CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202428Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 31, 2012
From	Gordana Diglisic, MD
Subject	Cross-Discipline Team Leader Review
NDA	202428
Applicant	Stiefel Laboratories, Inc.
Date of Submission	Letter date: July 29, 2011 CDER stamp date: July 29, 2011
PDUFA Goal Date	May 29, 2011
Proprietary Name / Established (USAN) names	TRADENAME (tazarotene)
Dosage forms / Strength	Foam, 0.1%
Proposed Indication(s)	Topical treatment of (b) (4) acne vulgaris in patients 12 years or older
Recommended:	*Approval*

1. Introduction

TRADENAME (tazarotene) Foam, 0.1%, is a topical drug product for which the applicant seeks approval under Section 505 (b) (1) of the Federal Food Drug and Cosmetic Act for the treatment of (b) (4) acne vulgaris in patients 12 years of age and older. This application is for a new dosage form of tazarotene.

The active ingredient, tazarotene, is a member of the acetylenic class of retinoids which is currently marketed in the United States in various topical dosage forms (gel, cream, both at 0.05% and 0.1%). The cream formulation is approved for the topical treatment of patients with plaque psoriasis at both strengths and the 0.1% cream is approved for (b) (4) acne vulgaris [TAZORAC® (tazarotene) Cream 0.05% and 0.1%; NDA 21184]. The cream formulation is also approved as an adjunctive agent for use in the mitigation (palliation) of facial fine wrinkling, facial mottled hyper- and hypopigmentation, and benign facial lentigines in patients who use comprehensive skin care and sunlight avoidance programs [AVAGE™ (tazarotene) Cream, 0.1%]. TAZORAC® (tazarotene) Gel 0.05% and 0.1% is approved for the topical treatment of patients with stable plaque psoriasis while the 0.1% gel formulation is approved for the topical treatment of patients with facial acne vulgaris of mild to moderate severity (NDA 20600).
Because tazarotene is a probable human teratogen, all tazarotene formulations drug products are contraindicated in female patients of childbearing potential who are or may became pregnant (Pregnancy Category X). The labeling recommends that a negative result for pregnancy test be obtained within 2 weeks prior to therapy, which should begin during a normal menstrual period. It also advises that females of childbearing potential should be

warned of the potential risk and need to use an effective method of contraception to avoid pregnancy.

The applicant has obtained a full right of reference from Allergen, Inc to NDA 20600 (TAZORAC® Gel), NDA 21184 (TAZORAC® Cream) and AVAGE™ (tazarotene) Cream to support this NDA.

This memo will summarize the findings of the multi-disciplinary review team and provide the rationale for my recommended action.

2. Background

The applicant opened the IND for tazarotene foam, 0.1% on August 28, 2009 with the protocols for Phase 3 trials W0260-301 and W0260-302, which were reviewed by the Agency. The protocols were not reviewed under a Special Protocol Assessment.

During their development program, the applicant interacted with the Agency at only one milestone meeting – PreNDA. This meeting was held on June 15, 2011.
At this meeting, the applicant was reminded of the advice letter sent on December 28, 2010 and advised to consider the content of this letter in preparing the NDA submission. This Agency letter gave the applicant final advice on the primary endpoint analysis as follows: *"The two analyses on the ISGA are likely to have substantial overlap. Although listed separately in the Agency's previous comments, to simplify the endpoint structure, the concept of two grade reduction as well as achieving a score of 0 or 1 at the end of the study could be combined into a single ISGA endpoint with success defined as 0 or 1 with two grades reduction. It should also be noted that because the inclusion criteria specify that the baseline ISGA will be 3 or higher, that in this case the combined endpoint will be the same as achieving 0 or 1."*

3. CMC

TRADENAME (tazarotene) Foam, 0.1% contains drug substance tazarotene (a member of the acetylenic class of retinoids) in an aerosol foam dosage form. Chemically, tazarotene is ethyl 6-[(4,4-dimethylthiochroman-6-yl) ethynyl]nicotinate (Molecular Formula: $C_{21}H_{21}NO_2S$; Molecular Weight: 351.46). It is pale yellow to yellow substance.
For most sections of the CMC Assessment for drug substance, reference is made to NDA 20600 for TAZORAC® (tazarotene) Gel, 0.05% ; 0.1%, NDA 21184 for TAZORAC® (tazarotene) Cream, 0.05% ; 0.1%, and for AVAGE™ (tazarotene) Cream, 0.1%. A Letter of Authorization (LOA) dated June 24, 2011 from Allergan, holder of NDA 20600 and NDA 21184 is provided in this NDA.

