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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 207071
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Product: FINACEA (azelaic acid) foam, 15%
Indication: (b) (4) rosacea
Applicant: Bayer HealthCare Pharmaceuticals Inc.
Review Division: Dermatology and Dental Products
Reviewer: Jianyong Wang, PhD
Supervisor/Team Leader: Barbara Hill, PhD
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1 Executive Summary

1.1 Introduction

Azelaic acid is a dietary constituent and is also produced in endogenous metabolism. It has been approved for the treatment of acne vulgaris under NDA 20428 (AZELEX Cream, 20%) and rosacea under NDA 21470 (FINACEA Gel, 15%). The sponsor intends to develop a new dosage form, FINACEA Foam, 15%, for the treatment of rosacea. The same dosage is proposed for FINACEA Foam, 15%, as approved for FINACEA Gel, 15%.

This NDA is a 505(b)(1) NDA from a Pharmacology/Toxicology perspective because the sponsor owns all the necessary nonclinical data for azelaic acid to support FINACEA Foam, 15%.

1.2 Brief Discussion of Nonclinical Findings

Azelaic acid has been shown to have anti-keratinizing, anti-bacterial and anti-inflammatory activities. However, the mechanism(s) by which azelaic acid interferes with the pathogenic events in rosacea are not clear.

Nonclinical safety pharmacology studies did not indicate significant effects of azelaic acid on intermediate metabolism, liver function, renal function, cardiovascular function, smooth muscle or the nervous system, under the study conditions.

Since azelaic acid is a straight chain dicarboxylic acid, it is anticipated that the main process of its elimination is by biotransformation. Systemically absorbed azelaic acid is metabolized by β -oxidation into shorter straight chain dicarboxylic acids (i.e., pimelic and glutaric acids), malonyl-CoA and acetyl-CoA. The results from an in vitro percutaneous absorption study indicate that similar systemic exposure is expected after topical administration of the azelaic acid foam and gel formulations.

Azelaic acid was evaluated for systemic toxicity in rats (27-week study) and monkeys (4-week study) following oral (gavage) administration. No significant systemic toxicity was noted in the two studies except lower body weight gain and thickening of the cuticular ridge of the stomach accompanied by evagination and epithelia overgrowth noted at high dose in the rat study. Dermal toxicity studies were conducted in dogs (26-week study) with 20% azelaic acid cream and in minipigs (13-week study) and mice (13-week study) with 15% azelaic acid pre-foam emulsion. No significant toxicity was noted in the three dermal studies. Only slight dermal irritation was noted in the dog study.

In genetic toxicology studies, azelaic acid was not mutagenic or clastogenic in a battery of in vitro and in vivo genotoxicity tests. There is no concern for its genotoxic potential.

A short-term dermal carcinogenicity study in transgenic mice (Tg.AC assay) was conducted with azelaic acid 15% gel. A statistically significant increase in the incidence of papillomas was noted in males in the vehicle and high dose groups. No effect was noted in females. There was no significant difference in the incidence of papillomas in the vehicle and high dose males, which suggested that the positive finding may be due to the vehicle only. However, considering the positive finding noted in this short-term Tg.AC assay, a 2-year dermal mouse carcinogenicity study is recommended to be conducted as a post-marketing requirement (PMR) with the azelaic acid pre-foam emulsion formulation.

Oral embryofetal developmental studies were conducted with azelaic acid in rats, rabbits, and monkeys. Azelaic acid was administered during the period of organogenesis in all three animal species. Embryotoxicity was observed in rats, rabbits, and monkeys at oral doses that generated maternal toxicity. No teratogenic effects were observed in these studies. An oral peri-and post-natal developmental study was conducted in rats. Embryotoxicity was observed at the high dose that generated maternal toxicity. In addition, slight disturbances in the post-natal development of fetuses were noted in rats at doses that generated maternal toxicity. No effects on sexual maturation of the fetuses were noted in this study.

Azelaic acid is an ocular irritant to the rabbit and monkey eye. It can be presumed that the Finacea Foam formulation will be an ocular irritant as well. The 15% azelaic acid pre-foam emulsion is a mild irritant to rabbit skin but did not show any dermal irritation in mice. No skin sensitization potential of azelaic acid was noted. A nonclinical phototoxicity study is not needed for the 15% azelaic acid pre-foam emulsion, since no significant absorption was noted from the UVB/UVA/visible light spectrum.

The multiples of human exposure based on BSA comparison between NOAELs identified in pivotal toxicology studies and the maximum recommended human dose are considered adequate. The proposed clinical use of FINACEA Foam, 15% is supported by nonclinical data.

1.3 Recommendations

1.3.1 Approvability

NDA 207071 for FINACEA Foam, 15% is approvable from a pharmacological/toxicological perspective, provided that the recommended changes in the label described in Section 1.3.3 are incorporated into the FINACEA Foam label.

1.3.2 Additional Non Clinical Recommendations

The sponsor has agreed to conduct a 2-year dermal mouse carcinogenicity study with the azelaic acid pre-foam emulsion formulation as a PMR. The proposed timeline for the conduct and reporting of the PMR study are listed below. The proposed timeline is acceptable from a Pharmacology/Toxicology perspective.

Marketing authorization of azelaic acid foam, 15% / initiation of the 104-week dermal carcinogenicity study in CD-1 mice: July 2015

Start of in-life phase: December 2015

End of in-life phase: December 2017

Draft report: March 2019

Final report / submission: July 2019

1.3.3 Labeling

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the FINACEA Foam label reproduced below.

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Finacea[®] Foam is (b) (4) indicated for the topical treatment of inflammatory papules and pustules of mild to moderate rosacea.

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Therefore, Finacea Foam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Dermal embryofetal developmental toxicology studies have not been performed with azelaic acid, 15% foam. Oral embryofetal developmental studies were conducted with azelaic acid in rats, rabbits, and cynomolgus monkeys. Azelaic acid was administered during the period of organogenesis in all three animal species. Embryotoxicity was observed in rats, rabbits, and monkeys at oral doses of azelaic acid that generated some maternal toxicity. Embryotoxicity was observed in rats given 2500 mg/kg/day [162 times the maximum recommended human dose (MRHD) based on body surface area (BSA)], rabbits given 150 or 500 mg/kg/day (19 or 65 times the MRHD based on BSA) and cynomolgus monkeys given 500 mg/kg/day (65 times the MRHD based on BSA) azelaic acid. No teratogenic effects were observed in the oral embryofetal developmental studies conducted in rats, rabbits and cynomolgus monkeys.

An oral peri- and post-natal developmental study was conducted in rats. Azelaic acid was administered from gestational day 15 through day 21 postpartum up to a dose level of 2500 mg/kg/day. Embryotoxicity was observed in rats at an oral dose of 2500 mg/kg/day (162 times the MRHD based on BSA) that generated some maternal toxicity. In addition, slight disturbances in the post-natal development of fetuses was noted in rats at oral doses that generated some maternal toxicity (500 and 2500 mg/kg/day; 32 and 162 times the MRHD based on BSA). No effects on sexual maturation of the fetuses were noted in this study.

(b) (4)

(b) (4)

12.1 Mechanism of Action

The mechanism(s) by which azelaic acid interferes with the pathogenic events in rosacea are unknown.

(b) (4)

(b) (4)

12.2 Pharmacodynamics

(b) (4)

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Systemic long-term animal studies have not been performed to evaluate the carcinogenic potential of azelaic acid. In a 26-week dermal carcinogenicity study using transgenic (Tg.AC) mice, Finacea Gel and the gel vehicle, when applied once or twice daily, did not increase the number of female Tg.AC animals with papillomas at the treatment site. No statistically significant increase in the number of animals with papillomas at the treatment site was observed in male Tg.AC animals after once daily application. After twice daily application, Finacea Gel and the gel vehicle induced a statistically significant increase in the number of male animals with papillomas at the treatment site when compared to untreated males. This suggests that the positive effect may be associated with the vehicle application. The clinical relevance of the findings in animals to humans is not clear.

Azelaic acid was not mutagenic or clastogenic in a battery of in vitro [Ames assay, (b) (4) -[HGPRT] assay in V79 cells (Chinese hamster lung cells), and chromosomal aberration assay in human

lymphocytes] and in vivo (dominant lethal assay in mice and mouse micronucleus assay) genotoxicity tests.

Oral administration of azelaic acid at dose levels up to 2500 mg/kg/day (162 times the MRHD based on BSA) did not affect fertility or reproductive performance in male or female rats.

2 Drug Information

2.1 Drug

CAS Registry Number: 123-99-9

Generic Name: Azelaic acid (b) (4) 15%

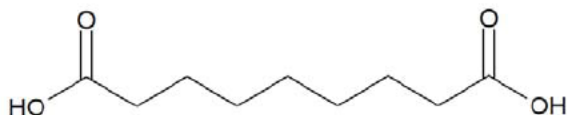
Code Name: ZK 62498, BAY 39-6251

Chemical Name: 1,7-Heptanedicarboxylic acid

Molecular Formula/Molecular Weight:

C₉H₁₆O₄ / 188.2

Structure Description:



Pharmacologic Class: Anti-keratinizing, anti-bacterial and anti-inflammatory agent

Reviewer's comments:

Although azelaic acid showed anti-keratinizing, anti-bacterial and anti-inflammatory activities in pharmacology studies, the clinical relevance is not clear. The mechanism(s) by which azelaic acid interferes with the pathogenic events in rosacea are unknown. There is no established pharmacologic class for azelaic acid in the FINACEA Gel label.

(b) (4)

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 20428 AZELEX (azelaic acid) Cream, 20%, acne vulgaris, DDDP, approved on 09/13/1995

NDA 21470 FINACEA (azelaic acid) Gel, 15%, rosacea, DDDP, approved on 12/24/2002
 IND 38271 azelaic acid cream, 20%, acne vulgaris, DDDP
 IND 61324 azelaic acid gel, 15%, rosacea, DDDP
 IND 63777 azelaic acid gel, 15%, acne vulgaris, DDDP
 IND 77516 azelaic acid foam, 15%, rosacea, DDDP

2.3 Drug Formulation

The composition of FINACEA (azelaic acid) Foam, 15% is listed in the following table (copied from submission).

Composition	Reference to Standard	Function	Amount [g]
Drug substance			
Azelaic acid (b) (4) drug substance	specification	Drug substance	15.00
Excipients			
Benzoic acid	USP/NF	(b) (4)	
Cetostearyl alcohol	USP/NF		
Dimethyl isosorbide	specification		
Medium-chain triglycerides	USP/NF		
Methylcellulose	USP/NF		
Mono- and di-glycerides	USP/NF		
Polyoxyl 40 stearate	USP/NF		
Polysorbate 80	USP/NF		
Propylene glycol	USP/NF		
Xanthan gum	USP/NF		
Sodium hydroxide ^a	USP/NF	(b) (4)	
Purified water	USP/NF		
Total			
(b) (4)			
(b) (4)			
a	(b) (4)		
b			
c			
d			
e			

2.4 Comments on Novel Excipients

There are no novel excipients. All the inactive ingredients are below approved levels listed in the FDA's database of inactive ingredients in approved drug products.

2.5 Comments on Impurities/Degradants of Concern

Impurities

Two degradation products were detected in stability studies: (b) (4)
(structures shown below). The two impurities can be formed by (b) (4)
respectively. (b) (4)

(b) (4)

The highest concentrations of the two degradants noted in long term stability samples are shown in the copied table below.

Table 1: Degradation products in 18 months stability samples

Storage conditions	30°C/65 % rh/upright	25°C/60 % rh/upright
Degradation products	(b) (4)	

The recommended maximum clinical daily dose of Finacea Form, 15% is 1 g, therefore, the maximum daily dose of azelaic acid is 150 mg. According to the ICH Q3B(R2) guidance, the qualification threshold for this maximum daily dose is 0.2%. The two degradants were detected at concentrations slightly higher the qualification threshold. Per the sponsor, both degradants are planned to have an upper limit of (b) (4) % in the specification for the drug substance ((b) (4) % in the final drug product). The sponsor has provided a scientific rationale, genotoxicity and repeat-dose toxicity data to support the proposed specification level. A safety evaluation is provided in Section 10 of this review. It is concluded that the proposed specification level for the two degradants is supported by toxicology data and considered acceptable.

Extractables and Leachables

Extraction studies using both aqueous solvent (aqueous buffer at pH 4) and organic solvent [n-hexane/isopropanol (90:10 v/v)] were performed to identify and quantify extractables resulting from the container-closure system. The following compounds were identified as potential leachables:

Potential leachables			
Name	CAS no.	Deriving from	Used detection technique
(b) (4)			LC/MS negative
			LC/MS negative
			LC/MS negative
			LC/MS negative
			LC/MS positive
			LC/MS positive
			LC/MS positive
			LC/MS positive
			LC/MS positive
			Headspace GC/MS

n.a.: no CAS no. assigned

A subsequent migration study was performed to identify and quantify leachables resulting from the container-closure system, with the following test schedule:

Storage condition	Test stations [months]								
	0	1	3	6	9	12	18	24	36
25 °C/60 % RH ^a	x	--	x	x	x	x	x	x	x
30 °C/65 % RH ^a	x	--	x	x	x	x	x	x	x
40 °C/75 % RH ^a	x	x	x	x	--	--	--	--	--

x test station

-- not required

^a The batches were stored in an inverted position (worst case)

The highest leachable concentrations detected during the migration study are listed in the copied table below.

Potential leachables			
Name	CAS no.	Concentration	Sample
(b) (4)			

A safety evaluation for the detected leachables is provided in Section 10 of this review. It is concluded that the leachables at detected levels do not pose significant safety risk during the proposed clinical use of the Finacea Foam product.

2.6 Proposed Clinical Population and Dosing Regimen

Clinical population: patients with inflammatory papules and pustules of mild to moderate rosacea.

Dosing regimen: Apply a (b) (4) amount of Finacea Foam twice daily (morning and evening) to the entire facial area, for up to 12 weeks.

Note: The tested maximum clinical dose in the Phase 3 trials was 0.5 g Finacea Foam applied twice daily for 12 weeks (1 g/day), which was the same maximum topical dose of Finacea Gel approved under NDA 21470.

2.7 Regulatory Background

AZELEX® (azelaic acid) Cream, 20% has been approved for the treatment of acne (initial approval 09/13/1995) under the sponsorship of Allergan (NDA 20428). FINACEA® (azelaic acid) Gel, 15% has been approved for the treatment of rosacea (initial approval 12/24/2002), initially under the sponsorship of Berlex (NDA 21470). Berlex now has become Bayer HealthCare Pharmaceuticals, the sponsor for this NDA. Berlex and Allergan co-marketed the drug product under NDA 20428. (b) (4)

However, the sponsor claims that all the pivotal toxicology studies conducted to support NDA 207071 are owned by either the sponsor or its mother company, Bayer AG, Germany. The sponsor submitted a list of toxicology studies conducted with azelaic acid, which are owned by Bayer, to this NDA (in SD 12). The toxicology studies listed in the submission contain all the necessary toxicology information to support a 505(b)(1) NDA submission. After consulting with the 505(b)(2) Coordinating Committee at CDER, it has been determined that this NDA submission is a 505(b)(1) NDA and a right-of-reference letter is not needed.

An End-of-Phase 2 meeting was conducted on 11/09/2011 and a Pre-NDA meeting was conducted on 07/09/2014, under the corresponding IND (IND 77516). It has been agreed during the two meetings that the results of the Tg.AC mouse assay conducted with Finacea (azelaic acid) Gel, 15% should be incorporated into the label for Finacea Foam, 15%, and that a dermal mouse carcinogenicity study will be conducted with the azelaic acid pre-foam formulation as a PMR.

3 Studies Submitted

3.1 Studies Reviewed

Pharmacokinetic Studies:

1. Validation of an LC-MS/MS Method for the determination of azelaic acid and pimelic acid in minipig plasma (Study# S318/08, sponsor's reference# A42924)
2. Validation of an LC-MS/MS Method for the determination of azelaic acid and pimelic acid in minipig plasma (Study# S324/08, sponsor's reference# A42929)
3. Validation of an HPLC-MS/MS Method for the determination of azelaic acid and pimelic acid in mouse plasma (Study# A62411, sponsor's reference# R-9265)
4. The in vitro percutaneous absorption of [14C]-azelaic acid (ZK62498) through human, hairless mouse and pig skin including metabolism in human skin (Study# 782463 070026K, sponsor's reference# A39236, reviewed under IND 77516)

General Toxicology Studies:

5. Systemic tolerance study in Beagle dogs after daily dermal administration over 26-27 weeks (Schering Report# 7080, reviewed under IND 38271)
6. Azelaic acid pre foam emulsion: a 13-week dermal toxicity study in mice (Study# 1575-014, sponsor's reference# R-9263)
7. Systemic tolerance study in monkeys (*Macaca fascicularis*) after daily per os (intragastric) administration over 28-29 days (Schering Report# 6517, reviewed under IND 38271)
8. A 13-week twice daily dermal toxicity study of azelaic acid (5%, 15%, 30%) pre-foam emulsion in Gottingen minipigs including a 4-week recovery period (Study# 1575-001, sponsor's reference# A42921, reviewed under IND 77516)
9. Systemic tolerance test in rats after daily intragastric administration over a period of 27 weeks (Schering Report# 7079, reviewed under IND 38271)

Genotoxicity Studies:

10. Evaluation of ZK 62498 in the Ames Salmonella/microsome mutagenicity test (Schering Report# 5239, reviewed under IND 38271)
11. ZK 62498: Evaluation in the Ames Salmonella/microsome mutagenicity test (Schering Report# 6874, reviewed under IND 38271)
12. Test report of study LMP 146: ZK 62498 – Detection of gene mutations in somatic mammalian cells in culture: HGPRT-test with V79 cells (Schering Report# 7081, reviewed under IND 38271)
13. ZK 62498: Evaluation of the clastogenic potential in the human lymphocyte test (Schering Report# 7082, reviewed under IND 38271)
14. Studies on the mutagenic potential of ZK 62498 in the mouse dominant lethal assay (Schering Report# 5461, reviewed under IND 38271)

15. Study of the mutagenic potential of azelaic acid (ZK 62498) in the mouse micronucleus test (Schering Report# A03118, reviewed under IND 63777)

Carcinogenicity Studies:

16. Azelaic acid pre-foam emulsion: a 104-week dermal carcinogenicity study in CD-1 mice (protocol)
17. Finacea: Short term carcinogenicity study in male and female Tg.AC mice with daily dermal administration over a period of 26 weeks (Study# TXST20040235, sponsor's reference# A24300, reviewed under NDA 21470)

Reproductive and Developmental Toxicology Studies:

18. Fertility study in the rat (Schering Report# 5943, reviewed under IND 38271)
19. Oral (gavage) teratology study in the rat (Schering Report# 5643, reviewed under IND 38271)
20. Embryotoxicity including teratogenicity study in rabbits by intragastric administration from day 6 to 27 of gestation (Schering Report# 5717, reviewed under IND 38271)
21. Teratology study in Cynomolgus monkeys (Schering Report# 5725, reviewed under IND 38271)
22. Peri- and postnatal study in rats after daily intragastric administration from day 15 postcoitum to day 21 postpartum (Schering Report# 5861, reviewed under IND 38271)

Special Toxicology Studies (including Local Tolerance Studies):

23. Local tolerance test of the vehicle of SH C 441 DA on the rabbit conjunctiva after a single application (Schering Report# 5706, reviewed under IND 38271)
24. Local tolerance test of SH C 441 DA (ZK 62.498) on the rabbit conjunctiva after a single application (Schering Report# 5738, reviewed under IND 38271)
25. SH C 441F: Local tolerance test on the monkey's (*Macaca fascicularis*) conjunctiva after a single application (Schering Report# 8639, reviewed under NDA 20428)
26. ZK 62498: Primary skin irritation study in rabbits (5-hour semi-occlusive application) (Study# B30993, sponsor's reference# A39237, reviewed under IND 77516)
27. ZK 62498: 4-week repeated dose dermal tolerance study in rabbits (5-hour semi-occlusive application) (Study# B31004, sponsor's reference# A39238, reviewed under IND 77516)
28. Azelaic acid pre foam emulsion: a 7-day dermal skin tolerability study in mice (Study# 110005T, sponsor's reference# R-9262)
29. Azelaic acid: Maximization test in guinea pigs to determine the potential sensitizing effect (Schering Report# 5200, reviewed under IND 38271)

30. Local lymph node assay (LLNA) in mice with pre-foam formulation vehicle and ZK 62498 pre-foam formulation 15% (Study# (b) (4) 1103100, sponsor's reference# A39239, reviewed under IND 77516)
31. Theoretical toxicity assessment of CAS (b) (4), n = 1), a leachable of "aza 15% foam" (drug substance azelaic acid) (Study# TOXT100073-1, sponsor's reference# AT06493)
32. Theoretical toxicity assessment of an impurity of azelaic acid (Study# TOXT100051-7, sponsor's reference# AT06502)
33. Structure-based assessment of potentially mutagenic impurities (Study# T101209-3, sponsor's reference# PH-37869)
34. Azelaic acid pre foam emulsion: a 4-week dermal toxicity study in mice (Study# 1575-016, sponsor's reference# R-9312)
35. Azelaic acid 15% foam: Toxicological assessment of degradation products
36. Azelaic acid 15% foam: Toxicological assessment of leachables

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

- Nonclinical reviews, NDA 21470
- Nonclinical reviews, IND 77516

4 Pharmacology

4.1 Primary Pharmacology

No pharmacology studies were included in this NDA submission as the sponsor stated that there is no pharmacological model for rosacea. It has been shown that azelaic acid has antimicrobial activity and effects on keratinization (from nonclinical reviews for NDA 21470 and IND 77516)

Azelaic acid has demonstrated in vitro bacteriostatic and bacteriocidal activity against a variety of aerobic and anaerobic bacteria including *Propionibacterium acnes* and *Staphylococcus aureus*. A reduction of follicular epithelial hyperplasia was observed after daily application of an ethanolic solution containing 20% azelaic acid or after daily application of azelaic acid 20% cream for 11 days to rabbit ears. Literature also showed other pharmacological activities of azelaic acid, including anti-inflammatory activities, inhibition of mitochondria and pigmented cell systems and inhibition on the generation/release of reactive oxygen species in neutrophils. However, considering the pathogenesis mechanism of rosacea is not clear, the relevance of these multiple pharmacological activities of azelaic acid to the treatment of rosacea is not known.

