CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 19, 2015
From	David L. Kettl, MD, FAAP
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 207071 Related IND 77516 0
Applicant	Bayer Health Care Pharmaceuticals, Inc.
Date of Submission	September 20, 2014
PDUFA Goal Date	July 30, 2015
Proprietary Name / Established (USAN) names	Finacea (azelaic acid) Foam 15%
Dosage forms / Strength	Topical foam
Proposed Indication(s)	Inflammatory papules and pustules of mild to moderate rosacea in adults
Recommended:	***Approval***

1. Introduction

Bayer Health Care Pharmaceuticals, Inc. submitted an original 505 (b)(1) application on September 20, 2014 for Finacea (azelaic acid) Foam 15%, a topical foam proposed for treatment of inflammatory papules and pustules of mild to moderate rosacea in adults.

The applicant currently markets Finacea (azelaic acid) Gel 15% for the topical treatment of inflammatory papules and pustules of mild to moderate rosacea. This submission is a 505(b)(1) application as the applicant owns all the necessary nonclinical data for azelaic acid to support the application for the azelaic acid foam, 15%, and established the safety and efficacy of this new formulation in clinical trials.

Azelaic acid is a dietary constituent and is also produced in endogenous metabolism. Azelaic acid is described as having anti-inflammatory, anti-keratinizing, anti-bacterial activities, but the precise mechanism by which azelaic acid interferes with the rosacea disease process is not well understood.

The applicant conducted one successful, adequate and well controlled Phase 3 clinical trial (Study 846) in which efficacy was demonstrated from screening to 12 weeks post-treatment compared to placebo. The foam formulation was also evaluated in an exploratory Phase 2 study (Study 140), a larger Phase 2 study (Study 120). The applicant has submitted the larger Phase 2 Study 120 as supportive of the Phase 3 Study.

Safety was substantiated on the analysis of the experience of the safety data from the clinical program of 746 subjects with papulopustular rosacea who were treated with azelaic acid foam, 15% in Phase 1, Phase 2, and Phase 3 development program for this product. In addition, two hundred eighty (280) healthy subjects were exposed to azelaic acid pre-foam emulsion, 15% in Phase 1 clinical trials.

There are no outstanding review issues as of the date of this review beyond conclusion of labeling negotiations with the applicant, and the final report for facility inspections from the Office of Compliance.

A REMS program is neither proposed by the applicant nor recommended by the Agency review team for this application given the safety conclusions of the team's review. Labeling is adequate to inform prescribers and patients of the known and expected adverse reactions and clinical risks, which are largely limited to local irritation reactions.

The primary clinical review, by Dr. Gary Chiang, concluded that Finacea Foam 15% is safe and effective for treatment of inflammatory papules and pustules of mild to moderate rosacea in adults. An approval action is recommended by the entire multidisciplinary review team pending completion of final labeling negotiations with the applicant. This CDTL review concurs with that recommendation to approve this application for this new foam formulation of azelaic acid.

2. Background

Rosacea is a common, chronic cutaneous disorder with clinical symptoms including facial redness, dilated blood vessels on facial skin, papules, pustules, and swelling. The exact cause of rosacea is unknown. There is no curative therapy. Mild disease may not require any treatment beyond cosmetics, but typical treatments include topical and systemic antibiotics, and more severe forms can often require lifelong treatment.

Azelaic acid is a naturally occurring aliphatic dicarboxylic acid and is present in animals, humans, and plants. For example, it is a natural constituent in whole grain cereals.

There are two approved NDA's for azelaic acid, which was first approved by the Agency in 1995 as Azelex Cream 20%, indicated for the topical treatment of mild-to-moderate inflammatory acne vulgaris. The latest revision to Azelex labeling was in June, 2003, and that label remains in the old labeling format.

Finacea (azelaic acid) Gel 15% was approved 12/24/2002 for topical treatment of the inflammatory papules and pustules of mild to moderate rosacea. This label has been converted to PLR content and format and served as the backbone for the label for the newly proposed foam formulation.

