

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202428Orig1s000**

**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/BLA REVIEW AND EVALUATION**

Application number: 202428  
Supporting document/s: 1, 6, and 11  
Applicant's letter date: 7/29/2011, 11/23/2011, and 2/21/2012  
CDER stamp date: 7/29/2011, 11/23/2011, and 2/21/2012  
Product: TRADENAME (Tazarotene) Foam, 0.1%  
Indication: Acne vulgaris  
Applicant: Stiefel, a GSK company, Research Triangle  
Park, NC  
Review Division: Dermatology and Dental Products  
Reviewer: Jiaqin Yao, PhD  
Supervisor/Team Leader: Barbara Hill, PhD  
Division Director: Susan Walker, MD  
Project Manager: Cristina Petruccelli Attinello

*Template Version: September 1, 2010*

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 202428 are owned by Stiefel or are data for which Stiefel has obtained a written right of reference.

Any information or data necessary for approval of 202428 that Stiefel does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 202428.

## TABLE OF CONTENTS

<b>1</b>	<b>EXECUTIVE SUMMARY .....</b>	<b>3</b>
1.1	INTRODUCTION .....	3
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS .....	3
1.3	RECOMMENDATIONS .....	3
<b>4</b>	<b>CONTRAINDICATIONS .....</b>	<b>6</b>
<b>2</b>	<b>DRUG INFORMATION .....</b>	<b>8</b>
2.1	DRUG .....	8
2.2	RELEVANT INDs, NDAs, BLAs AND DMFs .....	9
2.3	DRUG FORMULATION .....	9
2.4	COMMENTS ON NOVEL EXCIPIENTS .....	10
2.5	COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN .....	10
2.6	PROPOSED CLINICAL POPULATION AND DOSING REGIMEN .....	10
2.7	REGULATORY BACKGROUND .....	10
<b>3</b>	<b>STUDIES SUBMITTED .....</b>	<b>10</b>
3.1	STUDIES REVIEWED .....	10
3.2	STUDIES NOT REVIEWED .....	11
3.3	PREVIOUS REVIEWS REFERENCED .....	11
<b>4</b>	<b>PHARMACOLOGY .....</b>	<b>11</b>
<b>5</b>	<b>PHARMACOKINETICS/ADME/TOXICOKINETICS .....</b>	<b>11</b>
<b>6</b>	<b>GENERAL TOXICOLOGY .....</b>	<b>12</b>
6.1	SINGLE-DOSE TOXICITY .....	12
6.2	REPEAT-DOSE TOXICITY .....	12
<b>7</b>	<b>GENETIC TOXICOLOGY .....</b>	<b>29</b>
<b>8</b>	<b>CARCINOGENICITY .....</b>	<b>29</b>
<b>9</b>	<b>REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY .....</b>	<b>29</b>
<b>10</b>	<b>SPECIAL TOXICOLOGY STUDIES .....</b>	<b>31</b>
<b>11</b>	<b>INTEGRATED SUMMARY AND SAFETY EVALUATION .....</b>	<b>33</b>
<b>12</b>	<b>APPENDIX/ATTACHMENTS .....</b>	<b>33</b>

# 1 Executive Summary

## 1.1 Introduction

Tazarotene Gel was approved for topical treatment of psoriasis (0.05% and 0.1%) and acne vulgaris (0.1%) under NDA 20600 in 1996. Tazarotene Cream (0.1%) was also approved for psoriasis and acne vulgaris under NDA 21184 in 2001. The sponsor has obtained the right to refer to the information in NDAs 20600 and 21184 from Allergan to support this NDA with a new dosage form (Foam, 0.1%) containing the same active ingredient for acne vulgaris.

## 1.2 Brief Discussion of Nonclinical Findings

Topical treatment with 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. 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 is not a genotoxic or carcinogenic compound. However, tazarotene is a teratogen in rats and rabbits.

## 1.3 Recommendations

### 1.3.1 Approvability

This NDA is approvable from a Pharmacology/Toxicology perspective.

### 1.3.2 Additional Non Clinical Recommendations

None.

### 1.3.3 Labeling

The following wording is recommended for the nonclinical sections of the label. The reader is referred to the Appendix for a detailed discussion of the animal multiples of human exposure calculations used in this label.