The bulk drug product is an (b) (4) which is packaged in an aluminum container (b) (4) fitted with a valve, actuator, and a cover cap (cap does not contact the drug product). The can is pressurized with a

hydrocarbon propellant which is a mixture of propane, n-butane, and isobutane. The commercial drug product will be supplied in 10 g, 50 g and 100 g containers (size refers to the amount of drug product inside the can). The 10 g container is a physician sample package; the 50 and 100 g container are market packages.

The composition is described in the following table:

Table 1: Composition of Tazarotene Foam

Component [a]	Quantity [%w/w] [b]	Function	Reference to Standard
Tazarotene	0.10	API	In-house
Purified Water	(b) (4)		USP
Light Mineral Oil			NF
Diisopropyl Adipate			JP
Macrogol Cetostearyl Ether 12			Ph Eur
Potassium Sorbate			NF
Sorbic Acid			NF
Potassium Citrate, Monohydrate			USP
Butylated Hydroxytoluene			NF
Citric Acid, Anhydrous			USP

Abbreviations: API = Active Pharmaceutical Ingredient; USP/NF = United States Pharmacopoeia/National Formulary, Current Edition; PhEur = European Pharmacopoeia; JP = Japanese Pharmacopoeia

(b) (4)

Drug product specification includes tests for Appearance, Identification, Assay, and Impurities of the drug substance. Also included are compendial microbial tests (USP <61> and <62>), and compendial tests for Minimum Fill (<755>), Dispensing Rate, Delivered Amount, and Leakage Rate (all <601>). Tests for Dipensing Rate Delivered Amount, microbial contamination, along with a test for Weight Loss are performed as part of the stability specification.

Stability data through 18 month storage is provided for samples of two commercial batches of drug product, and data through 12 months storage is provided for samples of a third batch. Data support an expiration dating period of 18 months for the 10 g physician sample package, and 24 months for the 50 g and 100 g commercial packages.

The CMC reviewer concluded that the applicant has submitted sufficient information to assure the identity, strength, purity, and quality of the drug product (CMC review by Raymond P. Frankewich, Ph.D; Office of New Drug Quality Assessment; Division of New Drug Quality Assessment II, Branch IV; dated 03/16/12)

Recommendation from the Office of Compliance regarding facilities inspections for the drug substance and drug product is pending.

4. Nonclinical Pharmacology/Toxicology

In addition to the toxicology studies submitted within NDA 20600 (TAZORAC® Gel) and NDA 21184 (TAZORAC® Cream) that the applicant has obtained a full right of reference to, a 28-day dermal toxicity in rats, a 28-day dermal toxicity study in minipigs, and a 90-day dermal toxicity in rats have been conducted with tazarotene foam.

Topical treatment of tazarotene foam (up to 0.2%) in minipigs for 28 days caused only local dermal irritation associated with histopathological findings in the skin at the treatment site. The extent of dermal irritation elicited by topical treatment with tazarotene foam was less severe than the dermal irritation caused by topical treatment with tazarotene gel.
Rats were more sensitive to tazarotene foam than minipigs. In addition to local irritation seen at the treatment site, systemic toxicities including decreased body weight gains, alterations in hematology and clinical chemistry parameters, and organ weight changes were also seen in rats following topical treatment with tazarotene foam.

The exposure levels of tazarotenic acid, the major metabolite of tazarotene, following topical treatment with tazarotene foam in rats or minipigs were comparable to or less than those following topical treatment with tazarotene gel.
Tazarotene foam 0.1% was mildly irritating to the skin of the rabbit with slight or well-defined erythema seen at the treatment sites of skin. The study using LLNA indicated that tazarotene foam 0.1% would not be considered a sensitizer.