There is no established pharmacologic class for azelaic acid in the Finacea Gel label. [redacted] (b) (4)

The applicant opened their IND in July, 2007. An EOP 2 meeting was conducted on November 9, 2011 and a pre-NDA meeting was held on July 9, 2014.

3. CMC/Device

The CMC review was conducted by Dr. Hamid Shafiei and the Quality Microbiology review by Dr. Jessica Cole.

Finacea (azelaic acid) Foam, 15%, for topical administration is a new hydrophilic foam formulation containing 15% w/w [redacted] (b) (4) azelaic acid in an oil-in-water emulsion that is filled in an aluminum can with spray valve and cap and pressurized using a propellant for foam delivery. The proposed trade size is 50 grams, with a physician sample size of 30 grams.

Azelaic acid is a white, odorless crystalline solid. The drug substance is commercially produced [redacted] (b) (4). There are no novel excipients. There is one noncompendial excipient, dimethyl isosorbide. The to-be-marketed formulation is the same formulation used in the phase 3 trial and the registration stability batches.

The applicant references DMF's 9289 and [redacted] (b) (4), and was deemed adequate for the manufacturing process, process controls, in-process testing, packaging, and release and stability. An initial review issue regarding missing/incomplete establishment information was remedied in advance of the date of the filing letter. There were no review issues by the mid-cycle meeting.

The drug substance release specification for azelaic acid includes testing and acceptance criteria for appearance, identity, melting range, clarity of solution, color of solution, assay, related substances, [redacted] (b) (4), heavy metals, water content, residual solvents [redacted] (b) (4) particle size, and polymorphism. The proposed API specification is satisfactory.

The CMC review by Dr. Shafiei concluded that the applicant submitted sufficient information in the application, and the drug substance specification is deemed adequate to assure the identity, strength, purity, and quality of the drug substance.

The product quality microbiology review by Dr. Cole found no deficiencies with the product or carton/container information. There are no outstanding issues related to product quality.

No post marketing requirements or commitments are recommended, and there are no outstanding CMC issues beyond agreement on labeling, though the overall recommendation and final completion of the OPQ review is pending an "Acceptable" from the Office of Compliance for the facilities inspections.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review by Jianyong Wang, PhD concludes that there are no outstanding approvability issues for this application, and one recommended post marketing study to conduct a 2-year dermal mouse carcinogenicity study. Labeling changes for Sections 8, 12 and 13 of product labeling are proposed to be communicated the applicant.

Dr. Wang's review notes that 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.

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

The primary nonclinical issue identified by Dr. Wang for this application relates to the need for dermal carcinogenicity assessments and was discussed during the IND development. A short-term dermal carcinogenicity study in transgenic mice (Tg.AC assay) was previously 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 have been 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 was proposed to be conducted as a post-marketing

requirement (PMR) during the Pre-NDA meeting conducted under IND 77516, the corresponding IND for this foam formulation NDA.

The applicant previously 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 PMR study report.

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 following proposed timeline was deemed acceptable by the review team:

> Anticipated 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

The applicant relies on Pharmacology-Toxicology information and long term safety information from currently approved Finacea Gel, 15%, which is owned by the applicant. Thus, this application is reviewed under a 505(b)(1) regulatory pathway.

In consultation with the Division of Pediatric and Maternal Health – Maternal Health Team, the team's recommendation is to delay compliance with the final Pregnancy and Lactation Labeling Rule since given the projected action date of this application and, in addition, this product is not a new molecular entity. Proposed labeling will mirror that of the currently approved Finacea Gel 15% labeling.

There are no outstanding issues from Dr. Wang related to the nonclinical review and one recommended post marketing requirement as noted above

This application also received secondary concurrence review recommending approval from Dr. Barbara Hill.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review by Dr. Chinmay Shukla concluded that the application was acceptable from a Clinical Pharmacology perspective, pending agreement on recommended labeling changes.

The applicant assessed the bioavailability of azelaic acid and pimelic acid (metabolite) following twice daily repeated administration of azelaic acid foam, 15 % versus azelaic acid gel (Finacea Gel), 15 %, under maximal use conditions in a randomized crossover trial in 24 adult subjects with moderate papulopustular rosacea.