The following information regarding azelaic acid's pharmacological activity is contained in the Finacea Gel label.

12.1 Mechanism of Action

The mechanism(s) by which azelaic acid interferes with the pathogenic events in rosacea are unknown.

12.2 Pharmacodynamics

The pharmacodynamics of azelaic acid in association with the treatment of rosacea are unknown.

Reviewer's comment:

It is recommended that the same language be used for the Finacea Foam label.

4.2 Secondary Pharmacology

None.

4.3 Safety Pharmacology

No safety pharmacology studies were included in this NDA submission. The following safety pharmacology information was obtained from nonclinical reviews for NDA 21470.

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

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

Nonclinical safety pharmacology studies did not indicate significant effects of azelaic acid on intermediate metabolism, liver function, renal function, cardiovascular function, smooth muscle or the nervous system under the conditions used in these studies.

5 Pharmacokinetics/ADME/Toxicokinetics

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

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

^{14}C -Azelaic acid was almost completely absorbed in rats, rabbits, dogs and monkeys when given as a single oral (gavage) administration of a (b) (4) suspension at doses (1000 mg/kg in rats, 500 mg/kg in rabbits, 100 mg/kg in dogs and 150 mg/kg in monkeys) which were comparable to those used in toxicology studies. Excretion of the label was mainly in the urine (~50%) across all species.

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

The ^{14}C -label was rapidly distributed throughout rat body tissues after a single intravenous dose of 10 mg/kg ^{14}C -azelaic acid. High levels of radioactivity were found in the kidney (the main organ of excretion) and in the liver, and trace amounts of radioactivity appeared to cross the blood/brain barrier (brain, spinal cord). No radioactivity was detected in the fetuses of pregnant rats given a single 10 mg/kg dose of ^{14}C -azelaic acid intravenously. No differences in distribution pattern were observed between albino and pigmented rats. The ^{14}C -label was rapidly excreted (within 24 hours of injection) mainly through the urine (64%) and with respiratory air (18%). Only a trace amount of radioactivity (1.5%) was present in the feces.

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

intravenous dose of 10 mg/kg ^{14}C -azelaic acid. This result suggests that azelaic acid may be metabolized to a greater extent in monkeys than in other animals.

The in vitro skin penetration of ^{14}C -azelaic acid foam (using the 15% foam formulation minus the propellant) and ^{14}C -azelaic acid gel (15%) were compared using human, pig and hairless mouse skin in a flow through diffusion cell apparatus. No significant difference in the dermal delivery was noted between the foam and gel formulations (human skin: 0.94% and 1.27% of the applied dose for the foam and gel formulations, respectively; pig skin: 0.68% and 1.12% of the applied dose for the foam and gel formulations, respectively; hairless mouse skin: 4.49% and 3.74% of the applied dose for the foam and gel formulations, respectively). In addition, no significant difference in percutaneous steady state flux was noted between the foam and gel formulations. The results from this in vitro percutaneous absorption study indicate that similar systemic exposure is expected after topical administration of the azelaic acid foam and gel formulations.

The following pharmacokinetics information is contained in the Finacea Gel label.

12.3 Pharmacokinetics

The percutaneous absorption of azelaic acid after topical application of FINACEA Gel could not be reliably determined. Mean plasma azelaic acid concentrations in rosacea subjects treated with FINACEA Gel twice daily for at least 8 weeks are in the range of 42 to 63.1 ng/ml. These values are within the maximum concentration range of 24.0 to 90.5 ng/ml observed in rosacea subjects treated with vehicle only. This indicates that FINACEA Gel does not increase plasma azelaic acid concentration beyond the range derived from nutrition and endogenous metabolism.

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

6 General Toxicology

6.1 Single-Dose Toxicity

Azelaic acid was evaluated for its acute toxicological effects in male and female mice, male rats and male and female dogs following oral (gavage) and intraperitoneal administration.

Following single oral (gavage) doses of azelaic acid administered as a (b) (4) suspension, the minimum lethal doses were 3750 mg/kg (male mice) and 5000 mg/kg (female mice and male rats). After intraperitoneal administration, the minimum lethal doses were 400 mg/kg (male rats) and 500 mg/kg (male and female mice). A separate intraperitoneal study was conducted in male rats to determine the acute toxicity of sodium azelinate vs azelaic acid administered as a (b) (4) suspension. No

male rats died after intraperitoneal administration of up to 1000 mg/kg sodium azelinate. The main clinical signs noted in this study included apathy, disturbances in gait, prone position (conscious), eyelid closure, extended abdomen (mice and rats, intraperitoneal), accelerated respiration (rats, oral), unconsciousness and tremor (rats, intraperitoneal). Death occurred within 30 minutes to 7 days after intraperitoneal administration and 1.5 to 3 days after oral administration. The stomach and intestine were identified as potential target organs of toxicity in mice and rats. Necropsy findings in mice that died prematurely included punctiform black foci of the gastric glandular mucosa, white covering of the fatty tissue of the abdominal cavity and slight reddening of the intestine. Necropsy findings in rats that died prematurely included petechial hemorrhage of the gastric glandular mucosa, hemorrhage in the mucosa of the small intestine and prominent vessels of the gastrointestinal tract.

Emesis was observed immediately to 4.5 hours following single oral (gavage) doses of azelaic acid (at doses of 250 mg/kg and higher) administered as a (b) (4) suspension in dogs. Diarrhea also occurred 2.5 to 3.5 hours after dosing in dogs given azelaic acid at a dose level of 5000 mg/kg.

6.2 Repeat-Dose Toxicity

Repeat Dose Systemic Toxicology Studies:

Azelaic acid was evaluated for systemic toxicity in rats (27-week repeat dose study), monkeys (4-week repeat dose study) and dogs (6-month repeat dose study, not included in this NDA) following oral (gavage) administration.

Azelaic acid (0, 100 and 1000 mg/kg/day) was orally (gavage) administered as a daily (b) (4) suspension to rats for 27 weeks. Lower body weight gain (high dose), slightly lower food consumption (both dose groups) and slightly higher water consumption (high dose) were noted in treated animals compared to control animals. Postmortem findings included thickening of the cuticular ridge of the stomach (both dose levels) accompanied by evagination and epithelia overgrowth in the high dose animals. The NOAEL was identified as 100 mg/kg/day in this study.

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

Repeat Dose Dermal Toxicology Studies:

Dermal toxicity studies were conducted in rats (6-month repeat dose study, not included in this NDA) and dogs (26-week repeat dose study) with azelaic acid 20% cream and in minipigs (13-week repeat dose study) and mice (13-week repeat dose study) with azelaic acid 15% pre-foam emulsion.

Dermal doses of 0 (vehicle) and 300 mg/kg/day azelaic acid (20% cream) were applied to dogs once daily for 26 weeks. Each day the application site was occluded with gauze dressing for 24 hours after dosing. No treatment-related systemic effects were noted in this study. Slight irritation was noted at the application site, which was observed more frequently in treated animals compared with control animals. The systemic NOAEL was identified as 300 mg/kg/day (maximum feasible dose) in this study.

Dermal doses of 0 (untreated control), 0 (vehicle), 75, 225 and 450 mg/kg/day azelaic acid (5, 15, and 30% emulsion applied to 10% body surface area at 0.75 ml/kg/dose twice daily) were applied to minipigs for 13 weeks. The application area was semi-occluded with 4 to 5 layers of gauze for 6 hours per dose with 4 hours between doses. No treatment-related findings on mortality, clinical signs, dermal irritation, body weight, ophthalmoscopic evaluation, ECG, hematology or clinical chemistry parameters, organ weights, macroscopic or microscopic parameters were noted in this study. The NOAEL was identified as the high dose, 450 mg/kg/day (twice daily administration of 30% azelaic acid pre-foam emulsion). This dose was the maximum feasible dose (30% is the maximum feasible concentration in the foam formulation and 0.75 ml/kg/dose is the maximum feasible dose volume). The corresponding Day 90 azelaic acid AUC_{0-24 hr} values were 4423 ng·hr/ml in males and 4268 ng·hr/ml in females.

A 13-week repeat dose dermal toxicity study was conducted in mice with azelaic acid pre-foam emulsion as a dose range-finding study for a 2-year dermal mouse carcinogenicity study. This study is reviewed below.

Study title: Azelaic acid pre foam emulsion: a 13-week dermal toxicity study in mice

Study no.:	1575-014 (sponsor's reference# R-9263)
Study report location:	SD 1, NDA 207071
Conducting laboratory and location:	(b) (4)
Date of study initiation:	09/12/2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Azelaic acid pre-foam emulsion vehicle, lot# 1061501 Azelaic acid 5% pre-foam emulsion, lot# 1072801 Azelaic acid 15% pre-foam emulsion, lot# 1062101 Azelaic acid 30% pre-foam emulsion, lot# 1062301

Key Study Findings

It has been determined previously that 30% azelaic acid is the maximum feasible concentration in the pre-foam emulsion formulation (IND 77516 nonclinical review). Per the sponsor the dose volume of 5 ml/kg is the maximum feasible amount of the emulsion applied to 10% BSA in mice.

No significant treatment-related dermal or systemic toxicity was noted in the study. Minimal to mild epidermal hyperplasia and/or hyperkeratosis were observed at treated

skin sites in the vehicle control group and the three dose groups. These findings were considered vehicle-related effects.

The NOAEL was identified as the high dose, 3000 mg/kg/day (30% pre-foam emulsion applied twice daily at 5 ml/kg). The Week 13 AUC₀₋₂₄ values at high dose were 116 and 353 µg·hr/ml in male and female mice, respectively.

Methods

Doses:	0 (vehicle), 0 (untreated), 500, 1500, and 3000 mg/kg/day (5%, 15% and 30% emulsion)
Frequency of dosing:	Twice daily for 13 weeks (~8 hours apart)
Route of administration:	Dermal, non-occluded
Dose volume:	5 ml/kg/dose, applied to 10% BSA (10 ml/kg/day)
Formulation/Vehicle:	Provided by the sponsor
Species/Strain:	CD-1 mice
Number/Sex/Group:	10/sex/group
Age:	~6 weeks
Weight:	28.8-36.3 g for males, 21.7-28.1 g for females
Satellite groups:	TK animals: 8/sex for vehicle and untreated control, 21/sex/group for dose groups
Unique study design:	The animals were individually housed in suspended, stainless steel, wire-mesh type cages.
Deviation from study protocol:	None remarkable

Observations and Results

Mortality

No treatment-related mortality was noted. Several mice were found dead during the study; however, there was no relation to dose. These deaths included one vehicle control female, 2 TK males at low dose, and one untreated control TK female.

Clinical Signs

No significant treatment-related signs were noted.

Dermal Observation

The test site of main study animals was evaluated for erythema and edema beginning on Day 7 and weekly thereafter. No erythema or edema was noted at any time point.

Body Weights

Body weights for all animals were measured and recorded 3 days after receipt, prior to randomization, and weekly during the study. No significant treatment-related effects were noted.

Food consumption

Food consumption was measured and recorded weekly during the study for main study animals. No significant treatment-related effects were noted.

Ophthalmoscopy

Ophthalmoscopic examinations were conducted on all animals pretest and during Week 13 on main study animals in the two control groups and the high dose group. No significant treatment-related findings were noted.

Hematology

Hematology was examined prior to terminal necropsy. No significant treatment-related effects were noted.

Clinical Chemistry

Clinical chemistry was examined prior to terminal necropsy. No significant treatment-related effects were noted.

Gross Pathology

No significant treatment-related findings were noted.

Organ Weights

The following organs were weighed: adrenal gland, brain, heart, kidneys, liver, lungs, ovaries, pituitary gland, prostate, seminal vesicles, spleen, testes, thymus, thyroid with parathyroid glands, and uterus.

No significant treatment-related effects were noted.

Histopathology

Adequate Battery: Yes.

The following listed tissues were examined for animals in the two control groups and the high dose group. In addition, skin (treated and untreated) and gross lesions were also examined for the low dose and mid dose groups.

Adrenal gland, aorta, bone with marrow (femur and sternum), brain, epididymis, esophagus, eye, gallbladder, gut associated lymphoid tissue, heart, intestine (cecum, colon, rectum, duodenum, ileum, jejunum), kidney, lachrymal gland, larynx, liver, lung, lymph node (mandibular, mesenteric), mammary gland (females only), nerve (optic and sciatic), ovaries, pancreas, pituitary gland, prostate, salivary gland (mandibular, sublingual), seminal vesicle, skeletal muscle, skin (treated and untreated), spinal cord,

spleen, stomach, testis, thymus, thyroid (with parathyroid) gland, tongue, trachea, ureter, urinary bladder, uterus (with cervix), and vagina.

Peer Review: Yes

Histological Findings:

There were no significant test article-related microscopic findings. Vehicle-related microscopic findings were noted at the treated skin sites.

Minimal to mild epidermal hyperplasia and/or hyperkeratosis were observed at treated skin sites in the vehicle control group and the three dose groups. Hyperkeratosis was defined as an increase in the thickness of the keratin layer on the surface of the epidermis. Epidermal hyperplasia was defined as hyperplasia of all layers of the nucleated cells in the epidermis (basal, prickle, and granular cell layers). The incidence and severity of the microscopic findings at the treated skin sites was similar in the vehicle control group and the three dose groups (see the copied table below). Therefore, these findings were considered vehicle-related effects.

Test Article-related Microscopic Observations - Terminal										
Dose level: mg/kg/day	0		Naïve Control		500		1500		3000	
Sex	M	F	M	F	M	F	M	F	M	F
Number Examined	10	10	10	10	10	10	10	10	10	10
Skin, treated										
Hyperkeratosis, minimal	7	6	0	0	8	7	10	8	8	6
Hyperplasia, epidermal	10	10	0	0	9	9	10	8	10	9
-minimal	8	7	0	0	7	9	8	7	8	8
-mild	2	3	0	0	2	0	2	1	2	1
M - Male F - Female										

Toxicokinetics

Blood samples were collected in Weeks 4 and 13 for plasma analysis and TK analysis of azelaic acid and pimelic acid (a metabolite). As azelaic acid and pimelic acid occurring in plasma physiologically, low concentrations of azelaic acid and pimelic acid were found in plasma samples of vehicle control and untreated control animals during Weeks 4 and 13 (azelaic acid mean values were 0.0383 to 0.0636 µg/ml and pimelic acid mean values were 0.0187 to 0.0368 µg/ml). Per the sponsor, an investigation was conducted and it did not find any other cause for these values.

The TK parameters are listed in the following two tables.

Toxicokinetic Parameters for Azelaic Acid

Week	Dose (mg/kg/day)	Sex	AUC₀₋₂₄ (hr•µg/mL)	C_{max} (µg/mL)	T_{max} (hr)
4	500	Male	40.1	17.0	1.00
		Female	26.8	9.99	1.00
		Combined	33.4	13.5	1.00
	1500	Male	108	36.3	1.00
		Female	188	81.5	1.00
		Combined	148	58.9	1.00
	3000	Male	182	38.2	4.00
		Female	266	39.4	1.00
		Combined	224	38.8	2.50
13	500	Male	27.5	10.5	1.00
		Female	39.7	15.9	1.00
		Combined	33.6	13.2	1.00
	1500	Male	120	26.8	1.00
		Female	115	47.4	1.00
		Combined	118	37.1	1.00
	3000	Male	116	36.6	1.00
		Female	353	133	1.00
		Combined	234	84.9	1.00

Toxicokinetic Parameters for Pimelic Acid

Week	Dose (mg/kg/day)	Sex	AUC₀₋₂₄ (hr•µg/mL)	C_{max} (µg/mL)	T_{max} (hr)
4	500	Male	6.95	2.70	1.00
		Female	1.49	0.328	1.00
		Combined	4.22	1.52	1.00
	1500	Male	10.1	2.57	1.00
		Female	9.25	3.64	1.00
		Combined	9.66	3.10	1.00
	3000	Male	15.5	1.29	6.00
		Female	18.3	1.96	6.00
		Combined	16.9	1.62	6.00
13	500	Male	2.25	0.460	1.00
		Female	2.07	0.445	1.00
		Combined	2.16	0.452	1.00
	1500	Male	9.59	2.64	4.00
		Female	4.69	1.23	1.00
		Combined	7.14	1.94	2.50
	3000	Male	13.4	3.63	1.00
		Female	16.0	6.09	1.00
		Combined	14.7	4.86	1.00

The systemic exposure to azelaic acid was slightly higher in females than males at high dose. Mean AUC_{0-24} and C_{max} increased in approximate proportion to the increase in dose between 500 and 3000 mg/kg/day. Drug accumulation was not significant when comparing the combined AUC_{0-24} values at Weeks 4 and 13.

Dosing Solution Analysis

The test articles were directly provided by the sponsor. No dosing solution analysis was conducted in the study.

Reviewer's comments:

The chronic dermal toxicology study was conducted with 20% azelaic acid cream formulation in dogs. An in vitro skin penetration study showed that there was no significant difference in dermal absorption between the 15% azelaic acid foam and gel formulations using human, pig or hairless mouse skin. In addition, results from two in vivo percutaneous absorption studies indicate that the cream formulation provides a slightly higher systemic exposure after dermal administration compared to the gel formulation (IND 77516 nonclinical review). Therefore it is expected that the 20% cream formulation would generate higher systemic exposure compared to the 15% foam formulation. Overall the chronic dermal toxicology study in dogs conducted with 20% cream formulation and 13-week dermal toxicology studies in mice and minipigs conducted with 15% pre-foam emulsion are considered adequate for the dermal toxicity evaluation of the 15% azelaic acid foam.

7 Genetic Toxicology

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

The mutagenic potential of azelaic acid (0.01 to 10 mg/plate; 0.1 to 5 mg/plate) was evaluated in two Ames tests with direct plate incorporation in the presence and absence of metabolic activation. Azelaic acid was negative for mutagenicity when evaluated in either of these tests.

The mutagenic potential of azelaic acid (0, 0.19, 0.75, 1.32, and 1.88 mg/ml) was evaluated in vitro in the HGPRT assay in V79 cells in the presence and absence of metabolic activation. Azelaic acid was negative for mutagenicity when evaluated in this assay.

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

A single dose of azelaic acid (0, 500, 1000 and 2000 mg/kg) was orally (gavage) administered as a (b) (4) suspension to male mice to determine its genotoxicity in the dominant lethal assay. Following treatment, males were mated with untreated females for a mating period of 4 days. Females were replaced 11 times for a total of 48 days of breeding. Four of fifty males died in the high dose group. No significant genotoxicity was noted in any mating interval and no compound-related effects on fertility index, total implants, numbers of liver or dead implants or death index was observed in this study.

A single dose of azelaic acid (0, 500, 1000 and 2000 mg/kg) was orally (gavage) administered as a (b) (4) suspension to mice to evaluate its clastogenic potential in a mouse micronucleus assay. Bone marrow was obtained for analysis at 24 and 48 hours after dosing. Azelaic acid did not demonstrate clastogenicity under the conditions of this assay.

