cutaneous bacteria. J. Dermatol. Treat. 1:17-19; 2) Holland, et al. 1989. The interaction of azelaic acid with Propionibacterium acnes. Soc. Invest. Derm. 92(3):446. Abstracts of the ESDR-JSID-SID Tricontinental Meeting; and 3) King et al. 1985. The effect of azelaic acid on cutaneous microflora *in vivo* and *in vitro*. Abstract. J. Invest. Dermatol. 88:832-833. In all these studies, the azelaic acid had a deleterious effect on the organisms studied, but the studies were not standardized to a specific clinical susceptibility testing protocol. Using a killing curve protocol, Leeming, Holland, and Bojar (1986. The *in vitro* antimicrobial effect of azelaic acid. Br. J. Dermatol. 115:551-556) reported "MIC's" ranging from 0.031 to greater than 0.25 mol. per liter among Staphylococcus epidermidis, S. capitis, S. hominis, Propionibacterium acnes, P. granulosum, P. avidum, and Pityrosporum ovale. Again, these studies were not done using standardized clinical susceptibility testing protocols. The impact of these studies is somewhat muted by the uncertainty of the precise role of bacteria in the etiology of acne.

Mechanism(s) of Resistance Studies

Emergence of resistance could not be demonstrated in a continuous culture system (Holland and Bojar. 1989. The effect of azelaic acid on cutaneous bacteria. J. Dermatol. Treat. 1:17-19) While continuous culture technique may be the classical approach to demonstrate spontaneous mutations in bacterial cultures, these studies do not demonstrate the effect of continued upward selective pressure of increasing concentrations of antimicrobial

agents. Once more, the impact of these studies is muted by the uncertainty of the precise role of bacteria in the etiology of acne.

In vivo

Pharmacokinetics/Bioavailability (Human and animal)

The product is topically applied; pharmacokinetics is not germane to this product with respect to antimicrobial claims.

Animal Prophylactic and Therapeutic Studies

There is no reliable animal model for acne.

CLINICAL EFFICACY

Clinical Microbiology

Normally, this section of a review of microbiological data would contain comments on such details as the adequacy of identification of the clinical isolates in the clinical trials, evaluation of susceptibility testing parameters, and the relationship of resistance to pending use of the proposed antimicrobial drug. In a typical antimicrobial drug application, there is a clear relationship between the antimicrobial drug and the etiology of the condition being treated. As noted above, the precise etiology of acne and the pathogenic mechanisms for production of acne are not completely understood biochemically; it is not clear whether the biochemical changes which have been observed and provided in several papers in this submission can be unequivocally attributed to the microbial flora. Indeed, investigations by Leyden, McGinley, Mills, and Kligman (1975. *Propionibacterium* levels in patients with and without acne vulgaris. *Journal of Investigative Dermatology* 65:382-384) demonstrated that the presence or absence of acne was independent of *Propionibacterium* levels for young adults, although the converse was true of younger patients. These observations may be equivocal, but the preponderance of evidence links two organisms in particular to acne. The organisms are *Propionibacterium* and *Staphylococcus epidermidis*; it is true that their role has not been completely defined. Nevertheless, azelaic acid has activity against these organisms, although the activity has not been defined in the traditional manner associated with antimicrobial activity against clinical isolates. Overall, the listing of *Propionibacterium acnes* and *Staphylococcus epidermidis* in package inserts for antiacne products is appropriate, while the listing of other organisms is entirely too tenuous.

Package InsertIsolates Approved

Propionibacterium acnes and *Staphylococcus epidermidis*

Interpretative Criteria Established

N/A

From the microbiological perspective, the first three paragraphs of the **Clinical Pharmacology**: section of the draft package insert should be deleted and the following paragraph should be substituted:

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

The revisions noted above were made to accommodate the current state of knowledge with respect to the following: 1) microbial etiology of acne; 2) the pathogenic mechanisms required to produce acne; and 3) the susceptibility to azelaic acid of the most probable microbial causative agents of acne, *Propionibacterium acnes* and *Staphylococcus epidermidis*. In all cases, definitive scientific conclusions are not available. Thus, less than definitive statements were included in the revision. These statements were included because it is appropriate for the reader to have some inkling of the current status of investigations in this area, especially when the consensus of investigators in the area espouse the proposed concepts while being aware of the conditionality of the rigorous scientific proof of the statements. While the statements in the original version attempt to accomplish the same objectives, they can be interpreted as overly promotional and need to be considerably muted. The revised statements succinctly accomplish the objectives of the applicant and the FDA.

Chemistry, and Manufacturing Controls Review Notes:Preservatives Effectiveness Test

The formulation to be marketed met the preservatives effectiveness test as prescribed by the U.S.P. In addition, the marketed formulation without the preservative met the U.S.P. test. The test organisms included *Esherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans*, and *Aspérgillus niger*. Samples were artificially contaminated with 10^5 - 10^6 microorganisms per gram. As noted above, all tests met the USP requirements, and all tests except the Aspergillus inoculations met the more stringent B.P. requirements. Under the more stringent BP requirements, complete elimination of organisms is necessary; thus, additional counts of Aspergillus over time showed appropriate reductions. Clearly, the preservatives effectiveness exceeds that which is normally required domestically.

