CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202428Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	May 10th, 2012
From	Susan J. Walker, M.D., F.A.A.D.
Subject	Division Director Summary Review
NDA	202428
Applicant Name	Stiefel Laboratories, Inc
Date of Submission	July 29th, 2011
PDUFA Goal Date	May 29th, 2012
Proprietary / Established (USAN) Name	Fabior ™/ Tazarotene
Dosage Forms / Strength	Foam/ 0.1%
Proposed Indication(s)	Acne Vulgaris
Action	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Cross Discipline Team Leader	Gordana Diglisic, M.D.
Medical Officer Review	Denise Cook, M.D.
Statistical Review	Kathy Fritsch, Ph. D.
Pharmacology Toxicology Review	Jiaqin Yao, PhD
CMC Review	Raymond Frankewich, Ph.D.
Clinical Pharmacology Review	Chinmay Shukla, Ph. D.
Labeling Reviews DMEPA SEALD DMPP OPDP	 Teresa McMillan, PharmD Jeanne Delasko Sharon Mills, BSN, RN, CCRP Sheetal Patel, PharmD and Lynn Panholzer, Phar

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
DMEPA=Division of Medication Error Prevention and Analysis
SEALD-Study Endpoints and Labeling Development
DMPP- Division of Medical Policy Programs
OPDP- Office of Prescription Drug Promotion

Signatory Authority Review

1. Introduction

This application provides for the approval of a new topical dosage form (foam) for an active moiety currently marketed as a gel and a cream. The intended use is the treatment of acne vulgaris. The applicant has provided the necessary safety and efficacy information to support approval, and there are no outstanding issues. I concur with the recommendation of the review team for an APPROVAL action.

2. Background

The active ingredient, tazarotene, is a member of the acetylenic class of retinoids and is rapidly hydrolyzed by esterases into its active form of tazarotenic acid. Topical tazarotene formulations are approved as a gel (1997), and cream (2000) for treatment of acne, as a gel and cream for treatment of psoriasis, and as a cream for treatment of fine wrinkling. This application presented no unique issues or concerns beyond those usually attributed to the active moiety.

3. CMC

The chemistry reviewer, Dr. Frankewich, recommends that the application has provided sufficient information to assure the identity, strength, purity and quality of the drug product. The Office of Compliance issued and overall "Acceptable" recommendation for the facilities involved in this application on May 3rd, 2012. I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 18 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Shukla has extensively reviewed the clinical pharmacology information and his conclusions are described below. I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

Following topical application, tazarotene undergoes esterase hydrolysis to form its active metabolite, tazarotenic acid. Tazarotenic acid was highly bound to plasma proteins (greater than 99%). Tazarotene and tazarotenic acid were metabolized to sulfoxides, sulfones and other polar metabolites which were eliminated through urinary and fecal pathways.

Systemic exposure following topical application of Tazarotene Foam 0.1% was evaluated in one trial. Patients aged 15 years and older with moderate-to-severe acne applied approximately 3.7 grams of Tazarotene Foam 0.1% (N=13) to approximately 15% body surface area (face, upper chest, upper back, and shoulders) once daily for 22 days. On day 22, the mean (±SD) tazarotenic acid C_{max} was 0.43 (±0.19) ng/mL, the AUC_{0-24h} was 6.98 (±3.56) ng·hr/mL and the half-life was 21.7 (±15.7) hours. The median T_{max} was 6 hours (range 4.4 to 12 hours). The AUC_{0-24hr} for tazarotenic acid was approximately 50 fold higher compared with the parent compound tazarotene. The mean (±SD) half-life of tazarotene was 8.1 (±3.7) hours.

Accumulation was observed upon repeated once-daily dosing as the tazarotenic acid predose concentrations were measurable in the majority of subjects. Steady state was attained within 22 days of daily application. Once-daily dosing resulted in little to no accumulation of tazarotene as predose concentrations were mostly below the quantitation limit throughout the study.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

I have reviewed the primary reviews from the clinical reviewer Dr. Cook, the biostatistical review Dr Fritsch, and the summary review from the Cross Discipline Team Leader, Dr Diglisic. Their findings are summarized below and I concur with their conclusions. The applicant submitted data from two pivotal trials, W0260-301 and W0260-302 to establish the effectiveness of their product applied once daily for 12 weeks in the treatment acne vulgaris. These trials were multi-center (39 - Canada and the U.S.A.), prospective, randomized, double-blind, parallel group studies with two arms, active and vehicle. The population enrolled was subjects 12 to 45 years of age with acne vulgaris, a score of moderate (3) or severe (4) on the Investigator's Static Global Assessment (ISGA) scale, with 25 to 50 facial inflammatory lesions, and 30 to 125 facial non-inflammatory lesions at baseline.