## HIGHLIGHTS OF PRESCRIBING INFORMATION

### INDICATIONS AND USAGE

TRADENAME Foam is a retinoid indicated for the topical treatment of (b) (4) acne vulgaris in patients 12 years of age or older.

*Reviewer's comment:* The designation of the pharmacologic class for tazarotene is retinoid.

#### 4 **Contraindications**

TRADENAME Foam is contraindicated in (b) (4) pregnant. (b) (4) may cause fetal harm when administered to a pregnant woman. Tazarotene elicits teratogenic and developmental effects associated with retinoids after topical or systemic administration in rats and rabbits [see *Use in Specific Populations* (8.1)].

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued and the patient apprised of the potential hazard to the fetus [see *Warnings and Precautions* (5.5) and *Use in Specific Populations* (8.1)].

#### 8 **USE IN SPECIFIC POPULATIONS**

##### 8.1 **Pregnancy**

Pregnancy Category X:

There are no adequate and well-controlled studies with TRADENAME Foam in pregnant women. TRADENAME Foam is contraindicated in females who are or may become pregnant [see *Contraindications* (4)]. Females of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when TRADENAME Foam is used. The possibility that a female of child-bearing potential is pregnant at the time of institution of therapy should be considered. A negative serum or urine result for pregnancy test having a sensitivity down to at least 25 mIU/mL for hCG should be obtained within 2 weeks prior to TRADENAME Foam therapy, which should begin during a normal menstrual period, for females of childbearing potential.

In rats, tazarotene 0.05% gel administered topically during gestation days 6 through 17 at 0.25 mg/kg/day resulted in reduced fetal body weights and reduced skeletal ossification. Rabbits dosed topically with 0.25 mg/kg/day tazarotene gel during gestation days 6 through 18 were noted with single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies.

Systemic exposure (AUC) to tazarotenic acid at topical doses of 0.25 mg/kg/day tazarotene in a gel formulation in rats and rabbits were 15 and 166 times, respectively, the systemic exposure (AUC) in acne patients treated with 2 mg/cm<sup>2</sup> of tazarotene foam 0.1% over 15% body surface area.

As with other retinoids, when tazarotene was given orally to experimental animals, developmental delays were seen in rats, and teratogenic effects and post-implantation loss were observed in rats and rabbits at doses producing 13 and 325 times, respectively, the systemic exposure (AUC) in acne patients treated with 2 mg/cm<sup>2</sup> of tazarotene foam 0.1% over 15% body surface area.

In female rats orally administered 2 mg/kg/day tazarotene from 15 days before mating through gestation day 7, a number of classic developmental effects of retinoids

were observed including decreased number of implantation sites, decreased litter size, decreased numbers of live fetuses, and decreased fetal body weights. A low incidence of retinoid-related malformations was also observed. The 2 mg/kg/day tazarotene dose produced an  $AUC_{0-24hr}$  that was 42 times the systemic exposure (AUC) in acne patients treated with 2 mg/cm<sup>2</sup> of tazarotene foam 0.1% over 15% body surface area.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### *Carcinogenesis*

A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risk. Based on pharmacokinetic data from a shorter-term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat approximately 2 times the systemic exposure (AUC) in acne patients treated with 2 mg/cm<sup>2</sup> of tazarotene foam 0.1% over 15% body surface area.

A long-term topical application study of up to 0.1% tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1.0 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals. Systemic exposure (AUC) at the highest dose in mice was 49 times the systemic exposure (AUC) in acne patients treated with 2 mg/cm<sup>2</sup> of tazarotene foam 0.1% over 15% body surface area.

In evaluation of photo-carcinogenicity, median time to onset of tumors was decreased, and the number of tumors increased in hairless mice following chronic topical dosing with exposure to ultraviolet radiation at tazarotene concentrations of 0.001%, 0.005% and 0.01% in a gel formulation for up to 40 weeks.

#### *Mutagenesis*

Tazarotene was non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in a human lymphocyte assay. Tazarotene was non-mutagenic in the CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in the in vivo mouse micronucleus test.

#### *Impairment of Fertility*

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of tazarotene gel up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure at the 0.125 mg/kg/day dose in the rat would be equivalent to 7.6 times the systemic exposure (AUC) in acne patients treated with 2 mg/cm<sup>2</sup> of tazarotene foam 0.1% over 15% body surface area.

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1.0 mg/kg/day tazarotene.