Tazarotene is not genotoxic and not carcinogenic in rats and mice.
Tazarotene elicits teratogenic and developmental effects associated with retinoids after topical or systemic administration in rats and rabbits.

The reader is referred to the comprehensive review by Dr. Jiaqin Yao for a full discussion of the nonclinical pharmacology/toxicology data (dated 02/29/12). Drs. Yao and Hill did not recommend further nonclinical studies or Phase 4 commitments/requirements, and recommended an *Approval* action from a pharmacological/toxicological perspective.

5. Clinical Pharmacology/Biopharmaceutics

The applicant conducted one pharmacokinetic (PK) trial in subjects with acne vulgaris (W0260-105). The objective of this trial was to evaluate the plasma exposure of tazarotene and tazarotenic acid (active metabolite) following once daily administration of tazarotene foam, 0.1% in comparison with TAZORAC® (tazarotene) Gel, 0.1% in subjects 12 years and older with moderate to severe acne vulgaris (ISGA of 3 or greater) under maximal use conditions.

Thirty subjects (the youngest subject was 15 years of age; 11 male and 19 female) were enrolled and 29 subjects (13 tazarotene foam arm and 16 TAZORAC® Gel arm) completed the trial. One subject in the tazarotene foam arm withdrew consent and did not complete the trial. Approximately 3.7 grams of the study product was applied by the clinical staff once daily for 22 days to the face, upper chest, upper back and shoulders [approximately 15% body surface area (BSA)]. The bioavailability of tazarotene and tazarotenic acid on Day 22 following once daily administration of tazarotene foam was lower than once daily administration of TAZORAC® Gel. The geometric mean values of $AUC_{0\text{-}tau}$ and C_{max} of tazarotenic acid following the administration of the foam formulation were approximately 46% and 54% respectively, lower than those obtained following TAZORAC® Gel administration; while the geometric mean values of $AUC_{0\text{-}tau}$ and C_{max} of tazarotene following the administration of the foam formulation were approximately 28% and 44% respectively, lower than those obtained following gel administration. Therefore, based on the results of this trial, the applicant has established a biobridge between tazarotene foam and tazarotene gel, in order to rely on the Agency's finding of systemic and long-term safety for tazarotene gel.

The applicant has not conducted any formal drug-drug interaction studies.

Clinical pharmacology Team Labeling Recommendations:

The **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates recommended deletion:

7 Drug Interactions

No formal drug-drug interaction studies were conducted with TRADENAME Foam.

Concomitant dermatologic medications and cosmetics that have a strong drying effect should be **avoided** (b) (4) It is recommended to postpone treatment until the effects of these products subside before use of TRADENAME Foam is started.

(b) (4)

Concomitant use with oxidizing agents, such as benzoyl peroxide, may **cause degradation of tazarotene and may** reduce the clinical efficacy of tazarotene. If combination therapy is required, they should be applied at different times of the day (e.g. one in the morning and the other in the evening).

The impact of tazarotene on the pharmacokinetics of progestin-only oral contraceptives (i.e., minipills) has not been evaluated.

In a study of 27 healthy female subjects between the ages of 20 to 55 years receiving a combination oral contraceptive tablet containing 1 mg norethindrone and 35 mcg ethynyl estradiol, concomitant use of tazarotene did not affect the pharmacokinetics of norethindrone and ethynyl estradiol over a complete cycle.