Microbial limits test

The microbial limits were set at less than 500 organisms per gram with no detectable *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Enterobacteraciae* in 10 grams. Cultural conditions included incubation of casein hydrolysate-peptone medium at 30-35°C and Sabouraud's at 20-25°C. The microbial limits should be reduced from 500 organisms per gram to 100 organisms per gram.

Division of Anti-Infective Drug Products (HFD-520)
Microbiology and Drug Control Review Notes #2

NDA # 20-428

DATE COMPLETED: August 17, 1995

APPLICANT(NDA):

Aliergan
Dupont Drive
P.O. Box 19534
Irvine, CA 92713-9534

CHEM/THER. TYPE:

Anti-acne preparation

SUBMISSION REVIEWED: Original NDA volume

PROVIDING FOR: clinical and microbiological studies

PRODUCT NAMES(S):

Proprietary: Azelex

Non-Proprietary/USAN: azelaic acid 20% cream

Compendia: azelaic acid

**CHEMICAL NAME, STRUCTURAL FORMULAS, MOLECULAR FORMULA,
MOL. WT.**

1,7-heptanedicarboxylic acid; $\text{HOOC}-(\text{CH}_2)_7-\text{COOH}$;
 $\text{C}_9\text{H}_{16}\text{O}_4$; 188.22

DOSAGE FORMS(S) and STRENGTHS:

20% Cream

ROUTE(S) OF ADMINISTRATION:

Dermatological

PHARMACOLOGICAL CATEGORY:

Antiacne

INITIAL SUBMISSION:

Received by CDER: Filing date

Received by Reviewer: Filing date

Review Completed: 4 May, 1994

AMENDMENT(S)

Received by CDER: 3/9/95

Received by Reviewer: 8/16/95

Review Completed: 8/17/95

RELATED DOCUMENTS: None provided

REMARK(S):

This submission provides clarification from the applicant concerning the original commitment associated with the Microbial Limits test. The applicant notes that the intent of the original commitment was in conformity with the Microbial Limit of 100 colonies per gram of dosage form; the page with the Microbial Limits standards has been modified to eliminate certain confusing references. All CMC issues have been resolved with this submission.

The package insert still needs revision as noted below, based on the microbiological data in the original submissions.

CONCLUSIONS and/or RECOMMENDATIONS:

The application is approvable, except for these needed changes in the **Clinical Pharmacology** section. From the microbiological perspective, the following text should replace the microbiological portion of the draft package insert.

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

James R. King 8/17/95
James R. King
Microbiologist, HFD-520

cc: Orig. NDA # 20-428

HFD-473

HFD-635

HFD-502

HFD-520

HFD-520/Micro/King

HFD-520/MO/Vaughan

HFD-520/Pharm/Mainigi

HFD-520/Chem/DeCamp

HFD-520/CSO/Chapman

HFD-520/DepDir/LGavrilovich

HFD-520/SMicro/ASheldon

TS 8/17/95

ib 2/25/95

Chem

1.1
JAN 16 1995

DIVISION OF TOPICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-428 CHEM.REVIEW #: 1 REVIEW DATE: 6-3-94

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	2-28-94	2-28-94	3-7-94
AMENDMENT	4-6-94	4-7-94	

NAME & ADDRESS OF APPLICANT: Allergan Herbert Division of
Allergan Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92713-9534

DRUG PRODUCT NAME
Proprietary: AZELEX (azelaic acid) 20%
Cream
Nonproprietary/USAN: Azelaic acid 20% cream
Code Names/ #'s: AGN 191861
Chemical Type/
Therapeutic Class: 1 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:
Topical treatment of acne
vulgaris

DOSAGE FORM: Cream
STRENGTHS: 20%
ROUTE OF ADMINISTRATION: Topical application
DISPENSED: X Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT:

1,7-heptanedicarboxylic acid or
1,9-nonanedioic acid or
Lepargylic acid or Anchoic acid

HOOC-(CH₂)₇-COOH
C₉H₁₆O₄
CAS# 123-99-9

Mol.weight:188.22

PATENT STATUS:

4,292,326; for the treatment of hyperpigmentary dermatoses

4,386,104; for the treatment of acne
4,818,768; for the treatment of hyperpigmentary dermatoses
including malignant melanoma.

NDA 20-428
Allergan Herbert
Azelex

page 2

Allergan is requesting an Exclusivity period of 5 (five) years. However, the expiration date of the patents are not included.

SUPPORTING DOCUMENTS:

IND, (Allergan Herbert)
DMF letter of authorization
is signed by Dr. Deeg and Dr. Bohm dated August 7, 1993.
DMF, letter of
authorization to reference bulk drug manufacturer is signed
by Dr. Ahrens and Dr. Meske on 30/8/93. See chemist's
review completed by Nahid Mokhtari-Rejali dated 9/1/94.

AMENDMENTS:

Dated: April 6, 1994, a statement indicating that
facilities are ready for pre-approval inspection
after June 1, 1994.

CONSULTS:

Environmental Assessment consult was sent to Dr. Philip
Vincent on 4/26/94 (Appendix A). The consult was completed
and signed off by HFD-102 on 9/12/94. Tradename consult was
sent to the Labeling Committee on 9/6/1994 (Appendix B).
The tradename, Azelex, was reviewed and found to be not
acceptable on 10/11/94.