The following genetic toxicology information is contained in the Finacea Gel label.

Azelaic acid was not mutagenic or clastogenic in a battery of in vitro [Ames assay, HGPRT in V79 cells (Chinese hamster lung cells), and chromosomal aberration assay in human lymphocytes] and in vivo (dominant lethal assay in mice and mouse micronucleus assay) genotoxicity tests.

Reviewer's comments:

It is recommended the same language be used for the Finacea Foam label, with a minor editorial change: adding the word "assay" after HGPRT.

8 Carcinogenicity

A dermal carcinogenicity study in transgenic mice (Tg.AC assay) has been conducted with azelaic acid 15% gel as a post-marketing commitment (PMC) for NDA 21470. The study report was submitted on 11/07/2006 and reviewed by the Exec CAC on 09/11/2007. A summary of this study is provided below (NDA 21470 nonclinical review).

Topical doses of 0 (sheared control), 0 (hydrogel vehicle control), 31.2 and 62.4 mg/day azelaic acid were administered to Tg.AC mice (20/sex/dose). Hydrogel vehicle control and high dose azelaic acid gel were administered twice daily (0.2 ml/application) for 26 weeks. Low dose azelaic gel was administered once daily (0.2 ml/application) for 26 weeks. Two positive control groups were incorporated into this study. Topical doses of 1.25 µg/day TPA in acetone and 10 µg/day TPA in hydrogel were administered (0.2 ml/application) to Tg.AC mice (15/sex/dose), 3X/week, for 26 weeks. A previous dose ranging study had determined that the extent of skin papilloma formation was similar for the 10 µg/day TPA in hydrogel vehicle compared to 1.25 µg/day TPA in acetone after 26 weeks of administration to Tg.AC mice.

The vehicle caused a statistically significant increase in the incidence of male animals with papillomas (10/20) compared to untreated male animals (0/20) with no further increase noted after exposure to a high dose of the active (8/20). Therefore, a positive effect was noted in vehicle and high dose males compared to untreated males in the Tg.AC mouse assay. No statistically significant increase in the incidence of female animals with papillomas was noted in the low (1/20) and high dose groups (3/20) compared to untreated (3/20) and vehicle (0/20) treated groups. Therefore, no effect was noted in female animals in the Tg.AC mouse assay.

The Exec CAC conclusions after reviewing this study are provided below.

- 1) *The Committee agreed that the study was adequate.*
- 2) *The Committee concluded that the Tg.AC mouse assay was negative for female mice and positive for male mice, noting a statistically significant increase in the incidence of males with papillomas in the vehicle and high dose groups compared to untreated control. The Committee noted that there was no statistically significant difference in the incidence of males with papillomas in the vehicle and high dose groups which suggested that the positive effect may be due to the vehicle only. There was no statistically significant increase in the incidence of treated females with papillomas compared to vehicle or untreated females.*

A labeling supplement was requested to be submitted to incorporate the findings of the Tg.AC mouse assay conducted with FINACEA Gel and the labeling supplement was submitted on 04/06/2009. In addition, it was initially determined that a 2-year dermal mouse carcinogenicity study should be conducted as an additional PMC for FINACEA Gel based on the positive signal noted in the Tg.AC mouse assay. As the sponsor intends to develop a new foam formulation for azelaic acid, it was determined that a 2-year dermal mouse carcinogenicity study should also be conducted as a PMC for azelaic acid foam formulation. Subsequently after a comprehensive review of all positive Tg.AC mouse assay results that have been submitted to the Agency at that time, the need for a 2-year dermal carcinogenicity study as an additional PMC for Finacea Gel was re-evaluated and it was concluded that another dermal carcinogenicity study is not needed for Finacea Gel (NDA 21470 to nonclinical reviews).

During the Pre-NDA meeting conducted under IND 77516, the corresponding IND for this NDA, the sponsor proposed to conduct a 2-year dermal carcinogenicity study as a PMC for azelaic acid foam formulation. Further, the sponsor inquired if the results of the Tg.AC mouse assay conducted with Finacea gel do not need to be incorporated into the label of azelaic acid foam. The Division responded that it might be possible to remove the Tg.AC mouse assay conducted with Finacea gel from the azelaic acid foam label and replace it with the results of the dermal mouse carcinogenicity study conducted with azelaic acid foam. This will be determined after review of the final study report.

The sponsor submitted a 2-year dermal mouse carcinogenicity study protocol to the NDA and the protocol is summarized below.

Study title: Azelaic acid pre-foam emulsion: 104-week dermal carcinogenicity study in CD-1 mice (protocol)

Study no.: N/A
Study report location: N/A
Conducting laboratory and location: Unknown
Date of study initiation: Unknown
GLP compliance: Will be
QA statement: Will be
Drug, lot #, and % purity:

(b) (4)

Methods

Doses:

Frequency of dosing:
Route of administration:
Dose volume:
Formulation/Vehicle:
Species/Strain:
Number/Sex/Group:
Age:
Weight:
Satellite groups:

Unique study design:

Deviation from study protocol:

Observations

Mortality/Moribundity:
Detailed clinical examinations:
Dermal observations:

Body weight:

Food consumption:

Clinical Pathology:
TK:
Gross pathology:
Organ weights:

(b) (4)

The proposed timelines for the conduct and reporting of this dermal mouse carcinogenicity study are listed below.

Marketing authorization of azelaic acid foam, 15% / initiation of the 104-week dermal carcinogenicity study in CD-1 mice: July 2015

Start of in-life phase: December 2015

End of in-life phase: December 2017

Draft report: March 2019

Final report / submission: July 2019

Discussion:

Azelaic acid is a dietary constituent and is also produced in endogenous metabolism. Azelaic acid is mainly excreted unchanged in the urine but in part also undergoes β -oxidation to shorter dicarboxylic acids such as pimelic acid. β -oxidation was also indicated as metabolic pathway for azelaic acid in CD1-mice and therefore CD1-mouse is considered a relevant species for use in long-term carcinogenicity testing.

In the 13-week dose range-finding study in mice, azelaic acid pre-foam formulation was tested up to the maximum feasible dose (MFD) and no significant dermal or systemic toxicity was noted. Twice daily administration is consistent with the intended clinical administration of the drug product. The sponsor proposes to use the same doses in the 2-year carcinogenicity study that were tested in the 13-week toxicity study. (b) (4)

The sponsor's proposal is considered appropriate. The proposed timeline for this PMR study is also considered acceptable.

This carcinogenicity study protocol was presented to and reviewed by the Exec CAC on 03/10/2015. The Exec CAC conclusions after reviewing this protocol are provided below.

(b) (4)

The following carcinogenicity information is contained in the Finacea Gel label.

Systemic long-term animal studies have not been performed to evaluate the carcinogenic potential of azelaic acid. In a 26-week dermal carcinogenicity study using transgenic (Tg.AC) mice, FINACEA® Gel and the gel vehicle, when applied once or twice daily, did not increase the number of female Tg.AC animals with papillomas at the treatment site. No statistically significant increase in the number of animals with papillomas at the treatment site was observed in male Tg.AC animals after once daily application. After twice daily application, FINACEA® Gel and the gel vehicle induced a statistically significant increase in the number of male animals with papillomas at the treatment site when compared to untreated males. This suggests that the positive effect may be associated with the vehicle application. The clinical relevance of the findings in animals to humans is not clear.

Reviewer's comments:

It is recommended the same language be used for the Finacea Foam label at this time. The carcinogenicity information contained in the drug label should be updated once the 2-year dermal mouse carcinogenicity study is completed and submitted for review.

9 Reproductive and Developmental Toxicology

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

Azelaic acid (0, 50, 500 and 2500 mg/kg/day) was orally (gavage) administered as a (b) (4) suspension to rats in a combined fertility and embryofetal developmental study. The high dose for this study was based on the results of a 4-week oral repeat dose study in rats. High mortality was noted at 5000 mg/kg/day in the 4-week oral repeat dose study, so 2500 mg/kg/day was selected as the high dose in this study. Male rats were treated once daily for ~84 days (70 days prior to mating through 14 days of mating). Female rats were treated once daily for ~48 or 71 days (14 days prior to mating through Day 20 of gestation or Day 21 postpartum). No effects were

noted on the fertility of the P-generation or their offspring or the general reproductive performance of the F-generation. No teratogenicity was observed in the F-1 or F-2 generation pups. Two of thirty high dose males died during the study. Stertorous breathing was noted as a clinical sign in mid (1/30) and high dose (6/30) P-generation males. Lower body weight gain was noted in mid and high dose P-generation males (-4 and -20%, respectively). Lower body weight gain was noted in mid and high dose P-generation females (-3 and -15%, respectively). The total intra-uterine deaths (post-implantation loss) were 3.7 times higher in the high dose group compared to the control group. Pup weight in the offspring of high dose dams was slightly lower (1–6%) than controls on days 7, 14 and 21. The increase in embryoletality and decreased pup weight noted in the high dose group may have been due to the decrease in maternal body weight gain noted in the high dose group. The NOAEL for fertility and teratogenicity was identified as the high dose, while the NOAEL for embryotoxicity was identified as the mid dose.

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

Azelaic acid (0, 50, 150 and 500 mg/kg/day) was orally (gavage) administered as a (b) (4) suspension to pregnant female rabbits from gestation Day 6 to 27 inclusive in an embryofetal developmental study. The high dose was selected based on a dose range-finding study. A slight decrease in maternal body weight gain was noted in all treatment groups compared to control animals. The incidence of embryoletality was slightly higher in the mid (+4.1%) and high (+4.5%) dose groups compared to control animals. The slight increase in embryoletality noted in mid and high dose groups may have been related to the slight decrease in maternal body weight gain noted in these dose groups. An increased incidence of incomplete or no ossification of the 5th sternebra was observed in fetuses from all dose groups. No other effects were noted and this slight variation was considered not biologically relevant. Therefore, it was determined that no teratogenicity was observed in rabbits under the conditions of this study. The NOAEL for teratogenicity was identified as the high dose, while the NOAEL for embryotoxicity was identified as the low dose.

Azelaic acid (0, 50, 150 and 500 mg/kg/day) was orally (gavage) administered as a (b) (4) suspension to pregnant female monkeys from gestation Day 19 to 50 inclusive in an embryofetal developmental study. The high dose was selected based on

a dose range-finding study. A slight decrease in food consumption was noted in mid and high dose animals compared to control animals. Emesis was noted as a clinical sign in high dose animals. A higher incidence of spontaneous abortions was noted in high dose animals compared to control animals. The higher incidence of spontaneous abortions noted in the high dose group may have been related to the slight maternal toxicity noted in high dose animals (slight decrease in food consumption and emesis). No teratogenicity was observed in this study. The NOAEL for teratogenicity was identified as the high dose, while the NOAEL for embryotoxicity was identified as the mid dose.

In a peri- and post-natal developmental study, azelaic acid (0, 50, 500 and 2500 mg/kg/day) was orally (gavage) administered as a (b) (4) suspension to rats from Day 15 of gestation through Day 21 postpartum. Mortality was noted in the mid (1/25) and high (2/25) dose group F0 dams. A significant decrease in body weight gain was observed in the mid (-25%) and high dose (-24%) group F0 dams on Day 20 post coitum. The mortality rate of high dose F1 animals was significantly higher (+21%) than control animals. The body weights of high dose F1 animals were moderately lower (-16% in males, -9% in females) on Day 90 postpartum compared to control animals. The preimplantation loss was increased (+20%) in high dose F1 females compared to control animals. A slightly higher incidence of delayed ossification of single fetal bones was observed in the high dose F2 generation rats compared to control animals. This change was attributed to a slight disturbance in the reproductive performance of the high dose F1 females. This may have been associated with the toxicity noted in the high dose group. In summary, the mid and high dose levels expressed toxicity in F0 females (slightly increased mortality rates and decreased body weight gain) which produced slight disturbances in the post-natal development of F1 rats and in the reproductive performance of F1 females. The NOAEL for developmental toxicity was identified as the mid dose, while the NOAEL for maternal toxicity was identified as the low dose.

The following reproductive and developmental toxicity information is contained in the Finacea Gel label.

Teratogenic Effects: Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Therefore, FINACEA Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Dermal embryofetal developmental toxicology studies have not been performed with azelaic acid, 15% gel. Oral embryofetal developmental studies were conducted with azelaic acid in rats, rabbits, and cynomolgus monkeys. Azelaic acid was administered during the period of organogenesis in all three animal species. Embryotoxicity was observed in rats, rabbits, and monkeys at oral doses of azelaic acid that generated some maternal toxicity. Embryotoxicity was observed in rats given 2500 mg/kg/day [162 times the maximum recommended human dose (MRHD) based on body surface area

(BSA)], rabbits given 150 or 500 mg/kg/day (19 or 65 times the MRHD based on BSA) and cynomolgus monkeys given 500 mg/kg/day (65 times the MRHD based on BSA) azelaic acid. No teratogenic effects were observed in the oral embryofetal developmental studies conducted in rats, rabbits and cynomolgus monkeys. An oral peri-and post-natal developmental study was conducted in rats. Azelaic acid was administered from gestational day 15 through day 21 postpartum up to a dose level of 2500 mg/kg/day. Embryotoxicity was observed in rats at an oral dose of 2500 mg/kg/day (162 times the MRHD based on BSA) that generated some maternal toxicity. In addition, slight disturbances in the post-natal development of fetuses was noted in rats at oral doses that generated some maternal toxicity (500 and 2500 mg/kg/day; 32 and 162 times the MRHD based on BSA). No effects on sexual maturation of the fetuses were noted in this study.

Oral administration of azelaic acid at dose levels up to 2500 mg/kg/day (162 times the MRHD based on BSA) did not affect fertility or reproductive performance in male or female rats.

Reviewer's comments:

It is recommended that the same language be used for the Finacea Foam label at this time. The recommended maximum clinical dose for Finacea Foam is 1.0 g/day, which is the same topical dose of Finacea Gel approved under NDA 21470. Therefore the multiples of MRHD should remain the same as in the Finacea Gel label.

10 Special Toxicology Studies

Ocular Tolerance Studies

Ocular tolerance studies were conducted in rabbits and monkeys. 0.1 ml vehicle or a preservative-free formulation of azelaic acid 20% cream was administered to the rabbit eye. Moderate to severe ocular irritation was noted after the treatment with the cream formulation, with findings of reddening, swelling, erosion of cornea, secretion, eyelid closure and necrosis of parts of conjunctiva. Only a slight irritation was noted in the vehicle control group. A second ocular tolerance study was conducted in monkeys considering monkey eye is better comparable to human eye. A single application of 40 mg azelaic acid 20% cream was administered to the monkey eye and the treated eyes were rinsed 30 seconds after administration. Pain reactions were noted immediately after application and disappeared after rinsing. Local findings, including reddening, swelling and vessel injections of the conjunctiva were noted despite rinsing. These findings were transient and were no longer noted after 1 to 4 days.

The ocular irritation was judged to be mainly due to azelaic acid because only a slight irritation was noted with the cream vehicle alone. Azelaic acid appears to be an ocular irritant to the rabbit and monkey eye. It can be presumed that the 15% azelaic acid foam formulation will be an ocular irritant as well. No additional ocular irritation study is considered necessary.

Dermal Tolerance Studies

A single dose skin irritation study was conducted in rabbits. A single topical dose of 500 mg 15% azelaic acid pre-foam emulsion, 15% azelaic acid gel (two formulations) and vehicle pre-foam emulsion were applied to intact shaved skin under semi-occlusion for 5 hours. All test articles were mild irritants under the conditions of this study. Total reversibility was noted after 48 hours for vehicle pre-foam emulsion and two 15% azelaic acid gel formulations. Total reversibility was noted after 72 hours for the 15% azelaic acid pre-foam emulsion.

A 4-week repeat dose dermal tolerance study was conducted in rabbits. Topical doses of 250 mg 15% azelaic acid pre-foam emulsion, 15% azelaic acid gel (two formulations) and vehicle pre-foam emulsion were applied to intact shaved skin under semi-occlusion for 5 hours once daily for 4 weeks. After necropsy histopathological evaluation was conducted for both treated and untreated skin. No treatment-related effects on mortality, clinical signs or body weights were noted in this study. Very slight erythema was noted at all treatment sites throughout the 28-day treatment period. Minimal inflammatory cell infiltration was noted in untreated skin. Minimal to slight inflammatory cell infiltration, minimal to slight acanthosis and minimal scab formation was noted at all test article-treated skin sites. No significant difference in the extent of histopathological effects was noted for the 4 different test articles.

A 7-day repeat dose dermal tolerance study was conducted in mice with azelaic acid pre-foam emulsion. This study was not reviewed previously and is reviewed below.

Study title: Azelaic acid pre-foam emulsion: a 7-day dermal skin tolerability study in mice

Study no.:	1575-015, sponsor reference # 110005T
Study report location:	SD 1, NDA 207071
Conducting laboratory and location:	(b) (4)
Date of study initiation:	08/18/2011
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Azelaic acid pre-foam emulsion 15% or 30% were used as received from the sponsor
Formulation/Vehicle	Not specified in the study report

Key Study Findings

The tested high dose, 30% azelaic acid pre-foam emulsion applied at 5 ml/kg/dose twice daily, which is also the maximum feasible dose for this formulation, was well tolerated in mice, under the study conditions.

Methods

Topical doses of 0 (vehicle), 1500 and 3000 mg/kg/day azelaic acid (15% and 30% pre-foam emulsion applied at 5 ml/kg/dose twice daily, 8 hours apart) were administered to

10% BSA of intact mouse skin for 7 days. The high dose is the maximum feasible dose. Mortality, detailed clinical observation, skin irritation, body weight, food consumption and macroscopic observation were evaluated in this study.

Results

A single male at high dose was found dead on Day 7. No clinical signs or macroscopic findings were noted in this animal. Given that no other signs of systemic toxicity or mortalities were noted, this mortality was considered incidental and not related to treatment. No test article-related dermal irritation was noted in this study. No test article-related effects on body weight, food consumption or macroscopic findings were noted.

Skin Sensitization Studies

A local lymph node assay (LLNA) was conducted in mice with pre-foam formulation vehicle and 15% azelaic acid pre-foam emulsion. Test articles (25 µl) were applied daily over the entire dorsal surface of each mouse ear for 3 days. The proliferative response of the auricular lymph node (incorporation of ³H-methyl thymidine) was assessed 5 days following the initial application. Ear weights (obtained by punch biopsy) were measured after sacrifice. No lymphocyte proliferation was noted in mice, under the conditions of this study. No treatment-related effects on ear weights were noted in this study.

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

Phototoxicity Studies

The need for a nonclinical phototoxicity study is waived for the azelaic acid pre-foam emulsion, 15%, since no significant absorption was noted from the 290 – 700 nm UVB/UVA/visible light spectrum for azelaic acid in methanol or the vehicle pre-foam emulsion in methanol.

Safety Evaluation of Impurities

Two degradants, (b) (4), were analyzed for structural alerts using DEREK (version 13.0, Lhasa Ltd., Leeds, UK) and MULTICASE (version 2.4, Multicase Inc., Beachwood, OH, USA) software. DEREK is a computer-based expert system which compares the chemical structure of a test compound with structure-toxicity information stored in a database (rule base). MULTICASE is a QSAR-system which calculates an activity prediction based on the presence of activating biophores or inactivating biophores. No structural alerts or genotoxicity potential were identified for the two degradants in either program.

In addition, a 4-week repeat dose dermal toxicity study was conducted in mice with 15% azelaic acid pre-foam emulsion plus (b) (4), which is reviewed below. Per the sponsor, at the time the study was initiated only (b) (4) was known as a degradant. During further optimization of the analytical method (b) (4) was detected at a later time when the 4-week study was already ongoing. Therefore only (b) (4) was tested in this repeat dose study. Considering that the two compounds are chemically closely related and differ (b) (4) was tested at concentrations up to 10 times the specification limit of each (b) (4), this 4-week study is considered acceptable for qualification of the general toxicity of both degradants.

Study title: Azelaic acid pre foam emulsion: a 4-week dermal toxicity study in mice

Study no.:	1575-016 (sponsor's reference# 130011T)
Study report location:	SD 1, NDA 207071
Conducting laboratory and location:	(b) (4)
Date of study initiation:	09/23/2013
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Azelaic acid 15% pre-foam emulsion, lot# GLP H019 Azelaic acid 15% pre-foam emulsion + 0.075% azelaic acid monocetyler, lot# GLP H020 Azelaic acid 15% pre-foam emulsion + 0.75% azelaic acid monocetyler, lot# GLP H021

Key Study Findings

No significant treatment-related dermal or systemic toxicity was noted in the study. There were no significant microscopic findings associated with azelaic acid monocetyler administration. Minimal to mild epidermal hyperplasia was noted in all dose groups, which is considered related to the administration of the azelaic acid emulsion. This microscopic finding is not considered significantly adverse.