A total of 1485 subjects were enrolled in the Phase 3 trials. The mean age was similar between tazarotene foam and its vehicle, 18.7 years and 18.9 years, respectively. More than half of the subjects (58%) were age 12 to 17 years in both arms. Subjects were approximately evenly

distributed in terms of sex, 49% male and 51% female. The majority of the subjects were white (76%). Eighty one percent of subjects in the tazarotene foam arm and 80% of subjects in the vehicle foam arm were categorized as moderate disease, while 19% and 20%, respectively had severe disease. The mean non--inflammatory lesion count was 47.7 for the tazarotene arm and 48.0 in the vehicle arm while the mean inflammatory lesion count was 31.7 for the tazarotene arm and 32.2 for the vehicle arm.

The primary efficacy endpoints were the absolute change in lesions (inflammatory, non-inflammatory, and total), and success on the investigator's global assessment score. Successful outcome included demonstration of efficacy in both the lesion counts and the investigator's global assessment.

Reductions in Lesion Counts and Improvements in Investigator's Global Assessment at Week 12

	Study 1		**Study** 2	
	Tazarotene Foam N=371	**Vehicle Foam** N=372	Tazarotene Foam N=373	Vehicle Foam N=369
Inflammatory Lesions				
Mean absolute reduction from Baseline	18.0	14.0	18.0	15.0
Mean percent reduction from Baseline	58%	45%	55%	45%
Non-inflammatory Lesions				
Mean absolute reduction from Baseline	28.0	17.0	26.0	18.0
Mean percent reduction from Baseline	55%	33%	57%	41%
Total Lesions				
Mean absolute reduction from Baseline	46.0	31.0	43.0	33.0
Mean percent reduction from Baseline	56%	39%	56%	43%
Investigator's Global Assessment (IGA), n (%)				
Minimum 2-grade improvement *and* IGA of 0 or 1	107 (29%)	60 (16%)	103 (28%)	49 (13%)

8. Safety

During the development of Fabior™ Foam, 0.1%, 1906 subjects were evaluated, 1149 of whom were exposed to Fabior™ Foam. Of these, 390 subjects were enrolled in dermal safety studies (W0260-101, W0260-102, W0260-102, and W0260-102), for which the dose was not reflective of anticipated labeled use. Thirty subjects were enrolled in the bioavailability study (W0260-105), and 14 were exposed to tazarotene foam. Of the1485 subjects enrolled in the Phase 3 trials, 744 subjects were included in the tazarotene foam Intent-To-Treat (ITT) analysis set.

There were no deaths and no serious adverse events (SAEs) attributable to Fabior™ Foam, 0.1% during the development program.

The incidence of study product-related AEs was greater in the tazarotene foam group (22%) than in the vehicle foam group (3%). The most frequent adverse reactions were in the tazarotene foam group and included application site irritation (14%), application site dryness (7%), application site erythema (6%), and application site exfoliation (6%). Most adverse reactions were mild to moderate in severity and typically resolved in 2 -6 days. Nine (9/744; 1.2%) subjects in the tazarotene foam group and 3 (3/741; 0.4%) subjects in the vehicle group had either a photosensitivity reaction (burning sensation at the application site due to sun exposure) or frank sunburn. All of the reactions were mild or moderate and resolved. Collection of adverse events and assessment of local tolerance did not reveal unexpected safety signals and was consistent with events associated with other tazarotene products.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

The applicant conducted Phase 3 trials in subjects 12 years of age and older, the relevant population for acne vulgaris and the population for whom the applicant seeks labeling.

The applicant requested a partial pediatric waiver for children 0 to11years of age based on the rationale that "necessary studies are impossible or highly impracticable" and "the drug does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and is not likely to be used by substantial number of pediatric patients in that age group".

The application was presented to the Pediatric Review Committee (PeRC) on February 15, 2012. The committee concurred with the Division's recommendation to grant a waiver for pediatric patients aged 0-11 years.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- The proprietary name Fabior™ has been approved.

- Physician and patient labeling has been discussed with the sponsor and we have agreement on the contents.
- Carton and immediate container labeling discussions have been concluded with the sponsor and we agree with the contents.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – This product will be APPROVED

- Risk Benefit Assessment – I concur with the review team assessment that the benefits of this product outweigh the risks. This moiety is currently approved in other dosage forms, and this product has demonstrated systemic bioavailability to be less than that of a currently approved topical product.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies – None

- Recommendation for other Postmarketing Requirements and Commitments - None

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/s/

SUSAN J WALKER
05/11/2012