REMARKS/COMMENTS:

Azelaic acid is the subject of IND It is a
naturally occurring medium-chain saturated dicarboxylic
acid, which can be found in wheat, rye, and barley. For
this application, it is manufactured from beef tallow as a
starting material. On topical application, azelaic acid has
shown antimicrobial and antikeratinic characteristics with a
very low potential for toxicity. Azelaic acid is a simple
molecule with excellent safety and efficacy profile as
demonstrated in the clinical studies conducted by
and Allergan Herbert. Azelaic acid 20% cream (oil in
water) has been marketed by including
U.k., Germany, and France, Since 1989, under the tradename
Skinoren for the treatment of acne.

Azelaic acid (Emerox 1144; approx. 89%) is synthesized
by This material is then purified,
recrystallized and micronized by and
subsequently used in the manufacturing of the drug product

by From a manufacturing and control standpoint, the data and information submitted to this application are inadequate for approval of this application.

No DMF is provided for the manufacture of crude azelaic acid (Emerox). However, the applicant has submitted brief information regarding the starting materials, different steps of synthesis and specification. In this regard, if the applicant decides to change the supplier of azelaic acid, an appropriate amendment should be submitted to the DMF, since a different supplier may use a different natural source for the starting material.

The applicant has submitted a letter authorizing reference to DMF for manufacturing and control of pure and micronized azelaic acid. The review of this DMF has been completed by Nahid Mokhtari-Rejali, Ph.D., dated September 1, 1994. The DMF holder has been notified of inadequacies.

The major manufacturing and control concerns regarding the drug product are:

In respect to drug product specifications:

The information regarding degradation pathway is not provided. The applicant should attempt to decompose azelaic acid under forced conditions and submit a decomposition profile for the drug substance. It is recommended that the decomposition test be performed by GC assay (detection limit of 0.1%) to assure the purity of the drug substance during the shelf-life.

The particle size specification for the drug substance, in-process control and finished product differs throughout the application. This discrepancy should be explained.

The stability data through the shelf-life do not indicate the presence of any decomposition. Therefore, the release specification and stability specification for total decomposition products should be tighten to 0.7%. It should be noted that the limit of detection by TLC and GC is reported to be μg & ng respectively.

In regards to stability data:

The primary stability lots do not support the five years expiration date. Only 36 months stability data are provided for lot 02001, see page 23 of Review Notes. The

NDA 20-428
Allergan Herbert
Azelex

page 4

applicant should submit the updated stability data on the first five commercial batches (Primary stability lots) to support the proposed expiry date.

The data provided for supportive stability lots (#61181, 34011 & 34021) suggest that all the lots manufactured with the drug substance obtained from other sources (Imhausen and Fluka where recrystallization was performed) are different in physical characteristics (particle size: uniform, majority μm ; isolated crystal max. μm) from azelaic acid obtained from Schering AG (particle size: no particle μm , particles μm and μm), DMF. Provisions for milling the drug substance prior to manufacturing of the drug product is suggested.

It is recommended that efforts to develop an in-vitro release test be continued to establish its potential as a measure of the batch to batch uniformity of AZELEX cream during the manufacturing process and storage.

The EER was requested from the Office of Compliance on April 26, 1994 (CIRTS, EER #6096). An acceptable EIP was issued by CIN-DO for Henkel, manufacturer of crude azelaic acid on July 11, 1994. However, a copy of recommendation from San Juan-DO to withhold approval of this NDA was issued for manufacturer of drug products facility on December 14, 1994. The applicant has responded to the 483 items on November 4, 1994. The firm's response was reviewed by the inspector, and found to be inadequate. A draft copy of response to the FD 483, and inspector's evaluation are attached (Appendix C). The notification letter has not been received from the Office of Compliance as of today.

The method validation packages were sent to LOS-DL and the Division of Drug Analysis (DDA) Laboratories (St. Louis) on 8/29/94 (Appendix D). No response has been received as of this date.

These inadequacies are discussed in details in the Review Notes and are addressed in the Draft letter to the applicant.

NDA 20-428
Allergan Herbert
Azelex

page 5

CONCLUSIONS:

This application is not approvable from a manufacturing and control standpoint.

DMF is deficient. The DMF holder has been notified of the deficiencies. The CSO is to convey these deficiencies to the Applicant.

Nahid Mokhtari-Rejali

Nahid Mokhtari-Rejali,
Ph.D., Review Chemist

cc: Orig. NDA 20-428
HFD-540/Division File *w/o appendix C*
HFD-540/Mokhtari-Rejali/10/17/94 *w/o appendix*
HFD 540/Vaughan
HFD-540/Mainigi } *w/o appendix*
HFD-540/King
HFD-540/Chapman
HFD-540/WHDeCamp
HFD-102/Jerussi #1 only!
R/D Init by: SUPERVISOR *WA 11/17/95*
filename:N20-428.rv1

g-w 11/16/95

AUG 31

DIVISION OF TOPICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-428 CHEM. REVIEW #: 2 REVIEW DATE: 17-AUG-95

SUBMISSION/TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE

AMENDMENT/AC 09-MAR-95

NAME & ADDRESS OF APPLICANT: Allergan Herbert Division of Allergan Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92713-9534

DRUG PRODUCT NAME

Proprietary: AZELEX (azelaic acid) 20% Cream
Nonproprietary/USAN: Azelaic acid 20% cream
Code Names/#'s: AGN 191861
Chemical Type/
Therapeutic Class: 1 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Topical treatment of acne vulgaris

DOSAGE FORM: Cream
STRENGTHS: 20%
ROUTE OF ADMINISTRATION: Topical application
DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

1,7-heptanedicarboxylic acid, or
1,9-nonanedioic acid, or
lepargylic acid, or
anchoic acid
HOOC(CH₂)₇COOH Mol. weight: 188.23
C₉H₁₆O₄ CAS# 123-99-9

PATENT STATUS:

4,292,326; for the treatment of hyperpigmentary dermatoses
4,386,104; for the treatment of acne
4,818,768; for the treatment of hyperpigmentary dermatoses including malignant melanoma.