The NOAEL was identified as the high dose, 1500 mg/kg/day azelaic acid + 75 mg/kg/day azelaic acid monocetyler (15% azelaic acid pre-foam emulsion + 0.75% azelaic acid monocetyler, applied at 10 ml/kg/day), under the study conditions.

Methods

Doses: 0 (untreated), 1500 mg/kg/day azelaic acid, 1500 mg/kg/day azelaic acid + 7.5 mg/kg/day azelaic acid monocetylester (15% azelaic acid emulsion + 0.075% azelaic acid monocetylester), 1500 mg/kg/day azelaic acid + 75 mg/kg/day azelaic acid monocetylester (15% azelaic acid emulsion + 0.75% azelaic acid monocetylester)

Frequency of dosing: Twice daily for 28 days (~8 hours apart)

Route of administration: Dermal, non-occluded

Dose volume: 5 ml/kg/dose, applied to 10% BSA (10 ml/kg/day)

Formulation/Vehicle: Provided by the sponsor

Species/Strain: CD-1 mice

Number/Sex/Group: 10/sex/group

Age: ~7 weeks

Weight: 26.6-35.8 g for males, 21.7-27.7 g for females

Satellite groups: None

Unique study design: None

Deviation from study protocol: None remarkable

Observations and Results**Mortality**

No mortality was noted.

Clinical Signs

No significant treatment-related clinical signs were noted.

Dermal Observation

No erythema or edema was noted at any time point. All dermal scores were normal (zero).

Body Weights

No significant treatment-related effects were noted.

Food consumption

No significant treatment-related effects were noted.

Ophthalmoscopy

No significant treatment-related findings were noted.

Hematology

No significant treatment-related effects were noted.

Clinical Chemistry

No significant treatment-related effects were noted.

Gross Pathology

No significant treatment-related findings were noted.

Organ Weights

The following organs were weighed: adrenal gland, brain, epididymides, heart, kidneys, liver, lungs, ovaries, pituitary gland, salivary gland (mandibular), spleen, testes, thymus and thyroid with parathyroid glands.

No significant treatment-related changes were noted.

Histopathology

Adequate Battery: Yes.

The following listed tissues were examined for all animals.

Adrenal gland, aorta, bone with marrow (femur and sternum), brain, epididymis, esophagus, eye, gallbladder, gut associated lymphoid tissue, heart, intestine (cecum, colon, rectum, duodenum, ileum, jejunum), kidney, lachrymal gland, larynx, liver, lung, lymph node (mandibular, mesenteric), mammary gland (females only), nerve (optic and sciatic), ovaries, oviducts, pancreas, pituitary gland, prostate, salivary gland (mandibular, parotid, sublingual), seminal vesicle, skeletal muscle, skin (treated and untreated), spinal cord, spleen, stomach, testis, thymus, thyroid (with parathyroid) gland, tongue, trachea, ureter, urinary bladder, uterus (with cervix), vagina, and gross lesions.

Peer Review: No.

Histological Findings:

There were no significant microscopic findings associated with azelaic acid monocetyler administration. Minimal to mild epidermal hyperplasia was noted in all dose groups. Incidence and severity were similar across all three dose groups, indicating it is related to the administration of the azelaic acid emulsion (see the table below).

AZA 15% Emulsion-related Microscopic Observations Terminal Males and Females								
Group	1		2		3		4	
	M	F	M	F	M	F	M	F
Number Examined	10	10	10	10	10	10	10	10
Skin, treated								
Hyperplasia, epidermal	2	0	10	9	10	10	10	9
-minimal	2	0	10	8	7	8	8	6
-mild	0	0	0	1	3	2	2	3
Group 1 – Shear Control Group 2 – AZA 15% Emulsion Group 3 – AZA 15% Emulsion + 0.075% AZA Monocetylester Group 4 – AZA 15% Emulsion + 0.75% AZA Monocetylester								

Toxicokinetics

Not examined.

Dosing Solution Analysis

The test articles were directly provided by the sponsor. No dosing solution analysis was conducted in the study.

Reviewer's comments:

No structural alerts or genotoxicity potential were identified for the two degradants, (b) (4). The 4-week repeat dose dermal toxicity study in which (b) (4) was tested at topical doses up to 10 times the proposed specification level and no significant toxicity was noted. Considering the class of the two chemicals (with low toxicity potential) and the structure similarity between the two compounds, additional toxicology studies are not considered necessary. The toxicology data support the proposed specification level ((b) (4))% in drug substance, (b) (4)% in final drug product) for the two degradants.

Safety Evaluation of Leachables

The sponsor proposed to use a threshold of toxicological concern (TTC) approach for the safety evaluation of leachables, which is currently used for the safety evaluation of food contact substances by the FDA. The TTC value is (b) (4). According to the Product Quality Research Institute (PQRI) Leachables and Extractables Working Group, for orally inhaled and nasal drug product (OINDP), a safety concern threshold (SCT) is set as 0.15 µg/day, and a qualification threshold is set as 5 µg/day; for parenteral and ophthalmic drug product (PODP), a safety concern threshold (SCT) is set as (b) (4).

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Group^{1,2}. Considering Finacea Foam is a topical product with limited dermal absorption, the use of TTC for safety evaluation is considered conservative and acceptable.

- [REDACTED] (b) (4)

Its highest concentration detected in the migration study was [REDACTED] (b) (4) foam. Per the sponsor [REDACTED] (b) (4) was only in 2 out of 152 samples with [REDACTED] (b) (4) and [REDACTED] (b) (4) that is marginally above the TTC. 55 out of 152 samples were below the LLOQ of [REDACTED] (b) (4) and the majority of samples (92 out of 152) were above the LLOQ but below [REDACTED] (b) (4). Considering the dermal absorption of Finacea Foam is limited, such low exposure levels would not cause significant safety concern.

- [REDACTED] (b) (4)

Its detected concentration was below the LOD ([REDACTED] (b) (4) foam). Its daily exposure is below the TTC. [REDACTED] (b) (4) exhibits hormone-like properties and raises concerns regarding endocrine disruptor activity and effects on reproductive organs. Extensive international regulatory efforts have been made to evaluate its safety. FDA's current perspective, based on the most recent safety assessment (updated in November 2014), is that [REDACTED] (b) (4) is safe at the current levels occurring in foods^{3,4} (estimated dietary intake of 0.5 µg/kg/day for adults). The [REDACTED] (b) (4) exposure from the clinical use of Finacea Foam is much lower than the allowable daily intake level and there was no significant concern.

- [REDACTED] (b) (4)

Structure:



[REDACTED] (b) (4)

Its detected concentration was (b) (4) foam. Therefore its daily dermal exposure was (b) (4) for a 60 kg individual).

Per the sponsor, (b) (4) is used in the (b) (4). It is approved as an indirect food additive and food contact substance in the US. Acute toxicity of (b) (4) is low, with LD₅₀ values by oral and dermal routes higher than (b) (4). (b) (4) is not irritating to skin or eyes; no skin sensitization was observed in a human patch test. In oral repeat dose toxicity studies ranging from 28 days to 18 months, toxic effects were similar across studies showing effects on testis, liver and body weight gain. The NOAELs ranged from (b) (4). In an 8-week feeding study, (b) (4) was given to male mice and male rats at a level of (b) (4) in mice and (b) (4) in rats. No effects on body weight gain or reproductive organs were noted in mice while testicular toxicity was noted in rats. In a reproductive and developmental toxicity study in rats, the NOAEL for female reproductive toxicity was (b) (4) and the NOAEL for male reproductive toxicity was (b) (4). The NOAEL for developmental toxicity was (b) (4).

Bacterial reverse mutation tests and mammalian chromosomal tests were negative. No tumors were observed in an 18-month chronic feeding study in rats up to (b) (4)% corresponding to (b) (4) in males and (b) (4) in females. However this study is not qualified as a carcinogenicity study.

Overall, the lowest NOAEL was (b) (4) in rats based on testicular toxicity. This oral NOAEL level is equivalent to a human dose of (b) (4), which is over (b) (4)-fold higher than the dermal exposure level. There was no significant safety concern for the detected (b) (4) level.

- (b) (4)

Its detected concentration was below the LOD ((b) (4) foam). Its daily exposure was below the TTC and there was no significant safety concern.

- (b) (4)
(b) (4)

⁵ Refer to the FDA database

<http://www.accessdata.fda.gov/scripts>

(b) (4)

(b) (4) was analyzed for structural alerts using DEREK (version 13.0) and MULTICASE (version 2.4) software. No structural alert or genotoxicity potential was identified. In addition, a database search using VITIC Nexus (version 1.3.7, Lhasa Ltd.) showed negative Ames test data for cyclododecalactan, which is structurally similar to the compound (b) (4).

The detected concentrations for (b) (4) and below the LOD (b) (4) foam) (b) (4). Per the sponsor, (b) (4) is an (b) (4) with numerous commercial application including medical devices and food contact articles. (b) (4) was tested in a 2-year feeding studies in rats and a 1-year feeding study in dogs at dietary levels of (b) (4)%. No adverse effects or increases in cancer incidence were observed in these studies. In the rat study, daily doses at the end of study were (b) (4) in males and (b) (4) in females. Analytical test showed that water soluble extractables of (b) (4). Therefore, in the 2-year study the rats were orally exposed to (b) (4). The daily dermal exposure level of the (b) (4) for a 60 kg individual). The oral NOAEL in rats was considered (b) (4), equivalent to a human dose of (b) (4), which is over (b) (4)-fold higher than the dermal exposure level. There was no significant safety concern for the detected (b) (4) levels.

- (b) (4)

(b) (4)

Its detected concentration was (b) (4) foam. Therefore its daily dermal exposure was (b) (4) for a 60 kg individual).

(b) (4) is a suitable solvent for many organic molecules and is often used to (b) (4). Per the FDA's inactive ingredient database, it is used as an inactive ingredient in oral tablets and capsules (up to (b) (4)) and in transdermal film (up to (b) (4)). An oral reference dose of (b) (4) was determined by the US EPA⁶, which is over (b) (4)-fold higher than the dermal exposure level. There was no significant safety concern for the detected (b) (4) level.

⁶ <http://www.epa.gov> (b) (4)

- (b) (4)

Its detected concentration was below the LOD ((b) (4) foam). Its daily exposure was below the TTC and there was no significant safety concern.

Reviewer's comment:

Overall there was no significant safety concern for the detected leachables in the migration study.

11 Integrated Summary and Safety Evaluation

Azelaic acid is a dietary constituent and can be formed endogenously from longer-chain dicarboxylic acids, metabolism of (b) (4).

Azelaic acid has been shown to have anti-keratinizing, anti-bacterial and anti-inflammatory activities. However, the mechanism(s) by which azelaic acid interferes with the pathogenic events in rosacea are not clear.

In safety pharmacology studies of sodium azelinate, neurologic effects observed in rats following a single IV administration were limited to individual instances of mydriasis (400 mg/kg) and slightly reduced locomotor activity (800 mg/kg) in the Irwin test. IV administration of sodium azelinate in conscious rats as doses of 10, 50 and 250 mg/kg did not influence heart rate or blood pressure. Renal function of Wistar rats was not affected after single IV doses of sodium azelinate up to 1000 mg/kg.

Since azelaic acid is a straight chain dicarboxylic acid, it is anticipated that the main process of its elimination is by biotransformation. Systemically absorbed azelaic acid is metabolized by β -oxidation into shorter straight chain dicarboxylic acids (i.e., pimelic and glutaric acids), malonyl-CoA and acetyl-CoA. The results from an in vitro percutaneous absorption study indicate that similar systemic exposure is expected after topical administration of the azelaic acid foam and azelaic acid gel formulations.

Azelaic acid was evaluated for systemic toxicity in rats (27-week repeat dose study), monkeys (4-week repeat dose study) and dogs (6-month repeat dose study, not included in this NDA) following oral (gavage) administration.

Oral doses of 0, 100 and 1000 mg/kg/day azelaic acid were administered as a (b) (4) suspension to rats for 27 weeks. Lower body weight gain (high dose), slightly lower food consumption (both dose groups) and slightly higher water consumption (high dose) were noted in treated animals compared to control animals. Postmortem findings included thickening of the cuticular ridge of the stomach (both dose levels) accompanied by evagination and epithelia overgrowth in the high dose animals. The NOAEL was identified as 100 mg/kg/day in this study.

Oral doses of 0 and 250 mg/kg/day azelaic acid were orally administered as a (b) (4) suspension to monkeys for 4 weeks. No treatment-related effects were noted in this study. The NOAEL was identified as 250 mg/kg/day in this study.

Dermal toxicity studies were conducted in rats (6-month repeat dose study, not included in this NDA) and dogs (26-week repeat dose study) with 20% azelaic acid cream and in minipigs (13-week repeat dose study) and mice (13-week repeat dose study) with 15% azelaic acid pre-foam emulsion.

Dermal doses of 0 (vehicle) and 300 mg/kg/day azelaic acid (20% cream) were applied to dogs once daily for 26 weeks. No treatment-related systemic effects were noted in this study. Slight irritation was noted at the application site, which was observed more frequently in treated animals compared with control animals. The systemic NOAEL was identified as 300 mg/kg/day (maximum feasible dose) in this study.

Dermal doses of 0 (untreated), 0 (vehicle), 75, 225 and 450 mg/kg/day azelaic acid (5, 15, and 30% emulsion applied at 0.75 ml/kg/dose twice daily) were applied to minipigs for 13 weeks. No significant treatment-related dermal or systemic toxicity was noted in the study. The NOAEL was identified as the high dose, 450 mg/kg/day, which was the maximum feasible dose.

Dermal doses of 0 (untreated), 0 (vehicle), 500, 1500 and 3000 mg/kg/day azelaic acid (5, 15, and 30% emulsion applied at 5 ml/kg/dose twice daily) were applied to mice for 13 weeks. No significant treatment-related dermal or systemic toxicity was noted in the study. Minimal to mild epidermal hyperplasia and/or hyperkeratosis were observed at treated skin sites in the vehicle control group and the three dose groups. These findings were considered vehicle-related effects. The NOAEL was identified as the high dose, 3000 mg/kg/day, which was the maximum feasible dose.

In genetic toxicology studies, azelaic acid was not mutagenic or clastogenic in a battery of in vitro (Ames assay, HGPRT assay and chromosomal aberration assay) and in vivo (dominant lethal assay in mice and mouse micronucleus assay) genotoxicity tests. There was no concern for its genotoxic potential.

A short-term dermal carcinogenicity study in transgenic mice (Tg.AC assay) was conducted with azelaic acid 15% gel. Topical doses of 0 (sheared control), 0 (vehicle), 31.2 and 62.4 mg/day azelaic acid were administered to Tg.AC mice. Vehicle control and high dose were administered twice daily (0.2 ml/application) for 26 weeks, while low dose was administered once daily (0.2 ml/application) for 26 weeks. Topical doses of 1.25 µg/day TPA in acetone and 10 µg/day TPA in gel vehicle were administered (0.2 ml/application) 3 times a week for 26 weeks. A statistically significant increase in the incidence of papillomas was noted in males in the vehicle and high dose groups. No effect was noted in females. There was no significant difference in the incidence of papillomas in the vehicle and high dose males, which suggested that the positive finding may be due to the vehicle only.

Considering the positive finding noted in males in the Tg.AC mouse assay, a 2-year dermal mouse carcinogenicity study will be conducted as a PMR with the azelaic acid foam formulation. (b) (4)

The high dose is the maximum feasible dose. The carcinogenicity study protocol and proposed timeline are considered acceptable.

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

Azelaic acid (0, 50, 500 and 2500 mg/kg/day) was orally (gavage) administered as a (b) (4) suspension to rats in a combined fertility and embryofetal developmental study. Male rats were treated once daily for ~84 days (70 days prior to mating through 14 days of mating). Female rats were treated once daily for ~48 or 71 days (14 days prior to mating through Day 20 of gestation or Day 21 postpartum). No effects were noted on the fertility of the P-generation or their offspring or the general reproductive performance of the F-generation. No teratogenicity was observed in the F-1 or F-2 generation pups. Maternal and paternal toxicity was noted at high dose, indicated by decreased body weight gain. Embryotoxicity was noted at high dose, indicated by an increase of post-implantation loss and a decrease of pup weight, which might be due to the maternal toxicity. The NOAEL for fertility or teratogenicity was identified as the high dose, while the NOAEL for embryotoxicity was identified as the mid dose.

Azelaic acid (0, 50, 500 and 2500 mg/kg/day) was orally (gavage) administered as a (b) (4) suspension to pregnant female rats from gestation Day 6 to 15 inclusive in an embryofetal developmental study. No teratogenicity was observed in any of the dose groups. Maternal toxicity was noted at high dose, indicated by decreased body weight gain. Embryotoxicity was noted at high dose, indicated by an increase of post-implantation loss, which might be due to the maternal toxicity. The NOAEL for teratogenicity was identified as the high dose, while the NOAEL for embryotoxicity was identified as the mid dose.

Azelaic acid (0, 50, 150 and 500 mg/kg/day) was orally (gavage) administered as a (b) (4) suspension to pregnant female rabbits from gestation Day 6 to 27 inclusive in an embryofetal developmental study. A slight decrease in maternal body weight gain was noted in all treatment groups compared to control animals. The incidence of embryoletality was slightly higher in the mid dose and high dose groups, which might be related to the maternal toxicity. An increased incidence of incomplete or no ossification of the 5th sternebra was observed in fetuses from all dose groups. No other effects were noted and this slight variation was considered not biologically relevant. Therefore, it was determined that no teratogenicity was observed in this study.

The NOAEL for teratogenicity was identified as the high dose, while the NOAEL for embryotoxicity was identified as the low dose.

Azelaic acid (0, 50, 150 and 500 mg/kg/day) was orally (gavage) administered as a (b) (4) suspension to pregnant female monkeys from gestation Day 19 to 50 inclusive in an embryofetal developmental study. A slight decrease in food consumption was noted in the mid dose and high dose groups. Emesis was noted as a clinical sign in high dose animals. A higher incidence of spontaneous abortions was noted in high dose animals compared to control animals. The higher incidence of spontaneous abortions noted in the high dose group might be related to the slight maternal toxicity noted at high dose. No teratogenicity was observed in this study. The NOAEL for teratogenicity was identified as the high dose, while the NOAEL for embryotoxicity was identified as the mid dose.

Azelaic acid (0, 50, 500 and 2500 mg/kg/day) was orally (gavage) administered as a (b) (4) suspension to rats from Day 15 of gestation through Day 21 postpartum in a peri- and post-natal developmental study. Mortality was noted in the mid dose and high dose group F0 dams. A decrease in body weight gain was observed in the mid dose and high dose group F0 dams on Day 20 post coitum. The mortality rate of high dose F1 animals was higher than control animals. The body weights of high dose F1 animals were moderately lower on Day 90 postpartum. The pre-implantation loss was increased in high dose F1 females. A slightly higher incidence of delayed ossification of single fetal bones was observed in the high dose F2 generation rats. This change was attributed to a slight disturbance in the reproductive performance of the high dose F1 females. In summary, the mid dose and high dose expressed toxicity in F0 females (slightly increased mortality rates and decreased body weight gain) which produced slight disturbances in the post-natal development of F1 rats and in the reproductive performance of F1 females. The NOAEL for developmental toxicity was identified as the mid dose, while the NOAEL for maternal toxicity was identified as the low dose.

Azelaic acid is an ocular irritant to the rabbit and monkey eye. It can be presumed that the Finacea Foam formulation will be an ocular irritant as well. The 15% azelaic acid pre-foam emulsion is a mild irritant to rabbit skin but did not show any dermal irritation in mice. No skin sensitization potential of azelaic acid was noted in a local lymph node assay conducted in mice with 15% azelaic acid pre-foam formulation or in a maximization test conducted in guinea pigs in which azelaic acid was administered both intradermally and topically. A nonclinical phototoxicity study is not needed for the 15% azelaic acid pre-foam emulsion, since no significant absorption was noted from the 290 – 700 nm UVB/UVA/visible light spectrum.

Two degradants, (b) (4) and (b) (4), were identified in stability studies. QSAR analysis showed no structural alert or genotoxicity potential. A 4-week repeat dose dermal mouse toxicity study was conducted with 15% azelaic acid pre-foam emulsion plus (b) (4) up to (b) (4)%. No significant treatment-related dermal or systemic toxicity was noted in the study. Considering the class of the two chemicals (with low toxicity potential) and the structure similarity between the two compounds,

additional toxicology studies are not considered necessary. The toxicology data support the proposed specification level (b) (4) % in drug substance, (b) (4) % in final drug product) for the two degradants. A number of leachables were identified in a migration study conducted with the container-closure system. Safety evaluation was performed for each compound and it is concluded that there was no significant safety concern for the leachables at detected levels.