On Day 7, azelaic acid systemic concentrations were at steady state. PK parameters C_{max}, AUC_{0-12}, and AUC_{0-36} were calculated and demonstrated that systemic exposure (C_{max} and AUC_{0-12}) of azelaic acid following topical application of azelaic acid Foam, 15% were not higher than those observed following application of azelaic acid gel, 15% (Finacea® Gel).

The values of baseline uncorrected PK parameters for azelaic acid (mean ±SD) on Day 7 for azelaic acid foam were 51.8 ± 18.5 ng/mL, 442.0 ± 177.6 ng*hr/mL, and 1101.7 ± 338.1 ng*hr/mL for Cmax, AUC0-12, and AUC0-36, respectively and corresponding baseline corrected values were 40.1 ± 19.1 ng/mL, 322.8 ± 174.4 ng*hr/mL, and 852.7 ± 457.0 ng*hr/mL for Cmax, AUC0-12, and AUC0-36, respectively.

No dose ranging trials were conducted for this application for the new foam formulation.

The drug-drug interaction potential and QTc assessments were not assessed as the systemic exposure of the foam was not higher than previously observed in the Finacea Gel development program.

Dr. Shukla concludes that there is no approvability issue related to clinical pharmacology requirements, and no post marketing commitments or requirements are recommended.

6. Clinical Microbiology

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 relevance of these effects of azelaic acid to the treatment of rosacea in not known, as the etiology of rosacea is not definitively characterized.

The applicant asserts no antimicrobial claims, and submitted no new clinical microbiology data in this application for review.

Labeling will state that the mechanism of action is “unknown”, as also currently described in the Finacea Gel labeling. No specific clinical microbiology information will be included in the prescribing information.

7. Clinical/Statistical- Efficacy

The clinical review by Dr. Gary Chiang and the biostatistics review by Dr. Kathleen Fritsch conclude that there is adequate evidence to determine that azelaic acid foam 15% was superior to placebo in the treatment of inflammatory papules and pustules of mild to moderate rosacea in adults. All studies were conducted in the United States.

The clinical program for the new formulation consists of six new clinical trials:

- Two Phase 1 trials to assess skin irritation and sensitization potential
- A maximal use pharmacokinetic (PK) trial that assessed relative bioavailability (BA) of azelaic acid and pimelic acid (metabolite) following twice daily administration of the new foam formulation versus currently marketed Finacea® Gel in adult subjects with moderate rosacea
- Two Phase 2 efficacy and safety trials
- One Phase 3 trial

Azelaic acid foam, 15% was superior to vehicle foam on the primary efficacy endpoints in two studies conducted in adult subjects with rosacea. Dr. Fritsch notes that one of the two studies was designed as a Phase 2 study (Study 120) and the other study was designed as a Phase 3 study (Study 846). Even though it was designed as a Phase 2 study, the primary efficacy endpoints and corresponding analysis methods were adequately prespecified in Protocol 120. However, the analysis methods for secondary endpoints, including multiplicity adjustments, were not adequately prespecified in Protocol 120.

The protocol for the Phase 3 study (Study 846) adequately prespecified statistical methods for both the primary and secondary endpoints. The studies enrolled subjects age 18 and older with a diagnosis of papulopustular rosacea with an IGA score of moderate to severe, 12-50 inflammatory lesions, and persistent erythema with or without telangiectasia. Subjects were treated twice daily for 12 weeks.

The protocol for Phase 3 Study 846 was submitted as a Special Protocol Assessment. The Agency provided agreement regarding the overall design and primary endpoints, but the Agency did not provide agreements regarding the secondary endpoints. Study 846 defined three secondary endpoints: (1) percent change in inflammatory lesions from baseline to Week 12, (2) response rate (clear, minimal, or mild on the IGA) at Week 12, and (3) grouped change in erythema rating (improved, no change, or worsened) at Week 12.

The co-primary efficacy endpoints of IGA treatment success (clear or minimal) at Week 12 and absolute change in inflammatory lesions at Week 12 were statistically significant ($p<0.017$) in both studies.