Allergan is requesting an exclusivity period of five (5) years. However, the expiration dates of the patents are not included.

SUPPORTING DOCUMENTS:

IND (Allergan Herbert)
DMF letter of authorization signed by Dr. Deeg and
Dr. Bohm, dated 07-AUG-93.
DMF letter of authorization to reference bulk
drug manufacturer was signed by Dr. Ahrens and Dr. Meske on 30-AUG-93. See

NDA 20-428
Azelex (azelaic acid) 20% Cream
Allergan Herbert

page 2

chemist's review #1 of DMF dated 01-SEP-94, by Nahid Mokhtari-Rejali, Ph. D., and review #2, dated 08-AUG-95, by J. S. Hathaway, Ph. D.

AMENDMENTS:

Dated 18-AUG-95: letter of commitment to submit three post-approval supplements for issues noted in the Conclusions section herein.

Dated 06-APR-94: a statement indicating that facilities are ready for pre-approval inspection after 01-JUN-94.

Dated 07-APR-94: English translations of manufacturing records for the pivotal stability batches; provided in response to deficiency noted in non-approval letter of 20 FEB-95.

Dated 09-MAR-95: containing responses to the deficiencies listed in the non-approval letter of 28-FEB-95.

CONSULTATIONS:

Environmental Assessment consult was sent to Dr. Philip Vincent on 26-APR-94. The consult was completed and signed off by FD-102 on 12-SEP-94. The updated Environmental Assessment (EA), provided with the amendment to NDA 20-428 dated 09-APR-95, was sent for consultation on 07-AUG-95. Minor deficiencies in the public EA were identified. These were communicated to the applicant via letter and a teleconference on 10-AUG-95. The applicant has amended the EA to address the information needed for the non-confidential portion of the EA; the EA is acceptable based on the submission of the documents by FAX, and is subject to official submissions.

Tradenname consult was sent to the Labeling Committee on 06-SEP-94. The tradenname, AZELEX, was reviewed and found to be not acceptable on 11-OCT-94. In the amendment of 09-MAR-95, the sponsor addressed this issue by agreeing that they would not challenge any entities which propose non-proprietary names (INN or USAN) which resemble the proprietary name AZELEX™; they reserve the right to challenge proprietary names which may infringe on the proprietary name AZELEX™, whether or not they contain azelaic acid. This has been determined to be acceptable.

A microbiology consultation for the evaluation of applicant's response (amendment of 03-MAR-95) was sent to Dr. James R. King, HFD-520, on 8/95. This has been found to be acceptable.

The methods validation packages were sent to LOS-DL and the Division of Drug Analysis (DDA) Laboratories (St. Louis) on 29-AUG-94. No response has been received as of this date.

REMARKS/COMMENTS:

Azelaic acid is the subject of IND It is a naturally occurring, saturated medium-chain dicarboxylic acid, which can be found in wheat, rye, and barley. For this application, it is manufactured from the starting

Azelex (azelaic acid) 20% Cream
Allergan Herbert

material beef tallow. On topical application, azelaic acid has shown antimicrobial and antikeratinic characteristics, with a very low potential for toxicity. Azelaic acid is a simple molecule with an excellent safety and efficacy profile, as demonstrated in the clinical studies conducted by [redacted] and Allergan Herbert. Azelaic acid 20% cream (oil in water) has been marketed by [redacted] since 1989, for the treatment of acne in Europe, including U.K., Germany, and France, under the tradename Skinoren.

Azelaic acid (Emerox 1144; approx. 89%) is synthesized by [redacted] This material is then purified, recrystallized and micronized by [redacted] and subsequently used in the manufacturing of the drug product by [redacted]

No DMF has been provided for the manufacture of crude azelaic acid (Emerox 1144). However, the DMF holder has submitted brief information regarding the starting materials, route of synthesis and specifications for Emerox 1144. In this regard, should the DMF holder decide to change their supplier of azelaic acid, an appropriate amendment must be submitted to the DMF, since a different supplier may use a different natural source for the starting material. This requirement has been communicated to the DMF holder, and they have committed to this plan.

The applicant has submitted a letter authorizing reference to DMF [redacted] for manufacturing and control of purified and micronized azelaic acid. The review of this DMF, dated 01-SEP-94, was written by Nahid Mokhtari-Rejali, Ph.D. The DMF holder was notified of inadequacies in a letter dated 13-JAN-95. The DMF has subsequently been amended to address the inadequacies, and the changes have been reviewed. See Review #2, dated 08-AUG-95, by J. S. Hathaway, Ph. D.

The major manufacturing and control concerns regarding the drug product which were noted in Review #1 were addressed in the Amendment which is the subject of this review. For the analysis and review of the responses, see the Chemist's Notes section.