The multiples of human exposure based on BSA comparison between the NOAELs identified in pivotal toxicology studies and the maximum recommended human dose (MRHD) are shown in the table below.

Study	Route	NOAEL (mg/kg/day)		Human Equivalent Dose (mg/kg/day)	Multiples of human exposure*
General Toxicology					
27-week rat study	oral	100		16	6
4-week monkey study	oral	250		81	32
26-week dog study	dermal	300		162	65
13-week minipig study	dermal	450		426	170
13-week mouse study	dermal	3000		243	97
Carcinogenicity					
26-week Tg.AC mouse assay	dermal	Positive finding likely a vehicle effect			
2-year mouse assay	dermal	To be conducted			
Reproductive and Developmental Toxicology					
Fertility and embryofetal study in rats	oral	Fertility	2500	405	162
		Teratogenicity	2500	405	162
		Embryotoxicity	500	81	32
Embryofetal study in rats	oral	Teratogenicity	2500	405	162
		Embryotoxicity	500	81	32
Embryofetal study in rabbits	oral	Teratogenicity	500	162	65
		Embryotoxicity	50	16	6
Embryofetal study in monkeys	oral	Teratogenicity	500	162	65
		Embryotoxicity	150	49	20
Peri- and post-natal study in rats	oral	Developmental toxicity	500	81	32

*Based on BSA comparison to the maximum recommended human dose (MRHD), 1.0 g/day 15% azelaic acid foam (150 mg/day azelaic acid, 2.5 mg/kg/day for a 60 kg person).

It should be noted that the multiples of human exposure are very conservative for NOAELs identified in oral toxicology studies, considering that the dermal absorption after topical application of 15% azelaic acid foam is limited. Overall the toxicology information provided in this NDA submission supports the proposed clinical use of the

Finacea Foam, 15%. The proposed 2-year dermal mouse carcinogenicity study plan is also acceptable.

This NDA is approvable from a Pharmacology/Toxicology perspective, provided a 2-year dermal mouse carcinogenicity study will be conducted as a post-marketing requirement per the proposed timeline.

12 Appendix/Attachments

Appendix I: Executive CAC meeting minutes

Executive CAC

Date of Meeting: March 10, 2015

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Timothy McGovern, Ph.D., OND IO, Member
Albert Defelice, Ph.D., DCRP, Alternate Member
Barbara Hill, Ph.D., DDDP, Supervisor
Jianyong Wang, Ph.D., DDDP, Presenting Reviewer

Author of Draft: Jianyong Wang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

The Committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogenicity bioassay, as this does not affect the sponsor's ability to initiate the bioassay. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Standardized Study Data (December 2014) and the latest Study Data Technical Conformance Guide.

NDA #: 207071
Drug Name: FINACEA (azelaic acid) Foam, 15%
Sponsor: Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ

Background:

The sponsor submitted NDA 207071 on 09/30/2014 to pursue marketing approval of FINACEA (azelaic acid) Foam, 15% for the treatment of rosacea. A 2-year dermal mouse carcinogenicity study protocol and a dose range-finding study were included in the initial NDA submission. The 2-year dermal mouse carcinogenicity study will be conducted as a post-marketing commitment (PMC).

Two-year dermal mouse carcinogenicity study protocol:

Species/strain: CD-1 mouse

Number/sex/dose:

(b) (4)

Duration: 104 weeks

Route: Topical

Dose volume:

(b) (4)

Body surface area (BSA) treated:

Doses proposed:

Vehicle:

Dosing procedure:

Justification for Dose Selection:

(b) (4)

Executive CAC Recommendations and Conclusions:

(b) (4)

(b) (4)



Abby Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\n
/Division File, DDDP
/B. Hill, Supervisor, DDDP
/J. Wang, P/T reviewer, DDDP
/O. Laiyemo, Project Manager, DDDP
/A. Seifried, OND IO

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

/s/

JIANYONG WANG
05/06/2015

BARBARA A HILL
05/06/2015

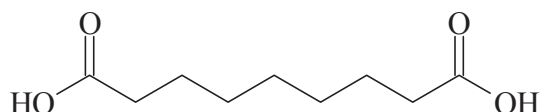
PHARMACOLOGY/TOXICOLOGY REVIEW

IND number: 77,516
Review number: 3
Sequence number/date/type of submission: 17 / 3-17-09 / 13 week dermal minipig study report
18 / 3-18-09 / Nonclinical information
21 / 5-11-09 / End of Phase 2 briefing document
Information to sponsor: Yes () No (X)
Sponsor and/or agent: Intendis, Inc.
340 Chainbridge Rd., PO Box 1000
Pine Brook, NJ 07058-1000
Manufacturer for drug substance: (b) (4) and Bayer
Schering Pharma AG, Germany

Reviewer name: Barbara Hill
Division name: Dermatologic and Dental Drug Products
HFD #: HFD-540
Review completion date: 6-3-09

Drug:

Trade name: N/A
Generic name: Azelaic acid foam, 15%
Code name: ZK 62498
Chemical name: 1,7-Heptanedicarboxylic acid
CAS registry number: 123-99-9
Molecular formula/molecular weight: C₉H₁₆O₄ / 188.2
Structure:



UV Absorption:

The sponsor included UVB/UVA/VIS spectrums (290 nm – 700 nm) of azelaic acid in methanol (1 mg/ml) and azelaic acid O/W emulsion (b) (4) in methanol in the original IND submission. The azelaic acid O/W emulsion is the azelaic acid foam formulation minus the propellant. No absorption was noted in either spectrum. Therefore, the need for a nonclinical photoirritation study was waived for azelaic acid foam, 15%.

Relevant INDs/NDAs/DMFs:

- 1) IND 38,271 (Azelaic acid 20% cream, acne; HFD-540; Sponsor – Allergan)
- 2) IND 61,324 (Azelaic acid 15% gel; papulo-pustular rosacea; HFD-540; Sponsor – Berlex)
- 3) IND 63,777 (Azelaic acid 15% gel; acne vulgaris; HFD-540; Sponsor – Berlex)
- 4) NDA 20-428 (Azelex {azelaic Acid} 20% cream; acne; HFD-540; approved 9-13-95; Sponsor – Allergan)
- 5) NDA 21-470 (Finacea {azelaic acid} 15% gel; papulopustular rosacea; HFD-540; approved 12-24-02; Sponsor – Intendis)

Note: The original sponsor of azelaic acid gel, 15% (Berlex) and the sponsor of Azelaic acid cream, 20% (Allergan) co-marketed Azelex (azelaic acid) cream, 20% under NDA 20-428. Therefore, some of the nonclinical toxicology data available for azelaic acid cream, 20% was used to support the safety of azelaic acid gel, 15%. The sponsor for NDA 21-470 changed to Intendis, Inc. after approval of the NDA. The transfer of NDA 21-470 to Intendis from Berlex was completed on May 19, 2005. The original IND submission indicated that both Intendis and Bayer Health Care Pharmaceutical (formerly Berlex) are affiliates of Bayer Schering AG, Germany.

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

Intended clinical population: Treatment of inflammatory papules and pustules and erythema of rosacea

Clinical formulation:

The quantitative composition of the azelaic acid foam, 15% formulation is provided in the following table.

Ingredient	% w/w
Azelaic acid	15.00
Medium chain triglycerides, USP/NF	(b) (4)
Cetostearyl alcohol, USP/NF	
Mono and diglycerides, USP/NF	
Benzoic acid, USP/NF	
Polyoxyl 40 stearate, USP/NF	
Methylcellulose, USP/NF	
Xanthan gum, USP/NF	
Polysorbate 80, USP/NF	
Dimethyl isosorbide ^a	
Propylene glycol, USP/NF	
Water, USP/NF	
Sodium hydroxide ^b , USP/NF	

a – Dimethyl isosorbide is a non-compendial excipient but is listed in the inactive ingredient database in a topical cream product at (b) (4)%. This topical cream is a corticosteroid product that could potentially be used over relatively large body surface areas for chronic conditions. Therefore, use of (b) (4)% dimethyl isosorbide is acceptable in the azelaic acid foam formulation.

b – Sodium hydroxide not needed to (b) (4)

(b) (4)

All of the excipients proposed for the azelaic acid foam formulation are less than contained in approved drug products. (b) (4)

Route of administration: Topical

Proposed clinical studies:

The sponsor submitted a clinical protocol titled “A multi-center, double-blind clinical trial to assess the efficacy and safety of topical azelaic acid foam, 15% twice daily compared to its vehicle twice daily in subjects with papulopustular roseacea” in the End of Phase 2 briefing document. This phase 3 clinical study will enroll 500 adult subjects with papulopustular rosacea (age ≥18 years). Patients will be randomized (1:1) to treatment with azelaic acid foam, 15% or vehicle foam. Patients will topically apply 0.5 g of the test article to the designated treatment site on the face twice daily for 12 weeks.

Safety will be assessed by assessing dermal irritation, adverse skin signs and symptoms and other adverse events at weeks 4, 8, 12 and 16 (4 week follow up timepoint).

The sponsor plans to conduct two Phase 3 clinical studies using an identical study protocol design as summarized above. In addition, the sponsor states that they will conduct two Phase 1 clinical studies (skin irritation and skin sensitization studies) and one open-label study clinical pharmacokinetic study to investigate the systemic exposure to azelaic acid after single and repeated application at steady state of topical azelaic acid foam, 15% in 12 – 15 subjects with papulopustular rosacea with the upper range of disease severity.

Previous clinical experience:

Finacea gel was approved for the treatment of inflammatory papules and pustules of rosacea on December 24, 2002. Finacea gel is applied to affected areas on the face twice daily

for 12 weeks. Azelex cream was approved for the treatment of acne on September 13, 1995. Azelex cream is applied to affected areas twice daily for 4 weeks.

The sponsor completed a Phase 2 clinical study titled “A 12 week exploratory, multicenter, double-blind, vehicle-controlled study to investigate the safety and efficacy of topical azelaic acid 15% foam twice daily in patients with papulopustular rosacea”. In this study 83 subjects were randomized 1:1 to receive 0.5 gm of either azelaic acid foam, 15% or vehicle foam twice daily for 12 weeks. The summary information provided in the End of Phase 2 briefing document indicates that the IGA based success rate was 38.9% and 15.0% for azelaic acid foam, 15% and vehicle foam, respectively. The sponsor also states that the most frequently reported adverse events were pruritus and application site irritation.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Background:

The sponsor has proposed to develop azelaic acid foam, 15% for the treatment of (b) (4) rosacea as a line extension for Finacea gel. The sponsor expects that the new formulation will be more convenient and elegant and will provide physicians and rosacea patients with a choice of formulations of azelaic acid 15%. The sponsor plans to reference all of the data in NDA 21-470 (Finacea gel) to support the safety of the new azelaic acid foam formulation. The sponsor states that they plan to conduct a limited number of nonclinical studies to characterize the safety of the new foam formulation. A pre-IND meeting was conducted with the sponsor on July 17, 2007. The original IND was submitted on November 13, 2007. One pharmacology/toxicology comment was relayed to the sponsor on February 6, 2008. A protocol for a 13 week dermal minipig toxicology study was submitted to the IND on March 18, 2008 (SDN 8). Comments concerning the nonclinical study protocol were relayed to the sponsor on April 14, 2009. The sponsor submitted a response in SDN 11 (date: May 2, 2008) that accepted all of the recommended study protocol modifications.

The final study report for the 13 week dermal minipig toxicology study conducted with azelaic acid foam, 15% was submitted on March 17, 2009 (SDN 17). This study is reviewed in this document. A validation report titled “Validation of an LC-MS/MS method for determination of azelaic acid and pimelic acid in minipig plasma” was included in SDN 18 (date: March 18, 2009). This method was used in the 13 week dermal minipig toxicology study.

Studies reviewed within this submission:

- 1) A 13-week twice daily dermal toxicity study of azelaic acid (5%, 15%, 30%) pre-foam emulsion in Gottingen minipigs including a 4-week recovery period (Study No. 1575-001)

Studies not reviewed within this submission:

- 1) Validation of an LC-MS/MS method for the determination of azelaic acid and pimelic acid in minipig plasma (Study No. VAL-31808)

Reviewer's comments: This study is not formally reviewed in this document. However, a brief evaluation of the study report indicated that the LC-MS/MS method used for the determination of azelaic acid and pimelic acid in minipig plasma was acceptable.

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2.6.6 TOXICOLOGY

2.6.6.3 Repeat-dose toxicity

Study title: A 13-week twice daily dermal toxicity study of azelaic acid (5%, 15%, 30%) pre-foam emulsion in Gottingen minipigs including a 4-week recovery period

Key study findings:

No treatment related findings on mortality, clinical signs, dermal irritation, body weight, ophthalmoscopic evaluation, electrocardiographic, hematology or clinical chemistry parameters, organ weights or macroscopic or microscopic parameters were noted in this study.

The NOAEL was indentified as twice daily administration of 30% azelaic acid pre-foam emulsion following 13 weeks of topical administration to minipigs, the highest dose evaluated in the study (which was the maximum feasible dose). The corresponding day 90 azelaic acid AUC_{0-24 hr} values were 4423 ng·hr/ml in males and 4268 ng·hr/ml in females. The corresponding day 90 pimelic acid AUC_{0-24 hr} values were 212 ng·hr/ml in males and 210 ng·hr/ml in females.

Study no.:	1575-001
Volume #, and page #:	SDN 17, electronic submission
Conducting laboratory:	(b) (4)
Date of study initiation:	5-1-08
GLP compliance:	Yes
QA report:	Yes
Drug, lot #, and % purity:	5% azelaic acid pre-foam emulsion, Lot# H1 70010 15% azelaic acid pre-foam emulsion, Lot# H1 70011 30% azelaic acid pre-foam emulsion, Lot# H1 70012
Vehicle:	Pre-foam emulsion clinical vehicle, Lot# H1 70031

Methods

Doses:	0% (untreated vehicle control) 0% (vehicle control), 5%, 15% and 30% azelaic acid pre-emulsion foam Corresponds to 0, 0, 1.88, 5.62 and 11.25 g azelaic acid/m ² , respectively
Species/strain:	Gottingen minipig
Number/sex/group or time point (main study):	4/sex/group
Route, formulation, volume, and infusion rate:	topical; vehicle; 0.75 ml/kg bid (this dose volume was the maximum volume that could be applied)
Satellite groups used for toxicokinetics or recovery:	Recovery: 2/sex/dose for control and high dose groups
Age:	4 – 5 months
Weight:	Males: 9.85 – 14.75 kg; Females: 10.3 – 13.85 kg
Sampling times:	N/A

Unique study design or methodology:

Test article was administered topically, semi-occluded for 6 hours per dose, twice daily, (separated by 4 hours) to a treatment area clipped free of hair (10% of the body surface area). The dosing site was semi-occluded with 4 to 5 layers of gauze and wrapped with Vetrap for 6 hours following application. The residual test article was removed using gauze moistened with tepid tap water and patted dry with clean dry gauze.

Observation and Times:

<u>Mortality:</u>	twice daily
<u>Clinical signs:</u>	twice daily
<u>Dermal irritation:</u>	daily for one week and weekly thereafter
<u>Body weights:</u>	weekly
<u>Ophthalmology:</u>	baseline, week 4 and 8
<u>ECG:</u>	baseline, weeks 4 and 8
<u>Hematology:</u>	baseline, weeks 4 and 8
<u>Clinical chemistry:</u>	baseline, weeks 4 and 8
<u>Gross pathology:</u>	necropsy
<u>Organ weights:</u>	adrenals, brain, epididymis, heart, kidneys, liver, ovaries, pituitary, prostate, spleen, testis, thymus, thyroid, and uterus
<u>Histopathology:</u>	The following organs were preserved from all animals in all treatment groups: adrenals, aorta, bone (femur, sternum), bone marrow (femur, sternum), brain, cecum, cervix, colon, duodenum, epididymis, esophagus, eyes, gall bladder, gross lesions, heart, ileum, jejunum, kidneys, liver, lungs, lymph nodes (mandibular, mesenteric), mammary gland (female only), optic nerve, ovaries, oviducts, pancreas, Peyer's patch, pituitary gland, prostate, rectum, salivary gland (mandibular, parotid, sublingual), sciatic nerve, seminal vesicles, skeletal muscle, skin (treated, untreated), spinal cord, spleen, stomach, testes, thymus, thyroid, tongue, trachea, ureters, urinary bladder, uterus and vagina

Histological examination was performed for all animals in all dose groups.

<u>Toxicokinetics:</u>	Blood samples were obtained on days 1, 28 and 90 at 0, 1, 3, 6 (end of first daily dose), 16 (end of second daily dose) and 24 hours post dose from all animals.
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Results:

<u>Mortality:</u>	No treatment related effects on mortality were noted in this study.
<u>Clinical signs:</u>	No treatment related effects on clinical signs were noted in this study.

<u>Dermal irritation:</u>	No treatment related effects on dermal irritation was noted in this study. Some incidences of well defined erythema and very slight edema were noted sporadically in vehicle treated and low, mid and high dose groups.
<u>Body weights:</u>	No treatment related effects on body weights were noted in this study.
<u>Ophthalmology:</u>	No treatment related effects on ophthalmologic parameters were noted in this study.
<u>ECG:</u>	No treatment related effects on ECG parameters were noted in this study.
<u>Hematology:</u>	No treatment related effects on hematology parameters were noted in this study.
<u>Clinical chemistry:</u>	No treatment related effects on clinical chemistry parameters were noted in this study.
<u>Gross pathology:</u>	No treatment related effects on macroscopic parameters were noted in this study.
<u>Organ weights:</u>	No treatment related effects on organ weights were noted in this study.
<u>Histopathology:</u>	No treatment related effects on microscopic parameters were noted in this study.
<u>Toxicokinetics:</u>	A summary of the mean pharmacokinetic parameters for azelaic acid and pimelic acid (primary metabolite) measured in this study is provided in the following two tables (copied from electronic study report).

Table A. Summary of Toxicokinetic Parameters of Azelaic Acid Following Dermal Administration of Azelaic Acid (b.i.d.) in Gottingen Minipigs®							
	Sex	Dose Level (Azelaic Acid b.i.d.)	T_{max} (hr)	C_{max} (ng/mL)		AUC_{0-24} (hr*ng/mL)	
			Median	Mean	SD	Mean	SD
Day 1	Male	Untreated Control	9.50	66.7	36.2	847	412
		Placebo Control	3.00	35.3	10.5	426	159
		5%	6.00	40.5	9.02	626	222
		15%	3.00	46.9	10.3	791	70.1
		30%	24.0	123	99.2	1364	678
Day 1	Female	Untreated Control	4.50	40.0	4.72	624	138
		Placebo Control	3.00	42.5	7.89	608	66.3
		5%	3.00	350	642	2617	4188
		15%	3.00	58.2	38.4	737	168
		30%	24.0	154	255	1336	981
Day 28	Male	Untreated Control	6.00	49.0	8.10	668	72.8
		Placebo Control	6.00	45.5	11.8	554	178
		5%	3.00	316	217	3870	2083
		15%	3.00	2546	4486	21786	35866
		30%	3.00	322	81.0	4087	908
Day 28	Female	Untreated Control	6.00	51.7	8.14	761	101
		Placebo Control	6.00	67.5	22.2	837	177
		5%	3.00	1372	1849	8512	8968
		15%	3.00	259	86.9	3233	715
		30%	3.00	340	44.4	4018	317
Day 90	Male	Untreated Control	3.00	57.8	28.0	669	240
		Placebo Control	6.00	48.2	19.0	584	204
		5%	3.00	454	399	3499	2277
		15%	3.00	1349	2206	8086	9934
		30%	4.50	305	132	4423	1562
Day 90	Female	Untreated Control	3.00	56.3	12.0	685	117
		Placebo Control	6.00	57.6	8.89	797	182
		5%	4.50	673	1059	7296	10887
		15%	3.00	4174	7974	38768	72753
		30%	3.00	278	53.4	4268	845

Table B. Summary of Toxicokinetic Parameters of Pimelic Acid Following Dermal Administration of Azelaic Acid (b.i.d.) in Gottingen Minipigs[®]							
	Sex	Dose Level (Azelaic Acid b.i.d.)	T _{max} (hr)	C _{max} (ng/mL)		AUC ₀₋₂₄ (hr*ng/mL)	
			Median	Mean	SD	Mean	SD
Day 1	Male	Untreated Control	3.00	6.18	0.879	106	13.4
		Placebo Control	4.50	5.54	0.602	94.5	21.2
		5%	6.00	4.94	0.656	88.7	14.6
		15%	9.50	7.10	2.97	124	65.3
		30%	6.00	7.73	2.89	131	51.2
Day 1	Female	Untreated Control	6.00	6.23	0.897	104	39.9
		Placebo Control	6.00	7.28	1.15	129	15.8
		5%	11.0	10.8	9.59	167	110
		15%	3.00	6.60	0.351	108	23.5
		30%	3.00	6.73	0.814	123	16.8
Day 28	Male	Untreated Control	3.00	8.18	2.62	108	11.8
		Placebo Control	6.00	7.27	1.43	109	17.5
		5%	6.00	17.9	12.0	199	80.6
		15%	6.00	123	211	1079	1664
		30%	6.00	18.2	8.09	268	117
Day 28	Female	Untreated Control	3.50	8.17	0.817	116	17.6
		Placebo Control	6.00	11.6	1.80	160	20.9
		5%	6.00	57.3	54.8	442	314
		15%	6.00	15.3	2.22	202	35.2
		30%	6.00	18.1	1.50	237	30.4
Day 90	Male	Untreated Control	3.00	6.95	1.42	89.1	16.4
		Placebo Control	3.00	6.51	2.17	87.5	15.2
		5%	3.00	14.4	11.5	132	79.6
		15%	4.50	38.5	49.1	325	256
		30%	3.00	12.9	7.77	212	97.2
Day 90	Female	Untreated Control	3.00	8.14	0.994	91.9	11.8
		Placebo Control	3.00	8.08	1.03	123	17.7
		5%	6.00	22.8	28.8	265	323
		15%	4.50	76.5	134	767	1263
		30%	6.00	14.8	3.84	210	42.5

An endogenous baseline level of circulating azelaic acid and pimelic acid was detected in untreated control and vehicle control groups at similar levels over all tested days. The study report concludes that as baseline data were rather homogenous though out the study, the concentrations found in the vehicle control group did not indicate a drug contamination.