12.3 Pharmacokinetics

Following topical application, tazarotene undergoes esterase hydrolysis to form its active metabolite, tazarotenic acid (b) (4) 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 TRADENAME Foam 0.1% was evaluated in one (b) (4) **trial**. Patients **aged 15 years and older** with moderate-to-severe acne applied approximately (b) (4) **3.7 grams** of TRADENAME Foam 0.1% (N=13) to **approximately** 15% body surface area once daily for 22 days. On day 22, the mean (±SD) tazarotenic acid C_{max} was 0.43 (±0.19) ng/mL, (b) (4) the AUC_{0-24h} was 6.98 (±3.56) ng·hr/mL; **and** the half-life was (b) (4) **The median T_{max} was 6 hours (range (b) (4) to 12 hours).** (b) (4) **The** AUC_{0-24h} for tazarotenic acid was approximately (b) (4) **50** (b) (4)-fold higher compared with **the parent compound** tazarotene, (b) (4) . **The mean (±SD) half-life of tazarotene was** (b) (4) **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 (b) (4) attained within 22 days of daily application. (b) (4)

Once-daily dosing resulted in little to no accumulation of tazarotene as predose concentrations were **mostly** below the quantitation limit throughout the study.

The reader is referred to the comprehensive review by Chinmay Shukla, Ph.D. for a full discussion of the clinical pharmacology data (dated 03/12/12).

The clinical pharmacology reviewer, Dr. Shukla, recommended *Approval* of this application.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

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 had moderate (ISGA grade 3) disease, while 19% and 20%, respectively had severe (ISGA grade 4) disease. The mean noninflammatory 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 ISGA success (two definition of success were defined: at least two grades reduction from baseline and achieving clear or almost clear). The trials were designed so that a successful outcome was defined as achieving statistical significance for two out of three lesion types and both definitions of ISGA success.

The efficacy results from the pivotal trials are presented in the Table 2:

Table 2 – Primary Efficacy Endpoints at Week 12 (ITT)

Endpoint	W0260-301			W0260-302		
	Tazarotene N=371	Vehicle N=372	p-value	Tazarotene N=373	Vehicle N=369	p-value
Absolute change[1]*:*						
Inflammatory	-17.6	-13.3	<0.001	-17.6	-14.3	<0.001
Non-inflammatory	-28.1	-16.2	<0.001	-25.9	-17.0	<0.001
Total	-45.8	-29.5	<0.001	-43.5	-31.3	<0.001
ISGA:						
2-Grade Improvement	132 (36%)	89 (24%)	<0.001	120 (32%)	67 (18%)	<0.001
Clear or Almost Clear	107 (29%)	60 (16%)	<0.001	103 (28%)	49 (13%)	<0.001

[1]Least squares means
Source: Statistical Review by Dr. Kathleen Fritsch; p 3; dated 03/14/12

The treatment effects were generally consistent across gender, race, age and geographic region subgroups.

The protocols included a number of secondary endpoints at various timepoints. These were

1. The percent change in lesion counts (total, inflammatory, and non-inflammatory) from baseline to Weeks 2, 4, 8, and 12.
2. Time to 50% reduction in total lesion counts.
3. The absolute change in lesion counts (total, inflammatory, and non-inflammatory) from baseline to Weeks 2, 4, and 8.
4. The proportion of subjects who have a minimum 2-grade improvement in ISGA score from baseline to Weeks 2, 4, and 8.
5. The proportion of subjects who have an ISGA score of 0 or 1 at Weeks 2, 4, and 8.
6. The proportion of subjects who have an SGA score of 0 or 1 at Weeks 2, 4, 8, and 12.

The mean percent reduction in inflammatory lesions was approximately 55% for tazarotene foam versus 44% for vehicle in both trials, while the mean percent reduction in non-inflammatory lesions was approximately 56% versus 34% in trial W0260-301 and 56% versus 41% in trial W0260-302. The median time to 50% reduction in total lesions was 8 weeks for tazarotene foam and 12 weeks for vehicle. Results for the percent change in lesion counts at Week 12 and the time to 50% reduction in total lesion counts are presented in Table 3:

Table 3 – Secondary Efficacy Endpoints (Percent Change in Lesion Counts at Week 12 and Time to 50% Reduction in Total Lesion Counts)