CONCLUSIONS:

This application is now approvable with respect to the chemistry, manufacturing and controls information submitted as amendments to NDA 20-428, subject to the condition of receipt of the post-approval commitments noted below:

1. Revised finished product release and stability specifications should be submitted. The revised specifications should incorporate the following addition:
"For microscopy, a particle size maximum of [redacted] micrometers (microns) for any single crystal, with no agglomerate particles greater than [redacted] micrometers (microns)."

This revision should be in effect prior to the first lot being placed into the stability program.

NDA 20-428
Azelex (azelaic acid) 20% Cream
Allergan Herbert

2. The applicant should submit a revised Testing Standard for the measurement of the consistency of Azelex Cream, addressing the following:
 - 1) Temperature control- The samples and apparatus are to be equilibrated at a specified temperature for a sufficient time (also specified) to ensure stable and uniform temperature range throughout the samples.
 - 2) The physical characteristics of the apparatus are to be specified in sufficient detail to allow reproduction of the equipment and measurement in other laboratories. Annotated scale drawings would be acceptable.
 - 3) A suitable reference material shall be tested concurrently with the drug product. Results shall be analyzed and reported in the same manner as for drug product.
 - 4) Measurements are to be reduced by conversion with the standard factor (a multiplier of 3, per Klein). In addition, the "Yield Value" equation, described in the Lachman, Lieberman and Kanig reference, should be used to report data in a reduced form, and may be normalized versus the reference measurements. All data manipulations must be defined and, preferably, referenced by literature citations.

3. The final revised version of the stability protocol, which should address content uniformity by including sampling from the top, middle and bottom of the tubes and report the results of these tests separately, should be submitted prior to entering the first commercial lot of Azelex Cream into the stability program.

4. A specification and release test for the bulk drug substance should be submitted for the detection and control of contaminating crystal-form, specifically, crystal form B utilizing X-ray Powder Diffraction.

J. S. Hathaway 8/21/95
 J. S. Hathaway, Ph.D.
 Review Chemist

Nahid Mokhtari-Rejali 8/21/95
 Nahid Mokhtari-Rejali, Ph. D.
 Review Chemist

cc: Orig. NDA 20-428
 HFD-540/DivFile
 HFD-540/Chem/NMRejali
 HFD-540/Chem/JSHathaway
 HFD-540/MO/BVaughan
 HFD-540/Pharm/KMainigi
 HFD- /Micro/JRKing
 HFD-540/ProjMgr/KKChapman
 HFD-540/SupChem/WHDeCamp/ R/D File by *WHD*

filename: C:\WF\FILES\NDA\20428\NDA20428R2.000

JW 8/31/95

DMF:

Title: Azelaic Acid

1. CHEM REVIEW #2

2. REVIEW DATE: 08-AUG-95

3. DMF INFORMATION REVIEWED:

Amendments

Type of Submission	Date of Submission	Type of Information
Amendment	26-JAN-95	CMC info revised
Amendment	07-JUL-95	Response to Deficiencies

4. PREVIOUS DOCUMENTS

Type of Document	Date of Document	Comment
Original	07-AUG-91	
Letter of Authoriz'n.	07-AUG-91	Allergan-Herbert Labs.
Revision	26-JAN-94	Replaced original DMF
Review #1	17-JAN-95	Deficiencies noted

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME:
ADDRESS:

REPRESENTATIVE: Dr. B. G. Schulz
Regulatory Affairs
Schering Aktiengesellschaft
D-13342 Berlin
Federal Republic of Germany

TELEPHONE: (0 30) 4 68-7495

6. ITEM REVIEWED:

NAME: Azelaic Acid
CODE NUMBER: ZK 62498
CHEMICAL NAME: nonanedioic acid
SYNONYMS: lepargylic acid, anchoic acid
CAS NUMBER: 123-99-9
MOLECULAR WEIGHT: 182.22
CHEMICAL FORMULA: C₉H₁₆O₄
STRUCTURAL FORMULA: HO₂C(CH₂)₇CO₂H

7. DMF REFERENCED FOR:

NDA: 20-428
APPLICANT NAME: Allergan-Herbert Div., Allergan, Inc.
LOA DATE: 26-JAN-95
DRUG PRODUCT NAME: AZELEX®
DOSAGE FORM: Cream
STRENGTH: 20% (w/w)
ROUTE OF ADMINISTRATION: Topical
INDICATION: Topical treatment of acne vulgaris

DMF

Page 4

Item 8: The holder has provided corrections to the nomenclature of a list of the impurities in azelaic acid.

**Reviewer's
Comment:** Acceptable

Item 9: Updated stability data were provided in the amendment dated 26-JAN-95. The drug substance is subjected to both ambient and accelerated conditions in the stability protocol, and is within specifications over the twelve month period covered.

**Reviewer's
Comment:** Acceptable

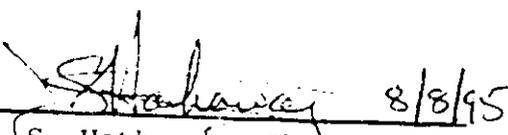
Item 10: The holder has provided a summary of known degradation conditions for azelaic acid and related compounds as well as literature references (listed in the cover letter). The conditions required for decomposition are sufficiently harsh that they may not be expected under reasonable storage conditions.

**Reviewer's
Comment:** Acceptable

12. CONCLUSIONS & RECOMMENDATIONS:

The DMF holder has responded to all deficiencies noted in Chemistry Review #1, dated 01-SEP-94 (and sent in a deficiency letter dated 17-JAN-95). The response was delayed due to the deficiency letter not being delivered to the holder.

