CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207071Orig1s000

SUMMARY REVIEW

Decisional Memorandum to the File

Date:	July 27, 2015
From:	Kendall A. Marcus, M.D. Director, Division of Dermatology and Dental Products
Subject:	Summary and Recommendations
NDA/BLA #:	207071 Bayer Health Care Pharmaceuticals, Inc.
Submission Date **PDUFA Goal**	September 20, 2014 July 30, 2015
Proprietary / Generic (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

1. Introduction/Background

Azelaic acid, the drug substance under consideration in this NDA, is an aliphatic dicarboxylic acid that naturally occurs in animals, humans and plants. It is endogenously formed from longer chain dicarboxylic acids, (b) (4) Azelaic acid was first approved for the treatment of mild-to-moderate rosacea in 1995 in the cream formulation Azelex Cream 20%. A gel formulation, Finacea Gel 15% was approved in 2002.

The proposed indication for Finacea Foam 15% is for the treatment of inflammatory papules and pustules of mild-to-moderate rosacea. This is identical to the indications for Azelex Cream 20% and Finacea Gel 15%. The precise pharmacological mechanisms of action for azelaic acid are not known but are proposed to include: inhibition of mitochondria and pigmented cell systems and inhibition action of the generation/release of reactive oxygen species in neutrophils.

Efficacy of the product was demonstrated in one adequate and well controlled Phase 3 clinical trial that evaluated 12-week treatment with Finacea (azelaic acid) Foam 15% as compared to placebo. A large Phase 2 trial was submitted as supportive of the Phase 3 trial. Safety was demonstrated through evaluation of the product in over 1000 clinical trial subjects.

2. CMC

The CMC review was conducted by Dr. Hamid Shafiei and the Quality Microbiology review by Dr. Jessica Cole. Please refer to their reviews for full details.

Finacea (azelaic acid) Foam, 15%, for topical administration is a new hydrophilic foam formulation containing 15% w/w (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.

Azelaic acid is a white, odorless crystalline solid. The drug substance is commercially produced by the (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 (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.

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, (b) (4), heavy metals, water content, residual solvents (b) (4), particle size, and polymorphism. The proposed API specification is satisfactory.

3. Nonclinical Pharmacology/Toxicology

Please refer to the review prepared by Jianyong Wang, PhD, the Pharmacology/Toxicology reviewer, for full details. The pharm/tox review team finds this NDA approvable. The NDA was considered to be a 505(b)(1) NDA from a Pharmacology/Toxicology perspective because the sponsor owns all the necessary nonclinical data for azelaic acid to support the Finacea (azelaic acid) Foam 15% application.

Azelaic acid was evaluated for systemic toxicity in rats and monkeys following oral gavage. No significant systemic toxicity was noted in the two studies. 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. 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 is presumed that Finacea (azelaic acid) Foam 15% formulation will be an ocular irritant as well.

The multiples of human exposure based on BSA comparison between NOAELs identified in pivotal toxicology studies and the maximum recommended human doses are considered adequate.

4. Clinical Pharmacology

Please refer to the review by Chinmay Shukla, Ph.D., the clinical pharmacology reviewer from the Office of Clinical Pharmacology/DCP III for full details. The clinical pharmacology review team considers this NDA approvable.

The applicant did not conduct any new dose finding trials. The dose and dosing regimen for Finacea (azelaic acid) Foam 15% was selected based on the dosing recommendation used in the currently approved Finacea (azelaic acid) Gel 15% formulation (NDA 021470). The applicant assessed relative bioavailability (BA) of azelaic acid and pimelic acid (metabolite) following twice daily repeated administration of Finacea (azelaic acid) Foam 15% versus Finacea (azelaic acid) Gel 15%, under maximal use conditions in a randomized crossover trial in 24 adult subjects with moderate papulopustular rosacea. Since azelaic acid is an endogenous substance and can also be absorbed from certain types of diets, each treatment period consisted of a two day baseline assessment of azelaic acid and pimelic acid systemic concentrations.