Endpoint	W0260-301		W0260-302	
	Tazarotene N=371	Vehicle N=372	Tazarotene N=373	Vehicle N=369
Percent change: Means				
Inflammatory	-57.5%	-45.2%	-54.5%	- 45.3%
Non-inflammatory	-55.1%	-33.2%	-56.7%	-41.2%
Total	-56.3%	-39.0%	-56.0%	-42.6%
Least Squares Means				
Inflammatory	-56.1%	-43.6%	-53.7%	-44.3%
Non-inflammatory	-56.2%	-33.2%	-56.1%	-40.7%
Total	-56.4%	-37.6%	-55.2%	-42.0%
Median days to 50% reduction	57	85	57	85

Source: Statistical Review by Dr. Kathleen Fritsch; p18; dated 03/14/12; Addendum p2; dated 3/27/12

As per Dr. Fritsch: "Although the applicant was advised that Protocols 301 and 302 should include multiplicity adjustments for the set of secondary endpoints (see Advice Letter for IND 105564 dated 12/9/2009), the applicant did not include any multiplicity adjustments for the secondary endpoints in the protocols or analyses. Typically in labeling, percent reduction in

lesions counts has been included as a supportive analysis for the absolute reduction in lesions. Without a protocol that included adjustments for secondary endpoints, it would not be appropriate to include other secondary endpoints in labeling, because the Type I error rate was not controlled."

In summary, the applicant has established the efficacy of their product in the treatment of acne vulgaris. It should be noted that the proposed indication is for "the topical treatment of (b) (4) acne vulgaris". However, acne vulgaris is the same disease whether it manifests itself solely on the face or whether it involves the upper back, shoulders, and upper chest. Therefore, based on the above data and the data from a comparative PK trial (W0260-105) between tazarotene gel and tazarotene foam under maximal use conditions in subjects with acne vulgaris (see Section 5), tazarotene foam should be approved for the treatment of acne vulgaris (without regard to the anatomical surface that it may involve).

The reader is referred to the reviews of Drs. Denise Cook (dated 03/30/12) and Kathleen Fritsch (dated 03/14/12 and 03/27/12) for a more complete discussion of the efficacy results.

8. Safety

During the development of TRADENAME Foam, 0.1%, 1906 subjects were evaluated, 1149 of whom were exposed to TRADENAME 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 TRADNAME Foam, 0.1% during the development program.

Overall, 2.6% (20/744) of subjects in the tazarotene foam group and < 1% (1/741) in the vehicle group discontinued from the pivotal trials due to the adverse reactions. The majority of adverse reactions were moderate in severity, however, 9 subjects in the tazarotene foam group discontinued from the trials because of a severe adverse reaction; all related to application site reactions.

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.

Urine pregnancy tests were performed for female subjects of childbearing potential in all the tazarotene foam trials. There were 5 pregnancies reported during the Phase 3 trials. All subjects were discontinued when their pregnancies were reported. One subject had been exposed to tazarotene foam for 25 days. The subject delivered healthy infant.
Tazarotene is a probable human teratogen and all tazarotene formulations drug products are contraindicated in female patients of childbearing potential who are or may became pregnant (labeled as Pregnancy Category X). The labeling recommends that a negative result for pregnancy test be obtained within 2 weeks prior to therapy, which should begin during a normal menstrual period. It also advises that females of childbearing potential should be warned of the potential risk and need to use an effective method of contraception to avoid pregnancy. The labeling for tazarotene foam should have the same information and recommendation.

The 120-day safety update was reviewed, and did not identify new safety signals.

The reader is referred to the clinical review by Dr. Denise Cook for discussion of the safety database.
No postmarketing commitments or requirements to address safety concerns are warranted.

9. Advisory Committee Meeting

Not applicable, as no Advisory Committee meeting was held.

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

N/A

12. Labeling

The proprietary name has not been established. The product is referred to as TRADENAME (tazarotene) Foam, 0.1%, in this review.