This DMF is deemed adequate to support the NDA referenced above. This decision should be conveyed to the DMF holder through the attached letter. Two non-deficient recommendations are included.


J. S. Hathaway, Ph. D.
Reviewing Chemist

cc: Orig. DMF
HFD-540/Division File
HFD-540/Chem/JSHathaway
HFD-540/DD/JKWilkin
HFD-540/Pharm/
HFD-540/Micro/
HFD-540/CSO/KKChapman
HFD-540/WHDeCamp/R/D Init by: 

filename: D09289r.002

DIVISION OF TOPICAL DRUG PRODUCTS
HFD-540
CHEMIST'S REVIEW #1

DMF

Date: September 1, 1994

APPLICANT:

FDA CONTACT: Dr. J. Meske, CMC Dossiermanagement

PRODUCT NAMES: Azelaic acid

SCHERING AG CODE NUMBER: ZK 62498

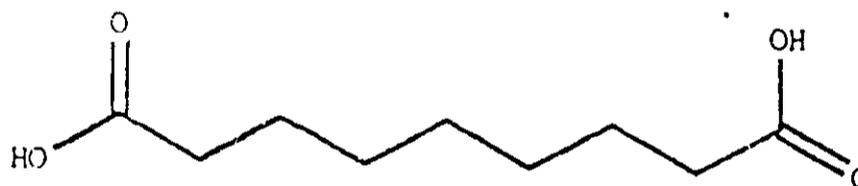
DOSAGE FORM AND ROUTE OF ADMINISTRATION:
n/a; Bulk active drug substance

PHARMACOLOGICAL CATEGORY: n/a

INDICATION: Topical treatment of acne vulgaris

STRUCTURAL FORMULA AND CHEMICAL NAMES:
1,7-heptanedicarboxylic acid.
HOOC-(CH₂)₇-COOH

Synonym:
Nonanedioic acid
Lepargylic acid
Anchoic acid



C₉H₁₆O₄
CAS# 123-99-9

Mol. weight: 188.22

INITIAL SUBMISSION:

Dated: May 22, 1991
Received: August 21, 1991

AMENDMENT (S):

Dated: October 14, 1992
Received: October 28, 1992

Dated: January 26, 1994
Received: February 1, 1994

SUPPORTING AND RELATED DOCUMENTS:

NDA 20-428 AZELEX (azelaic acid) 20% Cream,
Allergan Herbert.

IND

DMF
DMF
DMF

Letter of authorization to reference this DMF is signed by Dr. Meske on 8/30/93.

NOTE: No DMF reference is provided for the manufacturer of crude azelaic acid from

REMARKS:

The DMF is reviewed in support of Allergan Herbert NDA 20-428.

Detailed information is discussed in the Review Notes (Appendix A) and are addressed in the Draft letter to the DMF holder.

CONCLUSIONS AND RECOMMENDATIONS:

The DMF is not adequate to support the approval of the NDA 20-428. The attached letter should be sent to the DMF holder.

REVIEWER:

COMPLETED: DATE



Nahid Mokhtari-Rejali, Ph.D.

9/1/94

cc: Orig. NDA 20-428
HFD-540/Division File
HFD-540/Mokhtari-Rejali/12/19/94
HFD-540/Vaughan
HFD-540/Mainigi
HFD-540/King
HFD-540/Chapman
HFD-540/WHDeCamp
HFD-102/CKumkumian [#1 only]
R/D Init by: SUPERVISOR
DMF 9289

Uretero
N/A Ltr

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: Sept 2, 1994

From: Asoke Mukherjee Ph.D., HFD-102/007

Through: Phillip G. Vincent Ph.D., HFD-102

Subject: EA for Azelex, NDA 20-428

To: R. Cook, HFD-540

The initial review for environmental assessment of the above NDA has been completed. Following recommendations and comments have been suggested by the reviewer.

Environmental assessment of Azelaic acid 20% cream may not need documentation for items 7 through 11 and 15 of the format. However please note that data and information that are protected from disclosure by 18 U.S.C. 1905 or 21 U.S.C. 331(j) or 360j(c) shall not be included in environmental documents prepared under 21CFR 25.31a(3). Your application states that the entire EA assessment contains confidential and proprietary information and would not be released under FOI. The environmental impact of your application can not be determined unless you waive in writing confidentiality statement of the EA and make it releasible under FOI. However if any data are confidential, please attach it as confidential appendix in the EA.

For item #3

1. Provide the location and address for the manufacturing facilities of the drug substance and the drug product at Also provide the address for Allergan distribution center at Waco, Texas.

For item #4

2. Provide type of environment surrounding the facilities. Please indicate where the unused and expired products would be collected and disposed in the USA, the environment surrounding the area. Are there any river or wooded area near the manufacturing, distribution and disposal sites so that the ecosystem and water would be affected.

For item #5

3. Provide structural formula, molecular formula, physical properties for the active and inactive ingredients

For item #6

4. Provide calculations for supporting environmental emission of each substance used in the manufacturing of the drug substance, and the drug product at facilities. A certificate of recent inspection for the specific product from appropriate state, local and federal authorities on the environmental compliance for facilities is necessary.

Estimate the maximum yearly market volume of the drug product to aid in determining whether approval of the application could result in potentially significant environmental introductions from use of the product.