An increase in circulating levels of azelaic acid and pimelic acid was insignificant in low, mid and high dose animals on day 1. However, a non-dose dependent increase in azelaic acid


and pimelic acid levels were noted in low, mid and high dose groups on day 28. The increase in azelaic acid was much higher than pimelic acid. Systemic exposure was similar between day 28 and day 90, which indicates steady state was achieved by day 28. The variability in systemic exposure to azelaic acid and pimelic acid was very high in low, mid and high dose groups.

No gender difference in systemic exposure to azelaic acid and pimelic acid was noted in this study.

2.6.6.9 Discussion and Conclusions

The 13 week dermal minipig toxicology study conducted with up to 30% azelaic acid pre-foam emulsion administered topically twice daily is adequate to support conduct of the proposed Phase 3 clinical studies with twice daily topical administration of 0.5 mg azelaic acid foam, 15% for 12 weeks. In the original IND submission, the sponsor submitted final study reports for a dermal rabbit irritation study, a 4 week repeat dose dermal rabbit irritation study and a murine local lymph node assay with azelaic acid pre-foam emulsion, 15% and the vehicle pre-foam emulsion formulation. The results from these studies indicate that both test articles are mild irritants in rabbit skin, elicit very minimal erythema in rabbit skin after 4 weeks of daily administration and do not appear to have a sensitization signal. In addition, the results from an *in vitro* percutaneous absorption study (included in the original IND submission) conducted with human, mouse and minipig skin showed similar rates of penetration for the azelaic acid foam and gel formulations which provides an initial indication that similar systemic exposure may be expected after topical administration of the azelaic acid foam and gel formulations.

Two nonclinical post-marketing commitments (conduct of a dermal carcinogenicity study and a study to evaluate photoco-carcinogenic potential) were agreed upon for the approval of azelaic acid gel, 15% under NDA 21-470. (b) (4)



The final study report for the dermal carcinogenicity study conducted in Tg.AC mice with azelaic acid 15% gel was submitted on November 7, 2006. A summary of this study and corresponding results is provided below.

Topical doses of 0 (sheared control), 0 (hydrogel vehicle control), 31.2 and 62.4 mg/day azelaic acid were administered to Tg.AC mice (20/sex/dose). Hydrogel vehicle control and high dose azelaic acid gel were administered twice daily (0.2 ml/application) for 26 weeks. Low dose azelaic gel was administered once daily (0.2 ml/application) for 26 weeks. Two positive control groups were incorporated into this study. Topical doses of 1.25 µg/day TPA in acetone and 10 µg/day TPA in hydrogel were administered (0.2 ml/application) to Tg.AC mice (15/sex/dose),

3X/week, for 26 weeks. A previous dose ranging study had determined that the extent of skin papilloma formation was similar for the 10 µg/day TPA in hydrogel vehicle compared to 1.25 µg/day TPA in acetone after 26 weeks of administration to Tg.AC mice.

The vehicle caused a statistically significant increase in the incidence of male animals with papillomas (10/20) compared to untreated male animals (0/20) with no further increase noted after exposure to a high dose of the active (8/20). Therefore, a positive effect was noted in vehicle and high dose males compared to untreated males in the Tg.AC mouse assay. No statistically significant increase in the incidence of female animals with papillomas was noted in the low (1/20) and high dose groups (3/20) compared to untreated (3/20) and vehicle (0/20) treated groups. Therefore, no effect was noted in female animals in the Tg.AC mouse assay.

An Exec CAC meeting to discuss the results of this study was conducted on September 11, 2007. The Exec CAC recommendations and conclusions from this meeting are provided below.

- 1) The Committee agreed that the study was adequate.
- 2) The Committee concluded that the Tg.AC mouse assay was negative for female mice and positive for male mice, noting a statistically significant increase in the incidence of males with papillomas in the vehicle and high dose groups compared to untreated control. The Committee noted that there was no statistically significant difference in the incidence of males with papillomas in the vehicle and high dose groups which suggested that the positive effect may be due to the vehicle only. There was no statistically significant increase in the incidence of treated females with papillomas compared to vehicle or untreated females.

The Exec CAC meeting minutes and an additional Pharmacology/Toxicology comment were faxed to the sponsor on September 28, 2007. The additional Pharmacology/Toxicology comment is provided below.

“The sponsor should submit a labeling supplement that incorporates the findings of the Tg.AC mouse assay (per the Exec CAC minutes of 9-11-07) conducted with Finacea gel.”

The sponsor submitted their rationale why the positive findings noted in the vehicle treated and high dose males in the Tg.AC mouse assay is a false positive to NDA 21-470 on December 13, 2007. The following comment was relayed to the sponsor after review of the submitted information.

“The Exec CAC members were aware of the potential irritation induced by twice daily application of the vehicle and the high dose of azelaic acid gel noted in the Tg.AC mouse assay. The Exec CAC could not concur that the increase in papilloma formation was definitively due to a possible increase in irritation. Therefore, the Exec CAC determined that the Tg.AC mouse assay was negative for female mice and positive for male mice, noting a statistically significant increase in the incidence of males with papillomas in the vehicle and high dose groups compared

to untreated control. Since the Exec CAC determined that positive findings were noted in vehicle and high dose males in the Tg.AC mouse assay, then this information should be incorporated into the Finacea gel label.”

The sponsor submitted a labeling supplement to NDA 21-470 (SLR 005) on April 6, 2009 that incorporates the Tg.AC mouse study results. (b) (4)

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Summary:

The 13 week bridging dermal minipig toxicology study conducted with azelaic acid pre-foam emulsion, in combination with the nonclinical studies previously conducted with azelaic acid pre-foam emulsion, is adequate to serve as a nonclinical bridge to the nonclinical toxicology information for azelaic acid gel, 15% and azelaic acid cream, 20%. No additional nonclinical toxicology studies are recommended for azelaic acid foam, at this time.

Internal comments:

The following Pharmacology/Toxicology responses to the questions contained in the briefing document were relayed to the sponsor during the End of Phase 2 meeting conducted on June 10, 2009.

Question:

Intendis has the right of reference to the complete set of toxicology and pharmacology studies for earlier approved formulations of AzA, and has performed several bridging studies (including a 3 month minipig study) with the new foam formulation. Does the Division concur that the nonclinical studies conducted with AzA drug substance, those with earlier formulations, and the ones with the pre-foam emulsion are sufficient, and that no additional studies are needed to support the NDA filing for AzA Foam, 15%?

Response:

The overall nonclinical toxicology study package available for azelaic acid appears acceptable to support NDA filing for azelaic acid foam provided that the issues raised in the responses to the following two questions are adequately addressed prior to a NDA submission for azelaic acid foam.

Question:

AzA drug substance was negative for carcinogenic potential in the Tg.AC mice, and all excipients of the AzA Foam, 15% formulation are used in previously FDA approved dermal formulation. AzA is an endogenously occurring compound. The Sponsor anticipates in analogy to Finacea® 15% Gel that human systemic levels of AzA are not increased above their

endogenous levels following repeated dosing with our topical foam products. Intendis believes that there is no need for additional long-term carcinogenicity studies with the AzA Foam, 15%. Does the Agency concur?

Response:

We acknowledge receipt of a labeling supplement for Finacea (azelaic acid) gel, 15% (SLR 005) on April 6, 2009 that incorporates the results of the Tg.AC mouse assay conducted with azelaic acid gel. (b) (4)

You are reminded that the Exec CAC concluded on September 11, 2007 that the Tg.AC mouse assay conducted with azelaic acid gel was negative for female mice and positive for male mice, noting a statistically significant increase in the incidence of males with papillomas in the vehicle and high dose groups compared to untreated control. The Exec CAC noted that there was no statistically significant difference in the incidence of males with papillomas in the vehicle and high dose groups which suggested that the positive effect may be due to the vehicle only. There was no statistically significant increase in the incidence of treated females with papillomas compared to vehicle or untreated females.

We have concerns about the positive response noted in male mice in the Tg.AC mouse assay. A final determination for the possible need for additional dermal carcinogenicity studies conducted with either the azelaic acid gel or azelaic acid foam formulation has not been reached at this point in time.

Question:

The Sponsor would like to follow-up on nonclinical question 3 of the pre-IND meeting from July 17, 2007 (b) (4)

(b) (4)

(b) (4)

Response:

(b) (4)

(b) (4)

External Recommendations (to sponsor): None at this time.

APPENDIX/ATTACHMENTS

Linked Applications

Sponsor Name

Drug Name / Subject

IND 77516

INTENDIS INC

AZELAIC ACID 15%

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/s/

BARBARA A HILL

06/11/2009

Memorandum

To: IND 77,516

From: Barbara Hill, Ph.D., Pharmacology/Toxicology Supervisor

Re:

Submission date: 5-2-08

SDN: 11

Submission type: Response to information request

Drug: Azelaic acid foam, 15%

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

Indication: Treatment of inflammatory papules and pustules (b) (4) of rosacea

Sponsor: Intendis, Inc., Pine Brook, NJ

Review date: May 22, 2008

Introduction:

The sponsor has proposed to develop azelaic acid foam, 15% for the treatment of (b) (4) rosacea as a line extension for Finacea gel. The sponsor submitted a protocol for a 13 week dermal minipig toxicology study in SDN 8 (date: 3-18-08). This nonclinical study is being conducted to support conduct of Phase 3 clinical studies with a treatment duration of 12 weeks. Comments were relayed to the sponsor on April 4, 2008 via fax concerning the submitted study protocol. This submission contains the sponsor's response to some of the comments relayed to them.

Evaluation of sponsor's responses to previously relayed comments:

Reviewer's request:

Please clarify if the (b) (4) % azelaic acid pre-foam emulsion is the maximum feasible concentration.

Sponsor's response:

(b) (4)

Reviewer's comments:

The sponsor's response is acceptable.

Reviewer's request:

You should incorporate twice daily dosing in this study to mimic conditions of clinical use.

Sponsor's response:

The sponsor agrees and will administer the treatment twice daily. Two dosing periods of 6 hours each will be separated by a 4 hour rest. In consequence, time points for toxicokinetic analysis will be adjusted to: prior to dosing, 1 hour, 3 hours, 6 hours (end of dose 1), 16 hours (end of dose 2), and 24 hours.

Reviewer's comments:

The sponsor's response is acceptable.

Reviewer's request:

You should include histopathological analysis of a standard list of tissues for all vehicle treated animals in this study.

Sponsor's response:

Full histopathology will be done on the vehicle group (but not the "non treatment" group) and the highest dose level (30%). In consequence, these two groups will also be used for the recovery analysis.

Reviewer's comments:

The sponsor's response is acceptable.

Additional sponsor's comment:

The sponsor would like to inform the agency that pre-testing of the application of the pre-foam emulsion of (b) (4) revealed that according to its fluidity the maximum feasible dose is 0.75 g/kg and not 1.0 g/kg. This resulted in a reduction of the planned area dose from approximately 25 mg/cm² to 19 mg/cm² which is still ≥ 4 -fold higher than the clinical area dose of about ≤ 5 mg/cm².

Reviewer's comments:

The sponsor's proposal is acceptable.

Recommendations:

No regulatory action is indicated for this submission from a Pharmacology/Toxicology perspective, at this time.

Linked Applications

Sponsor Name

Drug Name

IND 77516

INTENDIS INC

AZELAIC ACID 15%

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/s/

BARBARA A HILL

05/22/2008

PHARMACOLOGY/TOXICOLOGY REVIEW

IND number: 77,516
Review number: 2
Sequence number/date/type of submission: 7 / 2-26-08 / Response to information request
8/ 3-18-08 / 13 week dermal minipig study
protocol

Information to sponsor: Yes (X) No ()

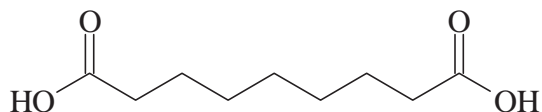
Sponsor and/or agent: Intendis, Inc.
340 Chainbridge Rd., PO Box 1000
Pine Brook, NJ 07058-1000

Manufacturer for drug substance: (b) (4) and Bayer
Schering Pharma AG, Germany

Reviewer name: Barbara Hill
Division name: Dermatologic and Dental Drug Products
HFD #: HFD-540
Review completion date: 4-3-08

Drug:

Trade name: N/A
Generic name: Azelaic acid foam, 15%
Code name: ZK 62498
Chemical name: 1,7-Heptanedicarboxylic acid
CAS registry number: 123-99-9
Molecular formula/molecular weight: C₉H₁₆O₄ / 188.2
Structure:



UV Absorption:

The sponsor included UVB/UVA/VIS spectrums (290 nm – 700 nm) of azelaic acid in methanol (1 mg/ml) and azelaic acid O/W emulsion (b) (4) in methanol in the original IND submission. The azelaic acid O/W emulsion is the azelaic acid foam formulation minus the propellant. No absorption was noted in either spectrum.

Relevant INDs/NDAs/DMFs:

- 1) IND 38,271 (Azelaic acid 20% cream, acne; HFD-540; Sponsor – Allergan)
- 2) IND 61,324 (Azelaic acid 15% gel; papulo-pustular rosacea; HFD-540; Sponsor – Berlex)
- 3) IND 63,777 (Azelaic acid 15% gel; acne vulgaris; HFD-540; Sponsor – Berlex)
- 4) NDA 20-428 (Azelex {azelaic Acid} 20% cream; acne; HFD-540; approved 9-13-95; Sponsor – Allergan)
- 5) NDA 21-470 (Finacea {azelaic acid} 15% gel; papulopustular rosacea; HFD-540; approved 12-24-02; Sponsor – Intendis)

Note: The original sponsor of azelaic acid gel, 15% (Berlex) and the sponsor of Azelaic acid cream, 20% (Allergan) co-marketed Azelex (azelaic acid) cream, 20% under NDA 20-428. Therefore, some of the nonclinical toxicology data available for azelaic acid cream, 20% was used to support the safety of azelaic acid gel, 15%. The sponsor for NDA 21-470 changed to Intendis, Inc. after approval of the NDA. The transfer of NDA 21-470 to Intendis from Berlex was completed on May 19, 2005. The original IND submission indicated that both Intendis and Bayer Health Care Pharmaceutical (formerly Berlex) are affiliates of Bayer Schering AG, Germany.

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

Intended clinical population: Treatment of inflammatory papules and pustules and erythema of rosacea

Clinical formulation:

The quantitative composition of the azelaic acid foam, 15% formulation is provided in the following table.

Ingredient	% w/w
Azelaic acid	15.00
Medium chain triglycerides, USP/NF	(b) (4)
Cetostearyl alcohol, USP/NF	
Mono and diglycerides, USP/NF	
Benzoic acid, USP/NF	
Polyoxyl 40 stearate, USP/NF	
Methylcellulose, USP/NF	
Xanthan gum, USP/NF	
Polysorbate 80, USP/NF	
Dimethyl isosorbide ^a	
Propylene glycol, USP/NF	
Water, USP/NF	
Sodium hydroxide ^b , USP/NF	

a – Dimethyl isosorbide is a non-compendial excipient but is listed in the inactive ingredient database in a topical cream product at (b) (4) %. This topical cream is a corticosteroid product that could potentially be used over relatively large body surface areas for chronic conditions. Therefore, use of (b) (4) % dimethyl isosorbide is acceptable in the azelaic acid foam formulation.

b – Sodium hydroxide not needed to (b) (4)

(b) (4)

All of the excipients proposed for the azelaic acid foam formulation are less than contained in approved drug products.

Route of administration: Topical

Proposed clinical studies:

The sponsor submitted a clinical protocol titled “A 12-week exploratory, multicenter, double-blind, vehicle-controlled study to investigate the safety and efficacy of topical azelaic acid 15% foam twice daily in patients with papulopustular rosacea” in the original IND submission. This phase 2 study will enroll 84 adult patients with papulopustular rosacea (age ≥18 years). Patients will be randomized (1:1) to treatment with azelaic acid foam, 15% or vehicle foam. Patients will topically apply 0.5 g of the test article to the designated treatment site on the face twice daily for 12 weeks.

Safety will be assessed by assessing dermal irritation, adverse skin signs and symptoms and other adverse events at weeks 4, 8 and 12.

Reviewer’s comments: It was determined that the proposed initial clinical study was reasonably safe to initiate from a pharmacological/toxicological perspective. The amount of each test article that will be applied in this initial clinical study is the same as was approved for Finacea gel.

The sponsor plans to conduct a Phase1 human pharmacokinetics study in papulopustular rosacea patients, two Phase 1 dermal safety studies (21-day cumulative irritation study and skin sensitization study) and two pivotal Phase 3 clinical studies in Q4/2008.

Previous clinical experience:

Finacea gel was approved for the treatment of inflammatory papules and pustules of rosacea on December 24, 2002. Finacea gel is applied to affected areas on the face twice daily

for 12 weeks. Azelex cream was approved for the treatment of acne on September 13, 1995. Azelex cream is applied to affected areas twice daily for 4 weeks.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Background:

The sponsor has proposed to develop azelaic acid foam, 15% for the treatment of (b) (4) rosacea as a line extension for Finacea gel. The sponsor expects that the new formulation will be more convenient and elegant and will provide physicians and rosacea patients with a choice of formulations of azelaic acid 15%. The sponsor plans to reference all of the data in NDA 21-470 (Finacea gel) to support the safety of the new azelaic acid foam formulation. The sponsor states that they plan to conduct a limited number of nonclinical and phase 1 clinical studies to characterize the safety of the new foam formulation. In addition, the sponsor plans to evaluate the safety and efficacy of the new foam formulation in two vehicle controlled double-blind phase 3 clinical studies. A pre-IND meeting was conducted with the sponsor on July 17, 2007. The original IND was submitted on November 13, 2007. One pharmacology/toxicology comment was relayed to the sponsor on February 6, 2008. The support document number (SDN) 7 submission contains the sponsor's response to this comment. The SDN 8 submission contains a protocol for a 13 week dermal minipig toxicology study.

Evaluation of Sponsor's Response to Pharmacology/Toxicology Comment:

Pharmacology/Toxicology Comment relayed on 2/6/08:

The Division notes that the sponsor plans to conduct a 3 month dermal minipig toxicology study with toxicokinetics with the foam formulation. The sponsor is referred to the guidance provided for the design of this study relayed during the pre-IND meeting conducted on July 17, 2007. This study should be conducted and a study report submitted to the IND for evaluation prior to initiation of Phase 3 clinical studies.

Sponsor's response

The sponsor provided a rather lengthy response to this comment, which is summarized briefly below.