Baseline corrected relative BA assessment at steady state demonstrated that systemic exposure (Cmax and AUC0-12) of azelaic acid following topical application of Finacea (azelaic acid) Foam 15% was not higher than that observed following application of Finacea (azelaic acid) Gel 15%.

5. Microbiology

Azelaic acid has *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 is not known, as the etiology of rosacea has not been fully elucidated. No specific clinical microbiology information will be included in product labeling.

6. Clinical/Statistical

Please refer to the reviews completed by Gary Chiang, M.D., the clinical reviewer, and Kathleen Fritsch, Ph.D., the biostatistical reviewer for full details of the efficacy review. They consider this NDA approvable from an efficacy perspective.

Efficacy of Finacea (azelaic acid) Foam 15% was adequately demonstrated in one Phase 3 and one Phase 2 clinical trial. Finacea (azelaic acid) Foam 15% was superior to vehicle foam ($p<0.017$) on the co-primary efficacy endpoints of Investigator Global Assessment (IGA) treatment success (clear or minimal) at Week 12 and absolute change in inflammatory lesions at Week 12.

The efficacy results are summarized from Dr. Fritsch's biostatistics review in the following 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	

The Phase 2 trial analysis methods for the grouped change in erythema rating were not adequately pre-specified nor were the results statistically significant, (b) (4)

The reviewers 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.

7. Clinical/Safety

Please refer to the review completed by Gary Chiang, M.D., the clinical reviewer, for full details of the safety review. This NDA is considered approvable from a safety perspective.

The safety database contains six clinical trials in which a total of 746 subjects received at least one dose of Finacea (azelaic acid) Foam 15%. Additionally, postmarketing exposure of patients to cream and gel formulations of azelaic acid is extensive and dates back to 1995. In 2013, approximately (b) (4) units of azelaic acid formulations were sold worldwide.

In Finacea (azelaic acid) Foam 15% treated subjects the most common adverse reactions were pain, pruritus, and paresthesia at the administrative site. Four serious adverse events were reported and included congestive cardiac failure, hepatotoxicity, cellulitis and deep vein thrombosis. None were considered to be related to study drug.

Hypersensitivity is considered a known safety concern for Finacea (azelaic acid) Foam 15% based on the postmarketing 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 the formulation. (b) (4) .

8. Advisory Committee Meeting

No regulatory issues were identified during the review of this application that required input from an advisory committee.

9. 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.

10. 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 received an "Acceptable" determination from the Office of Process and Facilities.

11. Labeling

The foam formulation will have a separate label from the existing Finacea Gel product at the applicant's request. Review of the proposed label was based on evaluation of clinical trial data and DMEPA, DRISK, and OPDP reviews.

Because this product is not a new molecular entity, changes to the label consistent with the Pregnancy and Lactation Labeling Rule (PLLR) will be deferred to a later time. Proposed labeling will mirror that of the currently approved Finacea (azelaic acid) Gel 15%.

Product labeling appears adequate to communicate safety information to prescribers.

12. Decision/Action/Risk Benefit Assessment

Regulatory Action: Approval

I concur with the recommendations of the multi-disciplinary review team to approve NDA 207071 Finacea (azelaic acid) Foam 15% for the treatment of the inflammatory pustules of mild to moderate rosacea in adults.

Risk-benefit assessment: Efficacy of Finacea (azelaic acid) Foam 15% was established in two adequate and well-controlled clinical trials. Safety of the product is demonstrated through data from the clinical development program as well as extensive post-marketing experience with the gel and cream formulations.

Postmarketing Risk Evaluation and Management Strategies: Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product. A Risk Evaluation and Mitigation Strategy (REMS) is not required.

Postmarketing requirements (PMR): Because of the finding of papillomas in the short-term dermal carcinogenicity study in transgenic mice, the applicant will be required to conduct a 2-year dermal mouse carcinogenicity study with the azelaic acid pre-foam emulsion formulation.

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/s/

KENDALL A MARCUS
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