For the distribution center at Texas, what would be the amount of the drug product per year that would be disposed. How would you dispose the drug product, packaging materials and the containers. Copy of certificates for incinerator, landfill etc. from appropriate state, local and federal authorities need to be attached.

Endorsements:

HFD-102/007 Asoke Mukherjee Ph.D.
Pharmacologist

HFD-102/ P.G. Vincent

C.C Original NDA 20-428
EA file
Div file/HFD-540
Supervisory Chemist/ HFD-540

20428E00.LAM

F/T by AM

Asoke Mukherjee
P.G. Vincent
9.12.94

NDA 20-428 - #1

Appendix B
Tradenname Consult

Consult # 347

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Ms. Yana Mille, Chair, HFD-600 MPN II

FROM: Division of Topical Drug Products (HFD-540)
Attention: Nahid Mokhtari-Rejali, Ph.D.
Phone: 443-6714

DATE: August 31, 1994

SUBJECT: Request for Assessment of a Trademark for a Proposed
Drug Product

WJK 8/31/94
WJA 9/6/94

Proposed Trademark: AZELEX

NDA/ANDA#: 20-428

Established name, including dosage form: Azelaic acid 20% Cream

Other trademarks by the same firm for companion products: Skinoren

Indications for use (may be a summary if proposed statement is lengthy): Topical treatment of acne vulgaris

Initial comments from the submitter: (concerns, observations, etc.)

Please comment on the suitability of the trade name. Azelaic acid 20% cream has been marketed by _____ in Europe, including U.K., Germany, and France, since 1989, under the trade name Skinoren for treatment of acne.

NOTE:

Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: NDA
HFD-540
HFD-540/Rejali
HFD-541/Chapman

COMPLETED

Consult #347 (HFD-540)

AZELEX

Azelaic Acid Cream 20%

A review revealed several names which look or sound like the proposed name: Azaline, Asmatex and Asmalix. Due to differences in dosage form (cream vs tablets or oral solution) and/or prescription status (Rx vs OTC), the Committee does not believe the similarity in names is likely to cause problems.

Azelex is clearly derived from the established name for the drug product. The key identifying syllables from azelaic acid are incorporated in the proposed trademark. The Agency supports the spirit of USAN in discouraging the undesirable practice of incorporating into the tradename the syllables used in an established nonproprietary name. Furthermore, we note the Forty-Sixth World Health Assembly has also expressed concern about proprietary names which include items or other descriptors derived from international nonproprietary names. The use of such items, particularly for single ingredient products, may create confusion in prescribing and dispensing medicines and interferes with the development of new international nonproprietary names.

For the reason cited above, the Committee finds the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

Yana Mille, Chair

10/11/94

NOTE: The Center's USAN representative, Robert Wolters, asked that the firm be reminded to submit the established name to USAN.

NDA 20-428 - #1

Appendix C

Establishment Inspection Documentation

NDA 20-428

FEB 28 1995

Allergan Herbert
Division of Allergan Inc.
Attn: Mr. Steve Buxbaum
Director, Worldwide Regulatory Affairs
P.O. Box 19534
Irvine, CA 92713

Dear Mr. Buxbaum:

Please refer to your February 28, 1994, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azelex (azelaic acid cream) 20% Cream.

We acknowledge receipt of your amendments dated April 6, June 15, June 24, July 8, August 4, and October 17, 1994.

We have completed our review of this application, as amended, and find that the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are as follows:

Chemistry, Manufacturing, and Controls

1. The discrepancy between the particle size specification for the finished product (μm) and the in-process controls (μm) should be clarified. The reports of the particle size in the primary stability batches (pp. 5 140-154) and the supportive stability batches (pp. 5 173-186) report no observations greater than μ . These values are consistently much smaller than the stated limits. The maximum particle size specification should be revised to a uniform value consistent with these studies and revisions submitted to this application.
2. A viscosity test should be added to the release specifications and results submitted. Although penetration may be considered as a conventional index of consistency for ointments and creams, we do not believe it can be correlated with viscosity.

3. The release and stability specifications for the drug product should be revised to provide for testing for decomposition products by the GC method. It is unclear in the stability reports (pp. 5 109-137) which of the two methods (TLC or GC) was used for the detection of decomposition products. This revised specification should be used for the first three production batches throughout shelf life, as well as for other batches placed into your ongoing stability program. If the results of these studies provide evidence that no decomposition of azelaic acid occurs, a supplemental application to delete the decomposition products test may be submitted.
4. The information regarding sampling of the filling process (page 5 003) is inadequate. Samples taken only at the end of the filling process are not representative of the entire batch. The number of samples collected for chemical analysis should be proportional to the batch size and should be taken throughout the filling process. This information should be submitted.
5. Updated stability data on the first five commercial batches ("primary stability lots") should be submitted. The submitted stability data do not support the proposed five-year expiration dating period. The longest reported study is 36 months for lot 02001.
6. The assay results of azelaic acid on page 5 113 describe the sampling as: "a: mixed sample, a: start, b: middle, c: end of the tube, x: average of b, c, d." Please clarify your actual experimental practice. The assay results for azelaic acid and benzoic acid are provided only for the mixed samples at time points through 12 months. The data should be reported for each individual point, e.g., top, middle and bottom of the tube and submitted.
7. On page 5 136, a 6% water loss is observed at 25°C after 3 months. Furthermore, the water content at time zero is substantially less than would be expected from the composition of the product. Water content should be included in the release and shelf-life specifications, rather than being performed only for information.
8. A description of the extensometer method (Testing Standard 1S 017a) should be submitted.
9. Viscosity and freeze-thaw cycle testing should be added to the stability protocol, and the results should be submitted.