Basically, the sponsor argues that since a topical azelaic acid cream formulation and recently a topical azelaic acid gel formulation have been approved and have no apparent post-marketing safety signals then the 3 month dermal minipig toxicology study should not be a prerequisite for initiation of Phase 3 clinical studies with azelaic acid 15% foam. The sponsor also states that good local tolerability of azelaic acid has been demonstrated in patients which provide additional information for not requiring the 3 month dermal minipig toxicology study prior to initiation of Phase 3 clinical studies with azelaic acid 15% foam.

Reviewer's comments: The purpose of the 3 month dermal minipig toxicology study to be conducted with the azelaic acid foam formulation is to serve as a nonclinical bridging study to the nonclinical toxicology information available for the azelaic acid cream and gel formulations. An additional purpose of the 3 month dermal minipig toxicology study is to assure that the toxicity profile for the azelaic acid foam formulation is not significantly different than for the azelaic acid cream and gel formulations. This information is necessary to support the initiation of Phase 3 clinical studies with a treatment duration of 12 weeks.

Review of toxicology study protocol:

Study title: A 13-week dermal toxicity study of azelaic acid 15% pre-foam emulsion in Gottingen minipigs including a 4-week recovery period

Study no.: 1575-001

Conducting laboratory: (b) (4)

Date of study initiation: 4-28-08

GLP compliance: Will be conducted under GLP compliance

Drug: Azelaic acid pre-foam emulsion

Vehicle: Vehicle pre-foam emulsion

Doses: Untreated control, vehicle control, 5%, 15% and 30% azelaic acid pre-foam emulsion

Species/Strain: Gottingen minipig, 4 months, 8 – 14 kg

Number/sex/group: Main study: 4/sex/dose; 4 week recovery: 2/sex/dose for untreated control and high dose groups

Route, volume: Topical, 1 g/kg/test article (25 mg/cm² per test article)

Methodology:

Test article will be administered daily to a clipped treatment area on the back of each animal (equal to 10% total body surface area) under semi-occlusion for 6 hours/day for 13 weeks.

Observation and times:

Mortality (daily), clinical signs (daily), skin irritation (daily during the first week and then weekly thereafter), body weights (weekly), hematology (weeks 13 and 17), clinical chemistry (weeks 13 and 17), ECG (weeks 13 and 17 at initiation of dosing and 1-2 hours post dose), ophthalmology (weeks 13 and 17), toxicokinetics (days 1, 28 and 90 at 0, 1, 3, 6, 8 and 24 hours post dose), gross necropsy, organ weights and histopathological analysis of all tissues from a standard list for untreated and high dose animals and analysis of target organs identified in high dose animals in vehicle, low and mid dose groups.

Reviewer's comments: Overall, the protocol appears acceptable. The sponsor was informed during the pre-IND meeting that use of azelaic acid pre-foam emulsion in this study would be acceptable. (b) (4)

The sponsor will be asked to include histopathological

analysis of a standard list of tissues for all vehicle treated animals and to incorporate twice daily dosing in this study to mimic conditions of clinical use.

External Recommendations (to sponsor):

It is recommended that the following information be relayed to the sponsor for IND 77,516:

- 1) The purpose of the 3 month dermal minipig toxicology study to be conducted with the azelaic acid foam formulation is to serve as a nonclinical bridging study to the nonclinical toxicology information available for the azelaic acid cream and gel formulations. An additional purpose of the 3 month dermal minipig toxicology study is to assure that the toxicity profile for the azelaic acid foam formulation is not significantly different than for the azelaic acid cream and gel formulations. This information is necessary to support the initiation of Phase 3 clinical studies with a treatment duration of 12 weeks.
- 2) The Division acknowledges submission of the protocol for the 3 month dermal minipig toxicology study. Overall, the protocol appears acceptable. (b) (4)
[REDACTED] You should incorporate twice daily dosing in this study to mimic conditions of clinical use. You should include histopathological analysis of a standard list of tissues for all vehicle treated animals in this study.

Linked Applications

Sponsor Name

Drug Name

IND 77516

INTENDIS INC

AZELAIC ACID 15%

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/s/

BARBARA A HILL

04/03/2008

Non-Clinical Reviewer

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

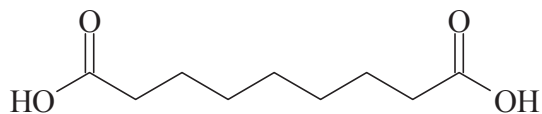
IND number: 77,516
Review number: 1
Sequence number/date/type of submission: 000 / 11-13-07 / Original IND submission
Information to sponsor: Yes (X) No ()
Sponsor and/or agent: Intendis, Inc.
340 Chainbridge Rd., PO Box 1000
Pine Brook, NJ 07058-1000

Manufacturer for drug substance: (b) (4) and Bayer
Schering Pharma AG, Germany

Reviewer name: Barbara Hill
Division name: Dermatologic and Dental Drug Products
HFD #: HFD-540
Review completion date: 12-6-07

Drug:

Trade name: N/A
Generic name: Azelaic acid foam, 15%
Code name: ZK 62498
Chemical name: 1,7-Heptanedicarboxylic acid
CAS registry number: 123-99-9
Molecular formula/molecular weight: C₉H₁₆O₄ / 188.2
Structure:



UV Absorption:

The sponsor included UVB/UVA/VIS spectrums (290 nm – 700 nm) of azelaic acid in methanol (1 mg/ml) and azelaic acid O/W emulsion (b) (4) in methanol in the IND submission. The azelaic acid O/W emulsion is the azelaic acid foam formulation minus the propellant. No absorption was noted in either spectrum.

Relevant INDs/NDAs/DMFs:

- 1) IND 38,271 (Azelaic acid 20% cream, acne; HFD-540; Sponsor – Allergan)

- 2) IND 61,324 (Azelaic acid 15% gel; papulo-pustular rosacea; HFD-540; Sponsor – Berlex)
- 3) IND 63,777 (Azelaic acid 15% gel; acne vulgaris; HFD-540; Sponsor – Berlex)
- 4) NDA 20-428 (Azelex {azelaic Acid} 20% cream; acne; HFD-540; approved 9-13-95; Sponsor – Allergan)
- 5) NDA 21-470 (Finacea {azelaic acid} 15% gel; papulopustular rosacea; HFD-540; approved 12-24-02; Sponsor – Intendis)

Note: The original sponsor of azelaic acid gel, 15% (Berlex) and the sponsor of Azelaic acid cream, 20% (Allergan) co-marketed Azelex (azelaic acid) cream, 20% under NDA 20-428. Therefore, some of the nonclinical toxicology data available for azelaic acid cream, 20% was used to support the safety of azelaic acid gel, 15%. The sponsor for NDA 21-470 changed to Intendis, Inc. after approval of the NDA. The transfer of NDA 21-470 to Intendis from Berlex was completed on May 19, 2005. The IND submission indicates that both Intendis and Bayer Health Care Pharmaceutical (formerly Berlex) are affiliates of Bayer Schering AG, Germany.

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

Intended clinical population: Treatment of inflammatory papules and pustules of rosacea (b) (4)

Clinical formulation:

The quantitative composition of the azelaic acid foam, 15% formulation is provided in the following table.

Ingredient	% w/w
Azelaic acid	15.00
Medium chain triglycerides, USP/NF	(b) (4)
Cetostearyl alcohol, USP/NF	
Mono and diglycerides, USP/NF	
Benzoic acid, USP/NF	
Polyoxyl 40 stearate, USP/NF	
Methylcellulose, USP/NF	
Xanthan gum, USP/NF	
Polysorbate 80, USP/NF	
Dimethyl isosorbide ^a	
Propylene glycol, USP/NF	
Water, USP/NF	
Sodium hydroxide ^b , USP/NF	

a – Dimethyl isosorbide is a non-compendial excipient but is listed in the inactive ingredient database in a topical cream product a (b) (4)%. This topical cream is a corticosteroid product that could potentially be used over relatively large body surface areas for chronic conditions. Therefore, use of (b) (4)% dimethyl isosorbide is acceptable in the azelaic acid foam formulation.

b – Sodium hydroxide (b) (4)

All of the excipients proposed for the azelaic acid foam formulation are less than contained in approved drug products.

Route of administration: Topical

Proposed clinical studies:

The sponsor submitted a clinical protocol titled “A 12-week exploratory, multicenter, double-blind, vehicle-controlled study to investigate the safety and efficacy of topical azelaic acid 15% foam twice daily in patients with papulopustular rosacea”. This phase 2 study will enroll 84 adult patients with papulopustular rosacea (age ≥ 18 years). Patients will be randomized (1:1) to treatment with azelaic acid foam, 15% or vehicle foam. Patients will topically apply 0.5 g of the test article to the designated treatment site on the face twice daily for 12 weeks.

Safety will be assessed by assessing dermal irritation, adverse skin signs and symptoms and other adverse events at weeks 4, 8 and 12.

Reviewer’s comments: The proposed initial clinical study is reasonably safe to initiate from a pharmacological/toxicological perspective. The amount of each test article that will be applied in this initial clinical study is the same as was approved for Finacea gel.

The sponsor plans to conduct a Phase 1 human pharmacokinetics study in papulopustular rosacea patients, two Phase 1 dermal safety studies (21-day cumulative irritation study and skin sensitization study) and two pivotal Phase 3 clinical studies in Q4/2008.

Previous clinical experience:

Finacea gel was approved for the treatment of inflammatory papules and pustules of rosacea on December 24, 2002. Finacea gel is applied to affected areas on the face twice daily for 12 weeks. Azelex cream was approved for the treatment of acne on September 13, 1995. Azelex cream is applied to affected areas twice daily for 4 weeks.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Background:

The sponsor has proposed to develop azelaic acid foam, 15% for the treatment of (b) (4) rosacea as a line extension for Finacea gel. The sponsor expects that the new formulation will be more convenient and elegant and will provide physicians and rosacea patients with a choice of formulations of azelaic acid 15%. The sponsor plans to reference all of the data in NDA 21-470 (Finacea gel) to support the safety of the new azelaic acid foam formulation. The sponsor states that they plan to conduct a limited number of nonclinical and phase 1 clinical studies to characterize the safety of the new foam formulation. In addition, the sponsor plans to evaluate the safety and efficacy of the new foam formulation in two vehicle controlled double-blind phase 3 clinical studies. A pre-IND meeting was conducted with the sponsor on July 17, 2007.

The nonclinical questions posed for the pre-IND meeting and corresponding responses provided during the meeting are provided below.

Question 1

Does the Agency concur that the nonclinical studies planned with the pre-foam emulsion, together with the other nonclinical data from NDA 21-470 and the literature will be sufficient to support the marketing approval of azelaic acid 15% foam?

Pharmacology/Toxicology response

The nonclinical studies that the sponsor has proposed for azelaic acid 15% foam in the briefing package together with the nonclinical data contained in NDA 21-470 for azelaic gel 15% gel and the literature may be acceptable to support the safety of azelaic acid 15% foam. The determination of the adequacy of the conducted nonclinical studies to support marketing approval will be determined after review of the final study reports.

It is acceptable to conduct the nonclinical studies with azelaic acid 15% foam as a pre-foam emulsion minus the propellant. If azelaic acid 15% foam is a primary skin irritant in rabbits, then it will be labeled as an ocular irritant as well. However, if azelaic acid 15% foam is not a primary skin irritant in rabbits, then conduct of an ocular irritation study in rabbits should be performed with azelaic acid 15% foam. The need for a nonclinical photoirritation study is waived since no absorption was noted in the UVB/UVA/VIS spectrum (290 – 700 nm) for either azelaic acid or azelaic acid 15% foam.

The adequacy of the proposed design for the 3 month dermal minipig toxicology study to be conducted with azelaic acid 15% foam is addressed under nonclinical question 2. (b) (4)

The possibility that the dermal carcinogenicity study conducted in Tg.AC mice with azelaic acid 15% gel can be used to support the safety of azelaic acid 15% foam is addressed under nonclinical question 3.

Question 2

Does the agency concur with the proposed design of the 3 month minipig study?

Pharmacology/Toxicology response

No. The design of repeat dose dermal toxicology studies should keep the treatment area constant (i.e., 10% body surface area) and vary the concentration of the active in the clinical formulation for the three dose groups. The high dose group should be the maximum feasible dose (i.e., maximum feasible concentration and maximum feasible volume), if tolerated. Each dose group should incorporate use of at least 4 animals/sex/dose. Dermal toxicology studies should include complete clinical pathology, histopathology and toxicokinetic analysis. The sponsor's proposal for incorporation of an untreated and vehicle control group in the 3 month dermal minipig toxicology study is common practice for repeat dose dermal toxicology studies.

Question 3

Does the Agency concur, that based on the rationale provided, no carcinogenicity / (b) (4) studies with azelaic acid 15% foam need to be performed?

Pharmacology/Toxicology response

(b) (4)

The Tg.AC mouse dermal carcinogenicity study is under review and the Agency requires the requested SAS dataset for this study to complete the review of this study. Therefore, the (b) (4) support the safety of the azelaic acid foam formulation can not be determined at this time.

(b) (4)

Studies reviewed within this submission:

- 1) The *in vitro* percutaneous absorption of [14C]-azelaic acid (ZK 62498) through human, hairless mouse and pig skin including metabolism in human skin (Study# 782463)
- 2) Primary skin irritation study in rabbits (5-hour semi-occlusive application) (Study# B30993)

- 3) ZK 62894: 4-week repeated dose dermal tolerance study in rabbits (5-hour semi-occlusive application) (Study# B31004)
- 4) Local lymph node assay (LLNA) in mice with pre-foam formulation vehicle and ZK 62498 pre-foam formulation 15% (Study# 1103100)

Note: A summary of the nonclinical toxicology data available for the Finacea gel that will be used to support the safety of the new azelaic acid foam, 15% formulation is provided in appropriate sections of this review document.

Studies not reviewed within this submission: N/A

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2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

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

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

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

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

The possible pharmacodynamic activities of azelaic acid were evaluated in several nonclinical models related to factors that may be associated with acne pathology. The relevance of this information for the treatment of papulopustular rosacea is not known.

The following information concerning azelaic acid pharmacological activity is contained in the Finacea gel label.

The mechanism(s) by which azelaic acid interferes with the pathogenic events in rosacea are unknown.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Refer to brief summary

Drug activity related to proposed indication: Refer to brief summary

2.6.2.3 Secondary pharmacodynamics – N/A

2.6.2.4 Safety pharmacology

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

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

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

Nonclinical safety pharmacology studies did not indicate significant effects for azelaic acid on intermediary metabolism, liver function, renal function, cardiovascular function, smooth muscle or the nervous system under the conditions used in these studies. No additional nonclinical safety pharmacology studies are recommended for azelaic acid foam at this time.

2.6.2.5 Pharmacodynamic drug interactions – N/A

2.6.3 PHARMACOLOGY TABULATED SUMMARY – N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

All of the absorption, distribution, metabolism and excretion (ADME) studies were conducted using ^{14}C -labelled azelaic acid. ^{14}C -Azelaic acid contained the ^{14}C label at both carboxyl groups. Measurement of unchanged drug and its metabolites was performed using HPLC-chromatography. It is anticipated that the main process of elimination of azelaic acid is by biotransformation (since azelaic acid is a straight chain dicarboxylic acid). Systemically absorbed azelaic acid is metabolized by β -oxidation into shorter straight chain dicarboxylic acids (i.e., pimelic and glutaric acids), malonyl-CoA and acetyl-CoA. Released acetate enters the Krebs cycle for energy production or is used for lipid synthesis. Therefore, in these ADME studies, exhaled ^{14}C -label ($^{14}\text{CO}_2$) indicated catabolism of the released acetate.

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

^{14}C -Azelaic acid was almost completely absorbed in rats, rabbits, dogs and monkeys when given as a single oral (gavage) administration of a (b) (4) suspension at doses (1000 mg/kg in rats, 500 mg/kg in rabbits, 100 mg/kg in dogs and 150 mg/kg in monkeys) which were comparable to those used in toxicology studies. Excretion of the label was mainly in the urine (~50%) across all species.

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

The ^{14}C -label was rapidly distributed throughout rat body tissues after a single intravenous dose of 10 mg/kg ^{14}C -azelaic acid. High levels of radioactivity were found in the kidney (the main organ of excretion) and in the liver, and trace amounts of radioactivity appeared to cross the blood/brain barrier (brain, spinal cord). No radioactivity was detected in the fetuses of pregnant rats given a single 10 mg/kg dose of ^{14}C -azelaic acid intravenously. No differences in distribution pattern were observed between albino and pigmented rats. The ^{14}C -label was rapidly excreted (within 24 hours of injection) mainly through the urine (64%) and with respiratory air (18%). Only a trace amount of radioactivity (1.5%) was present in the feces.

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

This result suggests that azelaic acid may be metabolized to a greater extent in monkeys than in other animals.

The following information concerning azelaic acid pharmacokinetics is contained in the Finacea gel label.

The percutaneous absorption of azelaic acid after topical application of FINACEA® Gel, 15%, could not be reliably determined. Mean plasma azelaic acid concentrations in rosacea patients treated with FINACEA® Gel, 15%, twice daily for at least 8 weeks are in the range of 42 to 63.1 ng/mL. These values are within the maximum concentration range of 24.0 to 90.5 ng/mL observed in rosacea patients treated with vehicle only. This indicates that FINACEA® Gel, 15%, does not increase plasma azelaic acid concentration beyond the range derived from nutrition and endogenous metabolism.

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

2.6.4.2 Methods of Analysis – N/A

2.6.4.3 Absorption – refer to brief summary

2.6.4.4 Distribution – refer to brief summary

2.6.4.5 Metabolism – refer to brief summary

2.6.4.6 Excretion – refer to brief summary

2.6.4.7 Pharmacokinetic drug interactions – N/A

2.6.4.8 Other Pharmacokinetic Studies

Study Title:	The <i>in vitro</i> percutaneous absorption of [14C]-azelaic acid (ZK 62498) through human, hairless mouse and pig skin including metabolism in human skin
Study No:	782463
Conducting laboratory:	(b) (4)
Date of study initiation:	5-7-07
GLP compliance:	Yes

The in vitro skin penetration of ¹⁴C-azelaic acid foam (using the foam formulation minus the propellant) and ¹⁴C-azelaic acid gel were compared using human, pig and hairless mouse skin in a flow through diffusion cell apparatus. No significant difference in the dermal delivery (sum of absorbed dose and exposed skin) was noted between the foam and gel formulation (human skin: 0.94% and 1.27% of the applied dose for the foam and gel formulation, respectively; pig skin: 0.68% and 1.12% of the applied dose for the foam and gel formulation, respectively;

hairless mouse skin: 4.49% and 3.74% of the applied dose for the foam and gel formulation, respectively). In addition, no significant difference in percutaneous steady state flux was noted between the foam and gel formulation (human skin: 0.31 and 0.45 $\mu\text{g equiv./cm}^2/\text{hr}$ for the foam and gel formulation, respectively; pig skin: 0.11 and 0.14 $\mu\text{g equiv./cm}^2/\text{hr}$ for the foam and gel formulation, respectively; hairless mouse skin: 1.18 and 0.37 $\mu\text{g equiv./cm}^2/\text{hr}$ for the foam and gel formulation, respectively). The results from this in vitro percutaneous absorption study indicate that similar systemic exposure is expected after topical administration of the azelaic acid foam and azelaic acid gel formulations.

Very minimal metabolism of ^{14}C -azelaic was noted in vitro in human split-thickness skin discs. Only 1.3% of the parent disappeared over the 24 hour incubation period and the more polar metabolite did not appear to co-chromatograph with either the ^{14}C -glutaric or ^{14}C -pimelic acid reference standards.

2.6.4.9 Discussion and Conclusions

No nonclinical pharmacokinetic studies are recommended for azelaic acid foam, at this time.

2.6.4.10 Tables and figures to include comparative TK summary – N/A

2.6.5 PHARMACOKINETICS TABULATED SUMMARY – N/A

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

Acute toxicology studies:

Azelaic acid was evaluated for its acute toxicological effects in male and female mice, male rats and male and female dogs following oral (gavage) and intraperitoneal administration. Following single oral (gavage) doses of azelaic acid administered as a (b) (4) suspension, the minimum lethal doses were 3750 mg/kg (male mice) and 5000 mg/kg (female mice and male rats). After intraperitoneal administration, the minimum lethal doses were 400 mg/kg (male rats) and 500 mg/kg (male and female mice). A separate intraperitoneal study was conducted in male rats to determine the acute toxicity of sodium azelinate vs azelaic acid administered as a (b) (4) suspension. No male rats died after intraperitoneal administration of up to 1000 mg/kg sodium azelinate. The main clinical signs noted in this study included apathy, disturbances in gait, prone position (conscious), eyelid closure, extended abdomen (mice and rats, intraperitoneal), accelerated respiration (rats, oral), unconsciousness and tremor (rats, intraperitoneal). Death occurred within 30 minutes to 7 days after intraperitoneal administration and 1.5 to 3 days after oral administration. The stomach and intestine were identified as potential target organs of toxicity in mice and rats. Necropsy findings in mice that died prematurely included punctiform black foci of the gastric glandular

mucosa, white covering of the fatty tissue of the abdominal cavity and slight reddening of the intestine. Necropsy findings in rats that died prematurely included petechial hemorrhage of the gastric glandular mucosa, hemorrhage in the mucosa of the small intestine and prominent vessels of the gastrointestinal tract.