The Phase 2 study (Study 120) analysis methods for the grouped change in erythema rating were not adequately prespecified, nor were the results even nominally statistically significant (nominal p=0.138), (b) (4)

Study 120 randomized 198 subjects to azelaic acid and 203 to vehicle. Study 846 randomized 483 subjects to azelaic acid and 478 to vehicle. Baseline demographics were generally balanced across the treatment groups in the two studies. The mean age was approximately 48 years with approximately 8% age 65 and older in Study 120 and 51 years with approximately 17% age 65 and older in Study 846. More than 70% of subjects were female. At least 95% of subjects were white. Approximately 28% of subjects in Study 120 and 20% of subjects in Study 846 were Hispanic/Latino.

The reviews conclude that treatment effects for the co-primary endpoints were generally consistent across subgroups and centers, and the treatment effect trends were generally consistent across various assumptions regarding missing data. There were insufficient subjects who reported a race other than white for meaningful subgroup analysis by age group or race. Treatment effects across age group, gender, and ethnicity were generally consistent in favor of azelaic acid.

The efficacy results are summarized from Dr. Fritsch's biostatistics review table:

Table 1 – Efficacy Results at Week 12

	Study 120		Study 846	
	Azelaic Acid N=198	Vehicle N=203	Azelaic Acid N=483	Vehicle N=478
Primary Endpoints				
IGA clear or minimal	86 (43.4%)	66 (32.5%)	155 (32.1%)	112 (23.4%)
	p=0.017		p=0.001	
Change in inflammatory lesions	-13.0 (0.6)	-9.7 (0.6)	-13.0 (0.4)	-10.2 (0.4)
	p < 0.001		p < 0.001	
Secondary Endpoint				
Grouped erythema rating				
Improved	123 (62.1%)	108 (53.2%)	297 (61.5%)	245 (51.3%)
No change	68 (34.3%)	91 (44.8%)	178 (36.9%)	221 (46.2%)
Worsened	7 (3.5%)	4 (2.0%)	8 (1.7%)	12 (2.5%)
	p=0.138		p=0.001	

While not mentioned in the Biostatistical review, the clinical team noted that there is a substantial marketing history since 2002 for Finacea Gel 15%, with well described efficacy and safety. The postmarketing experience with the gel formulation is also supportive of efficacy of the newly proposed azelaic foam formulation, and was considered in Agency meeting advice regarding the level of evidence required for this foam application.

The review team concludes are no outstanding issues related to demonstration of efficacy beyond agreement on final product labeling.

8. Safety

The applicant presented an adequate safety database consisting of six clinical trials/studies in which a total of 746 subjects received at least one dose of azelaic acid foam 15%. In addition, two hundred eighty (280) healthy subjects were exposed to azelaic acid pre-foam emulsion, 15% in Phase 1 clinical trials.

Safety data were reviewed by Dr. Gary Chiang, who notes in the clinical review that there is also a large postmarketing safety database for cream and gel formulations of azelaic acid which dates back to 1995. In 2013, approximately (b) (4) units of azelaic acid formulations were sold worldwide, with an estimated 3.02 million person-months (approximately 251,710 person-years) of exposure in 2013 (based on the current Periodic Safety Update Report (PSUR) covering the period 03 Jan 2013 – 02 Jan 2014).

Approximately 32% of azelaic acid subjects and 25% of vehicle subjects experienced at least one adverse event during the trials. Approximately 1.5% of subjects discontinued treatment due to adverse events. The most common adverse reactions were the administration site conditions of pain, pruritus, and paresthesia.

In the analysis of Phase 2 and Phase 3 clinical trials, a total of 11 serious TEAEs (including one case of death) were reported: 4 SAEs in subjects treated with azelaic acid foam, 15% and 7 SAEs in subjects treated with vehicle. The death occurred in a subject randomized to vehicle. The SAEs (presented as PTs) included cases of cardiac failure congestive, hepatotoxicity, cellulitis and deep vein thrombosis in subjects included in the azelaic acid foam, 15% group as well as gastroenteritis viral, hemorrhage, accidental death, post-concussion syndrome, intervertebral disc degeneration, thyroid cancer and bipolar disorder in subjects included in the vehicle group. None of the SAEs were assessed by the investigator or the Agency review to be related to study drug.