10. Information regarding the degradation pathway should be provided, including information about the decomposition of bulk azelaic acid under forced conditions. A decomposition profile for the drug substance should be submitted.
11. The stability protocol (page 5 188) should be revised as follows:
 - (a) to provide for additional test stations at 3 and 9 months;
 - (b) to perform the homogeneity test at the top, middle and bottom of the tube; and
 - (c) to report to us and to withdraw from the market any lot that fails to meet specifications.
12. Deficiencies have been identified in DMF for the purification and micronization of azelaic acid. A letter has been sent to the DMF holder advising them of these deficiencies. Until these are adequately resolved, the new drug application remains not approvable.

Environmental Assessment

Please note that data and information that are protected from disclosure by 18 U.S.C. 1905 or 21 U.S.C. 331(j) or 360(j)(c) shall not be included in environmental documents prepared under 21 CFR 25.31a(3). A "Finding of No Significant Impact" (FONSI) for your application can not be prepared unless you waive in writing the confidentiality of the environmental assessment and make it releasable under the Freedom of Information Act. However, if any data are confidential, an attachment noted as a confidential appendix in the environmental assessment section may be provided, along with a non-confidential summary.

In addition, the following recommendations should be addressed in the environmental documents:

1. The location and address for the manufacturing facilities of the drug substance and the drug product in should be provided.
2. The type of environment (e.g., urban, suburban) surrounding the facilities should be provided.

3. Calculations in support of environmental emissions of each substance used in the manufacturing of the drug substance and of the drug product should be provided for the facilities. A certificate of recent inspection for the specific product from appropriate state, local, and federal authorities on the environmental compliance of the facilities should be submitted.
4. The structural formula, molecular formula, and physical properties for the active and inactive ingredients should be submitted.
5. An estimation of the maximum yearly market volume of the drug product to assess potential significant environmental risks from use of this product should be submitted.

Microbiology

The Microbial Limits Test standard should be reduced to organisms per gram instead of organisms per gram. This revision should be submitted.

Clinical

We request that you submit a commitment to conduct a Phase 4 study to investigate hypopigmentation as a possible adverse event. The results from the study should be provided when they are available.

In addition, we have the following comments and requests for information that should be addressed:

1. The development of an in-vitro release test should be considered. Such a test may be useful as a measure of batch-to-batch uniformity of Azelex cream during the manufacturing process and storage.
2. Pregnancy outcome results for patients from study AZEL-221-8466, who were exposed to the active drug, should be reported and submitted.
3. An English translation of the Klein reference for the micro-penetration test, mentioned on page 5 044, should be provided.

4. The name "azelaic acid" is not a United States Adopted Name (USAN) name. An application for acceptance of this name as a USAN should be submitted.
5. The name Azelex is derived from the International Nonproprietary Name (INN) azelaic acid. The use of proprietary names that are derived from INN or USAN names may interfere with the development of new INN and USAN names. Therefore, we recommend that you choose a different proprietary name.
6. A safety update report in accordance with the requirement of 21 CFR 314.50(d)(5)(vi)(b) should be submitted.

We reserve comment on the proposed labeling until the new drug application is found adequate in all other respects.

Please note that we cannot approve this application until we are informed that all sites involved in manufacture of the bulk drug and drug product have been found to be in compliance with good manufacturing procedures and are able to perform the production procedures specified in this NDA application.

In accordance with the policy described in 21 CFR 314.102(d) of the new drug regulations, you may request an informal conference with the members of the Division of Topical Drug Products to discuss in detail the deficiencies in this application and what further steps you need to take to secure approval. The meeting is to be requested at least 15 days in advance.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.120. In the absence of any such action, the Food and Drug Administration (FDA) may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

Should you have questions regarding this application, please contact Ms. Kennerly K. Chapman, Project Management Staff, at 301-594-0301.

Sincerely yours,

 2/28/95

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-428

7

cc:

Orig NDA 20-428
HFD-2/MLumpkin
HFR-PA200/LOS-DO
HFD-500
HFD-80
HFD-540
HFD-540/DDir/Wilkin
HFD-540/SMO/Chambers *WKC 2/23/95*
HFD-540/MO/Vaughan/rd1/24/95
HFD-540/Chem/Rejali/rd1/27/95
HFD-540/Pharm/Mainigi/rd1/24/95
HFD-520/Micro/King/rd1/24/95
HFD-426/Biopharm/Felsor
HFD-710/Biostat/Harkins
HFD-540/ClinRev/Joyce
HFD-540/PMS/Chapman/n20428.na/rd1/20/95
rd/LRipper/2/15/95 *for 2/15/95*
jb/revised/2/28 '95

Concurrence only:

HFD-540/DDir/Wilkin/2/2/95 *7/20/28/95*
HFD-540/SMO/Chambers/rd1/23/95
HFD-540/SCHEM/DeCamp/rd1/27/95
HFD-540/ActSPharm/Alam/rd1/24/95
HFD-540/SPMS/Cook/rd1/23/95 *with L 2/24/95*

NOT APPROVABLE