Emesis was observed immediately to 4.5 hours following single oral (gavage) doses of azelaic acid (at doses of 250 mg/kg and higher) administered as a (b) (4) suspension in dogs. Diarrhea also occurred 2.5 to 3.5 hours after dosing in dogs given azelaic acid at a dose level of 5000 mg/kg.

Repeat Dose Systemic Toxicology Studies:

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

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

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

Azelaic acid (0, 100 and 1000 mg/kg/day) was orally (gavage) administered as a daily (b) (4) suspension to male and female rats for 27 weeks. Lower body weight gain (1000 mg/kg/day), slightly lower food consumption (both dose groups) and slightly higher water consumption (1000 mg/kg/day) were noted in treated animals compared to control animals. Postmortem findings included thickening of the cuticular ridge of the stomach (both dose levels) accompanied by evagination and epithelia overgrowth in the high dose animals. The NOAEL dose identified in this study was 100 mg/kg/day.

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

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

Repeat Dose Dermal Toxicology Studies:

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

Azelaic acid 20% cream (0, 50, 100 and 300 mg/kg/day) was applied dermally on a daily basis (bid for low and mid dose groups; tid for high dose group) to rats for 6 months, with a one month recovery period. No treatment related effects were noted in the study. Plasma drug levels for azelaic acid and pimelic acid (primary metabolite) were obtained at week 2 and month 6 in the study. Plasma levels for azelaic acid and pimelic acid increased proportionately following dermal application. After 2 weeks, the plasma azelaic acid concentrations were 158 ± 70 , 490 ± 285 and 866 ± 523 ng/ml for the 50, 100 and 300 mg/kg/day dose groups, respectively. Azelaic acid plasma values after 6 months were 126 ± 27 , 255 ± 126 and 791 ± 573 ng/ml, respectively. The plasma levels of pimelic acid ranged from 12.3 to 44.1 ng/ml over the dose range tested in this study. The dermal NOAEL was identified in this study as 300 mg/kg/day.

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

Reviewer's Comments: It is important to note that the 26 week dermal toxicity study in dogs, the 4 and 27 week oral toxicity study in rats and the 4 week oral toxicity study in monkeys were

submitted under the IND for azelaic acid 20% cream (IND 38,271). The 6 month systemic toxicity study in dogs and the 6 month dermal toxicity study in rats were submitted with the NDA submission for azelaic acid 20% cream (NDA 20-428). The last two studies that were submitted with the NDA were conducted with a more adequate dose range (low, mid and high dose groups).

In summary, the toxicology of systemically administered (b) (4) suspensions of azelaic acid was assessed in acute studies conducted in mice, rats and dogs and repeat dose systemic toxicity studies in rats, monkeys and dogs. Dermal toxicology studies conducted with the azelaic acid 20% cream included repeat dose studies in rats and dogs.

The sponsor did not conduct any nonclinical repeat dose dermal toxicology studies with the azelaic acid 15% gel formulation. However, the sponsor included the results from two nonclinical in vivo percutaneous absorption studies conducted in rats and dogs in the NDA 21-470 submission. Both of these studies compared the percutaneous absorption of azelaic acid 20% cream and azelaic acid 15% gel. In rats, at the highest dose (300 mg/kg; equivalent to the high dose in the dermal toxicology study conducted in rats), the absorption of the cream formulation was almost two-fold higher than the gel (2.4% and 1.3%, respectively) after a single 24 hour non-occluded dose. In the dog, after a single dermal application of 150 mg/kg (~1/2 the high dose used in the repeat dose dermal toxicology study in dogs) of the azelaic acid 20% cream and the azelaic acid 15% gel, the percutaneous absorption was 1.16% and 0.43%, respectively. In summary, it appears that the results from these two in vivo percutaneous absorption studies indicate that the cream formulation provides a slightly higher systemic exposure after dermal administration compared to the gel formulation. This results suggests that the results from the repeat dose dermal toxicology studies conducted with azelaic acid 20% cream formulation would provide sufficient data to support the use of the azelaic acid 15% gel formulation. It would not be expected to see an increased level of systemic toxicity after repeat dose administration of the azelaic acid 15% gel formulation compared to the azelaic acid 20% cream formulation based on the results of the in vivo percutaneous absorption studies conducted in rats and dogs.

In addition, the sponsor submitted to IND 63,777 the results from two special toxicology studies that were conducted to assess the local tolerance of single and repeated (28 days) topical applications of azelaic acid 15% gel in rabbits. The local tolerance of repeated applications (28 days) in rabbits of azelaic acid 15% gel was compared with that of azelaic acid 20% cream. Azelaic acid 15% gel and vehicle gel were very slightly irritating on intact rabbit skin and more severely irritating on abraded rabbit skin after single topical application under semi-occlusion. Azelaic acid 15% gel and the vehicle gel formulation were slightly more irritating on intact rabbit skin than azelaic acid 20% cream during 4 weeks of repeat application. It is anticipated that the azelaic acid 15% gel would cause a slightly greater level of irritation in a repeat dose dermal toxicology study conducted in either rats or dogs.

During the pre-IND meeting, the sponsor was provided guidance for the design of a 3 month dermal minipig to be conducted with the azelaic foam, 15% formulation. The sponsor states in the IND submission that they plan to conduct a 3-month dermal minipig toxicology study with toxicokinetics with the foam formulation. The sponsor will be referred to the

guidance provided during the pre-IND meeting for this study and reminded that this study should be conducted prior to initiation of Phase 3 clinical studies.

Genetic toxicology:

The following information is included in the Finacea gel label for the genetic toxicity of azelaic acid.

“Azelaic acid was not mutagenic or clastogenic in a battery of *in vitro* (Ames assay, HGPRT in V79 cells {Chinese hamster lung cells}, and chromosomal aberration assay in human lymphocytes) and *in vivo* (dominant lethal assay in mice and mouse micronucleus assay) genotoxicity tests.”

Carcinogenicity:

Two nonclinical post-marketing commitments were included in the approval letter for Finacea gel. The first nonclinical post-marketing commitment was for a study to determine the photoco-carcinogenic potential associated with azelaic acid 15% gel. The second nonclinical post-marketing commitment was for a dermal carcinogenicity study conducted in Tg.AC mice with azelaic acid 15% gel.

(b) (4)



The sponsor submitted a protocol for the dermal carcinogenicity study conducted with azelaic acid gel in Tg.AC mice and a final study report for a 4 week dermal dose ranging study in FVB/N mice on July 11, 2003. The Exec CAC meeting to discuss the dermal carcinogenicity study protocol in Tg.AC mice was conducted on August 19, 2003. The Exec CAC meeting minutes, which included Exec CAC recommendations for modification of the protocol, were relayed to the sponsor on August 21, 2003.

The sponsor submitted the final study reports for the feasibility study conducted with TPA dissolved in the hydrogel and the Tg.AC mouse dermal carcinogenicity study conducted with azelaic acid gel to NDA 21-470 on November 7, 2006. An Exec CAC meeting to discuss the results of this study was conducted on September 11, 2007. The dosing regimen used for the Tg.AC mouse assay and a brief summary of the results are provided below.

Dosing table for Tg.AC mouse assay

Group	Treatment	Dose	Dose Volume (ml)	Dose Frequency	Number of Animals	
					Males	Females
1	Untreated (sheared) control	--	--	Untreated	20	20
2	Hydrogel vehicle control	0	0.2	Twice daily ^a	20	20
3	Low dose: 15% azelaic acid gel	31.2 mg/day	0.2	Once daily	20	20
4	High dose: 15% azelaic acid gel	62.4 mg/day	0.2	Twice daily ^a	20	20
5	TPA in acetone	1.25 µg/day	0.2	3X/week ^b	15	15
6	TPA in hydrogel vehicle	10 µg/day	0.2	3X/week ^b	15	15

a – Twice daily doses separated by 5-6 hours

b – 3X/week dosing performed on Monday, Wednesday, Friday

Test article (0.2 ml) was administered topically to a shaved treatment site (6 cm²) (either once daily, twice daily or 3X/week) for 26 weeks.

The vehicle caused a statistically significant increase in the incidence of male animals with papillomas (10/20) compared to untreated male animals (0/20) with no further increase noted after exposure to a high dose of the active (8/20). Therefore, a positive effect was noted in vehicle and high dose males compared to untreated males in the Tg.AC mouse assay. No statistically significant increase in the incidence of female animals with papillomas was noted in the low (1/20) and high dose groups (3/20) compared to untreated (3/20) and vehicle (0/20) treated groups. Therefore, no effect was noted in female animals in the Tg.AC mouse assay.

The Exec CAC meeting minutes and additional pharmacology/toxicology comments regarding this study were relayed to the sponsor on September 28, 2007. The Exec CAC recommendations and conclusions for this study are provided below.

- 1) The Committee agreed that the study was adequate.
- 2) The Committee concluded that the Tg.AC mouse assay was negative for female mice and positive for male mice, noting a statistically significant increase in the incidence of males with papillomas in the vehicle and high dose groups compared to untreated control. The Committee noted that there was no statistically significant difference in the incidence of males with papillomas in the vehicle and high dose groups which suggested that the positive effect may be due to the vehicle only. There was no statistically significant

increase in the incidence of treated females with papillomas compared to vehicle or untreated females.

The Pharmacology/Toxicology comments that were relayed to the sponsor for this study are provided below.

The sponsor should submit a labeling supplement that incorporates the findings of the Tg.AC mouse assay (per the Exec CAC minutes of 9-11-07) conducted with Finacea gel.

Reproductive toxicology:

The following information is included in the Finacea gel label for the reproductive toxicity of azelaic acid. Finacea gel is designated as Pregnancy Category B.

“Oral administration of azelaic acid at dose levels up to 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area) did not affect fertility or reproductive performance in male or female rats.

There are no adequate and well-controlled studies of topically administered azelaic acid in pregnant women. The experience with FINACEA® Gel, 15%, when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy. Dermal embryofetal developmental toxicology studies have not been performed with azelaic acid, 15%, gel. Oral embryofetal developmental studies were conducted with azelaic acid in rats, rabbits, and cynomolgus monkeys. Azelaic acid was administered during the period of organogenesis in all three animal species. Embryotoxicity was observed in rats, rabbits, and monkeys at oral doses of azelaic acid that generated some maternal toxicity. Embryotoxicity was observed in rats given 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area), rabbits given 150 or 500 mg/kg/day (19 or 65 times the maximum recommended human dose based on body surface area) and cynomolgus monkeys given 500 mg/kg/day (65 times the maximum recommended human dose based on body surface area) azelaic acid. No teratogenic effects were observed in the oral embryofetal developmental studies conducted in rats, rabbits and cynomolgus monkeys.

An oral peri- and post-natal developmental study was conducted in rats. Azelaic acid was administered from gestational day 15 through day 21 postpartum up to a dose level of 2500 mg/kg/day. Embryotoxicity was observed in rats at an oral dose that generated some maternal toxicity (2500 mg/kg/day; 162 times the maximum recommended human dose based on body surface area). In addition, slight disturbances in the postnatal development of fetuses was noted in rats at oral doses that generated some maternal toxicity (500 and 2500 mg/kg/day; 32 and 162 times the maximum recommended human dose based on body surface area). No effects on sexual maturation of the fetuses were noted in this study.

Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed during pregnancy.”

Special toxicology:

Azelaic acid pre-foam emulsion, 15%, azelaic acid 15% gel and vehicle pre-foam emulsion were mild irritants after a single 5 hour semi-occlusive application to rabbits and elicited very slight erythema to rabbit skin throughout the 28 day treatment period with a 5 hour semi-occlusive application/day. Azelaic acid pre-foam emulsion, 15% and vehicle pre-foam emulsion did not elicit a positive response in the mouse local lymph node assay. The need for a nonclinical photo-irritation study is waived for the azelaic acid pre-foam emulsion, 15% since no absorption was noted from 290 – 700 nm for azelaic acid in methanol or the vehicle pre-foam emulsion in methanol.

2.6.6.2 Single-dose toxicity

No nonclinical single-dose toxicity studies were included in this submission.

2.6.6.3 Repeat-dose toxicity

No nonclinical repeat-dose toxicity studies were included in this submission.

2.6.6.4 Genetic toxicology

No nonclinical genetic toxicology studies were included in this submission.

2.6.6.5 Carcinogenicity

No nonclinical carcinogenicity studies were included in this submission.

2.6.6.6 Reproductive and developmental toxicology

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

2.6.6.7 Local tolerance

No nonclinical local tolerance studies were included in this submission.

2.6.6.8 Special toxicology studiesStudy #1

Study title Primary skin irritation study in rabbits (5-hour semi-occlusive application)

Key findings: Azelaic acid pre-foam emulsion, 15%, vehicle pre-foam emulsion and two azelaic acid gel 15% formulations were mild irritants to rabbit skin after a 5 hour semi-occlusive application.

Study no.: B30993
Volume #, and page #: 2, 695
Conducting laboratory: (b) (4)
Date of study initiation: 5-23-07
GLP compliance: Yes
QA reports: Yes
Drug, lot #, and % purity: Azelaic acid pre-foam emulsion, 15%, Batch# GLP C004
Azelaic acid gel 15% (Skinoren 15% gel, European formulation), Batch# 44087A
Azelaic acid gel 15% (Finacea 15% gel), Batch# 10 FK-808
Vehicle: Vehicle pre-foam emulsion, Batch# GLP C005

Methods

New Zealand white rabbits (1 male and 2 females) received a single dermal application of 500 mg of each test article applied to an intact shaved skin site (four sites per animals; 6 cm²/site) under semi-occlusion for 5 hours. Each treatment site was evaluated for signs of dermal irritation immediately after patch removal and at 24, 48 and 72 hours post patch removal.

Results:

All four test articles were mild irritants under the conditions of this study. Total reversibility was noted after 48 hours for vehicle pre-foam emulsion and both azelaic acid 15% gel formulations. Total reversibility was noted after 72 hours for the azelaic acid pre-foam emulsion, 15%.

Study #2

Study title ZK 62894: 4-week repeated dose dermal tolerance study in rabbits (5-hour semi-occlusive application)

Key findings: Azelaic acid pre-foam emulsion, 15%, vehicle pre-foam emulsion and two azelaic acid gel 15% formulations elicited very slight erythema to rabbit skin throughout the 28 day treatment period with a 5 hour semi-occlusive application/day. Treatment related microscopic effects noted at the treated skin site included minimal to slight inflammatory cell infiltration, minimal to slight acanthosis and minimal scab formation at all test article treated skin sites with no significant difference in the extent of histopathological effects noted for the 4 different test articles.

Study no.: B31004
Volume #, and page #: 2, 730
Conducting laboratory: (b) (4)
Date of study initiation: 5-30-07
GLP compliance: Yes
QA reports: Yes

Drug, lot #, and % purity: Azelaic acid pre-foam emulsion, 15%, Batch# GLP C004
Azelaic acid gel 15% (Skinoren 15% gel, European formulation), Batch# 44087A
Azelaic acid gel 15% (Finacea 15% gel), Batch# 10 FK-808

Vehicle: Vehicle pre-foam emulsion, Batch# GLP C005

Methods

New Zealand white rabbits (2 males and 2 females) received a dermal application of 250 mg of each test article applied to an intact shaved skin site (four sites per animals; 6 cm²/site) under semi-occlusion for 5 hours once daily for 4 weeks. The treatment site was cleaned with lukewarm tap water and cotton wool after each daily treatment. Safety parameters evaluated in this study included mortality (daily), clinical signs (daily), dermal irritation (daily after patch removal) and body weights (weekly). A complete necropsy was performed for each animal after the 4 week treatment period and treated and untreated skin was processed for histopathological assessment.

Results:

No treatment related effects on mortality, clinical signs or body weights were noted in this study. Very slight erythema was noted at all treatment sites throughout the 28 day treatment period. Minimal inflammatory cell infiltration was noted at untreated skin. Minimal to slight inflammatory cell infiltration, minimal to slight acanthosis and minimal scab formation was noted at all test article treated skin sites. No significant difference in the extent of histopathological effects noted at the treated skin sites was noted for the 4 different test articles.

Study #3

Study title Local lymph node assay (LLNA) in mice with pre-foam formulation vehicle and ZK 62498 pre-foam formulation 15%

Key findings: Azelaic acid pre-foam emulsion, 15% and vehicle pre-foam emulsion did not elicit a positive response in the mouse local lymph node assay.

Study no.: 1103100
Volume #, and page #: 1, 490
Conducting laboratory: (b) (4)
Date of study initiation: 6-12-07
GLP compliance: Yes
QA reports: Yes
Drug, lot #, and % purity: Azelaic acid pre-foam emulsion, 15%, Batch# GLP C004
Vehicle: Vehicle pre-foam emulsion, Batch# GLP C005
Positive control: 25% alpha-hexylcinnamaldehyde in acetone: olive oil (4:1)

Methods

Dose groups: negative control (acetone: olive oil {4:1}), vehicle control (pre-foam emulsion), positive control and azelaic acid pre-foam emulsion, 15%

Study design:

Test article (25 µl) was applied daily over the entire dorsal surface of each mouse ear (CBA/Ca mice; 5 females/dose) for 3 days. The proliferative response of the auricular lymph node (incorporation of ³H-methyl thymidine) was assessed 5 days following the initial application. Ear weights (obtained by punch biopsy) were obtained after sacrifice.

Results:

No lymphocyte proliferation was noted in mice, under the conditions of this study. The positive control elicited the appropriate response in this study. No treatment related effects on ear weights were noted in this study. The mean S.I. values for the negative control, vehicle control, positive control and azelaic acid pre-foam emulsion, 15% groups were 1.00, 1.37, 4.72 and 0.92, respectively.

2.6.6.9 Discussion and Conclusions

The sponsor has included a right to reference all of the nonclinical toxicology study information used to support approval of Finacea gel, 15% in this IND. In addition, the sponsor has conducted a dermal rabbit irritation study, a 4 week repeat dose dermal rabbit irritation study and a murine local lymph node assay with azelaic acid pre-foam emulsion, 15% and the vehicle pre-foam emulsion formulation. The results from these studies indicate that both test articles are mild irritants in rabbit skin, elicit very minimal erythema in rabbit skin after 4 weeks of daily administration and do not appear to have a sensitization signal. In addition, the results from an vitro percutaneous absorption study conducted with human, mouse and minipig skin showed similar rates of penetration for the azelaic acid foam and gel formulations which provides an initial indication that similar systemic exposure may be expected after topical administration of the azelaic acid foam and gel formulations.

Adequate nonclinical toxicology data is available for azelaic acid to indicate that the proposed Phase 2 clinical study is reasonably safe to initiate from a pharmacological/toxicological perspective. The sponsor will be reminded that the 3 month dermal minipig toxicology study should be conducted prior to initiation of Phase 3 clinical studies.

2.6.6.10 Tables and Figures – N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY

Refer to summaries provided above.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Summary:

The proposed Phase 2 clinical study is reasonably safe to initiate, from a pharmacological/toxicological perspective, based on the nonclinical toxicology study data available for azelaic acid foam.

External Recommendations (to sponsor):

It is recommended that the following information be relayed to the sponsor for IND 77,516:

- 1) The Division notes that the sponsor plans to conduct a 3 month dermal minipig toxicology study with toxicokinetics with the foam formulation. The sponsor is referred to the guidance provided for the design of this study relayed during the pre-IND meeting conducted on July 17, 2007. This study should be conducted and a study report submitted to the IND for evaluation prior to initiation of Phase 3 clinical studies.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ____ No ____

cc:

DDDP/DIV DIR/WALKER
DDDP/PHARM SUP/BROWN
DDDP/PHARM/HILL
DDDP/MO/LIEDTKA
DDDP/PM/CARR

APPENDIX/ATTACHMENTS

Linked Applications

Sponsor Name

Drug Name

IND 77516

INTENDIS INC

AZELAIC ACID 15%

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

/s/

BARBARA A HILL

12/11/2007

Non-Clinical Reviewer

PAUL C BROWN

12/13/2007

Non-Clinical Reviewer