The applicant submitted proposed labeling in the format that complies with the Physicians' Labeling Rule. Professional and patient labeling were reviewed, and negotiations regarding their content are ongoing at the time of close of this review.
Significant changes incorporated into revised draft labeling, following labeling review, include (the applicant's language is provided and changes are delineated by strikeout and underline for additions):

- HIGHLIGHTS OF PRESCRIBING INFORMATION:
  Warnings and Precautions
  - Fetal Risk: TRADENAME contains tazarotene, which is a teratogenic substance. TREDENAME is contraindicated in pregnancy. Females of childbearing potential should have a negative pregnancy test within 2 weeks prior to initiating treatment and use an effective method of contraception during treatment. (5.1)

- FULL PRESCRIBING INFORNMATION
  Adverse Reactions
  6.1 Clinical Trials
  - Most adverse reactions were mild to moderate in severity. Overall, 2.6% (20/744) of patients discontinued TRADENAME Foam because of local skin reactions.
  - The following was added to Table 1: Incidence of Adverse Reactions in ≥ 1 % of Patients with TRADENAME Foam:
    - Application site photosensitivity (including sunburn): 8 (1%) for TRADENAME foam and 3 (<1%) for vehicle foam.

  - Local skin reactions, dryness, erythema, and peeling actively assessed by the investigator and burning/stinging and itching reported by the patient were evaluated at baseline and during treatment, ~~and end of treatment~~ (b) (4) (b) (4) During the 12 weeks of treatment, each local skin reaction peaked at week 2 and gradually reduced thereafter with the continued use of (b) (4) TRADENAME Foam.

  7 **Drug Interactions and 12.3 Pharmacokinetics Section**

(Clinical Pharmacology recommendation regarding labeling: see Section 5 of this review)

14 Clinical Studies

Absolute and percent reductions in lesion counts and the IGA scale after 12 weeks of treatment in these two studies are shown in Table 3. [redacted] Each study needed to have a statistically significant reduction in two out of three lesion counts at Week 12.

The applicant's table was replaced with the following table:

Table 3: Reductions in Lesion Counts and Improvements in Investigator's Global Assessment at Week 12

	Study 1		Study 2	
	[redacted] TRADENAME Foam N=371	Vehicle Foam N=372	[redacted] TRADENAME Foam N=373	Vehicle Foam N=369
Inflammatory Lesions				
Mean absolute reduction from Baseline	18.0	14.1	17.8	14.7
Mean percent reduction from Baseline	57.5%	45.2%	54.5%	45.3%
Non-inflammatory Lesions				
Mean absolute reduction from Baseline	27.9	16.7	25.6	18.2
Mean percent reduction from Baseline	55.1%	34.3%	56.7%	41.2%
Total Lesions				
Mean absolute reduction from Baseline	45.8	30.8	43.3	32.9
Mean percent reduction from Baseline	56.3%	39.0%	56.0%	42.6%
Investigator's Global Assessment (IGA), n (%)				
Minimum 2-grade improvement *and* IGA of 0 or 1	107 (28.9%)	60 (16.1%)	103 (27.6%)	49 (13.3%)

17 Patient Counseling Information

The following statements were recommended to be added to this section:

Inform the patient of the following:

- Fetal risk associated with TRADENAME for females of childbearing potential. Advise patients to use an effective method of contraception during treatment to avoid pregnancy. Advise the patient to stop medication if she becomes pregnant and call her doctor.
- If undue irritation (redness, peeling, or discomfort) occurs, reduce frequency of application or temporarily interrupt treatment. Treatment may be resumed once irritation subsides.
- Avoid contact with the eyes.
- Keep out of the reach of children.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: *Approval*

- I concur with the recommendations of the multi-disciplinary review team for approval of NDA 202428, TRADENAME (tazarotene) Foam, 0.1% pending agreement of the applicant with the recommended labeling revisions and recommendation from the Office of Compliance regarding facilities inspections for the drug substance and drug product.

Risk Benefit Assessment

- The risk-benefit ratio supports approval of this product for the treatment of acne vulgaris

Recommendation for Postmarketing Risk Evaluation and Management Strategies

- Postmarketing risk management beyond professional labeling, prescription status, and routine pharmacovigilance is not needed.

Recommendation for other Postmarketing Requirements and Commitments

- None

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

/s/

GORDANA DIGLISIC
04/11/2012