Dermal safety studies were conducted with the foam formulation in healthy volunteers. Cumulative irritation was higher than vehicle, but no evidence of a sensitizing potential was noted. However, hypersensitivity is considered a known safety concern for azelaic acid foam, 15% based on the post-marketing surveillance data received for other topical azelaic acid containing formulations and the well-known risk of propylene glycol and cetostearyl alcohol

which are contained as excipients in azelaic acid foam, 15%. (b) (4)

This CDTL review concurs with the conclusion of the primary medical officer review by Dr. Chiang that the limited local safety issues identified, in conjunction with the demonstration of efficacy described above, represent an overall acceptable risk benefit determination adequate to support an approval action for this application.

9. Advisory Committee Meeting

The review team determined early in the application review cycle that this new foam formulation for azelaic acid presented no novel or complex regulatory issues that required the input of an advisory committee. None was conducted for this application.

10. Pediatrics

The applicant requested a waiver in their Pediatric Study Plan for all subsets of the pediatric population due to studies being impossible or highly impractical as the number of pediatric subjects with rosacea is extremely small. The PeRC concurred with the Division recommendation to grant a full waiver.

11. Other Relevant Regulatory Issues

No issues related to financial disclosures, GCP issues, or patent issues were identified in the review of the application.

GMP inspections are pending an "Acceptable" determination from the Office of Compliance for the facilities inspections as of the date of this CDTL review.

Given the nature of the development program and the twelve year marketing history for the related gel formulation, The Division of Scientific Investigators (DSI) was not consulted to review study sites related to the conduct of clinical trials. No irregularities were noted by the review team during the review.

There are no outstanding regulatory issues that impact the approval of this application.

12. Labeling

The trade name of "Finacea" has been accepted by Office of Medication Error Prevention and Risk Management (OMEPRM/DMEPA). The foam formulation will have a separate label from the existing Finacea Gel at the applicant's request.

Review of the proposed label submitted by the applicant was based on evaluation of the clinical trials for the NDA as well as DMEPA, DRISK, and OPDP consultative reviews.

Given the projected action date of this application and the fact that this product is not a new molecular entity, PLLR changes to the label will be deferred to a later time. Proposed labeling will mirror that of the currently approved Finacea Gel 15% labeling.

Labeling is adequate to communicate necessary safety information to prescribers. Final agreement on Agency proposed labeling, including carton/container labeling, is pending as of the date of this CDTL review.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The conclusion of the clinical review, and that of the review team, and concurred by this CDTL review, is that safety and efficacy of azelaic acid foam 15% has been adequately demonstrated by the clinical development program for the treatment of inflammatory papules and pustules of mild to moderate rosacea in adults. An approval action is recommended pending successful completion of ongoing labeling negotiations.

- Risk Benefit Assessment

Efficacy has been adequately demonstrated by the applicant, and the safety findings are not unexpected given the nature of this new foam formulation.

The benefits of azelaic acid 15% foam outweigh the risks when used as recommended in the prescribing information, and this CDTL review concurs with the review team that this application should be approved. The conclusion that this application should be approved is shared by each review discipline, and there are no outstanding approvability issues beyond final agreement of draft labeling and terminology related to the post marketing commitment. As noted above, GMP inspections are pending an "Acceptable" determination from the Office of Compliance for the facilities inspections as of the date of this CDTL review.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

The review team, in consultation with Agency representatives from OSE, concluded that a REMS is neither required nor recommended for this product. Labeling is adequate to inform prescribers and patients of expected adverse events and risks.

- Recommendation for other Postmarketing Requirements and Commitments

The only post marketing requirement is for a 2-year dermal mouse carcinogenicity study with the azelaic acid pre-foam emulsion formulation.

The timeline below was proposed by the applicant and is acceptable to the Agency:

> Anticipated 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

- Recommended Comments to Applicant

There are no comments to be conveyed to the applicant beyond agreement of final labeling and verification of final agreement on the post marketing requirement. Labeling negotiations are ongoing with the applicant as of the date of this review, but there are only minor differences to be resolved as of the date of this CDTL review.

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/s/

DAVID L KETTL
06/18/2015