Systemic exposure (AUC) at the highest dose in rats was 23 times the systemic exposure (AUC) in acne patients treated with 2 mg/cm<sup>2</sup> of tazarotene foam 0.1% over 15% body surface area.

No effect on parameters of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through gestation day 7 with oral doses of tazarotene up to 2.0 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose [see *Pregnancy* (8.1)]. That dose produced a systemic exposure (AUC) in rats that was 42 times the systemic exposure (AUC) in acne patients treated with 2 mg/cm<sup>2</sup> of tazarotene foam 0.1% over 15% body surface area.

Reproductive capabilities of F1 animals, including F2 survival and development, were not affected by topical administration of tazarotene gel to female F0 parental rats from gestation day 16 through lactation day 20 at the maximum tolerated dose of 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure (AUC) in the rat would be equivalent to 7.6 times the systemic exposure (AUC) in acne patients treated with 2 mg/cm<sup>2</sup> of tazarotene foam 0.1% over 15% body surface area.

The following wording for the labeling on the nonclinical information was proposed by the sponsor:

## HIGHLIGHTS OF PRESCRIBING INFORMATION

### INDICATIONS AND USAGE

TRADENAME Foam is a retinoid prodrug indicated for the topical treatment of (b) (4) acne vulgaris in patients 12 years of age or older.

### 4 Contraindications

(b) (4)

(b) (4)

Systemic exposure to tazarotenic acid is dependent upon the extent of the body surface area treated. In patients treated topically over sufficient body surface area, exposure could be in the same order of magnitude as in orally treated animals. (b) (4)

(b) (4) tazarotene is a teratogenic substance, and it is not known

what level of exposure is required for teratogenicity in humans. [see *Clinical Pharmacology* (12)].

### 8.1 Pregnancy

(b) (4) Pregnancy Category X:

(b) (4) of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when TRADENAME Foam is used. The possibility that a (b) (4) of child-bearing potential is pregnant at the time of institution of therapy should be considered. A negative serum or urine result for pregnancy test having a sensitivity down to at least (b) (4) mIU/mL for hCG should be obtained within 2 weeks prior to TRADENAME Foam therapy, which should begin during a normal menstrual period, for females of childbearing potential. (b) (4)

There are no adequate and well-controlled studies in pregnant women. (b) (4)

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

Tazarotene was non-mutagenic in the Ames assay (b) (4) and did not produce structural chromosomal aberrations in a human lymphocyte assay. Tazarotene was non-mutagenic in the CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in the *in vivo* mouse micronucleus test.

No impairment of fertility was observed in male rats treated for 70 days prior to mating (b) (4) female (b) (4) treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of tazarotene gel up to 0.125 mg/kg/day. (b) (4)

(b) (4)

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1 mg/kg/day tazarotene. (b) (4) (b) (4), resulting in an exposure that was 23 (b) (4) times (b) (4)  $AUC_{0-24h}$  in acne patients treated with 2 mg/cm<sup>2</sup> of tazarotene foam 0.1% over a 15% (b) (4) body surface area. No effect on parameters of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through GD 7 with oral doses of tazarotene up to 2 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at 2 mg/kg/day. [see *Contraindications* (4).] The  $AUC_{de}$  at the highest dose was (b) (4) 42.4 times the maximum  $AUC_{0-24h}$  in acne patients treated with 2 mg/cm<sup>2</sup> of tazarotene foam 0.1% over a 15% (b) (4) body surface area.

(b) (4)

## 2 Drug Information

### 2.1 Drug

CAS Registry Number  
118282-40-3

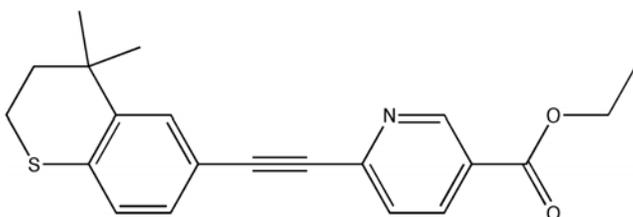
Generic Name  
Tazarotene

Code Name  
NA

Chemical Name  
Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate

Molecular Formula/Molecular Weight  
C<sub>21</sub>H<sub>21</sub>NO<sub>2</sub>S / 351.5

Structure or Biochemical Description



Pharmacologic Class  
Retinoid

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 105564, NDAs 20600 and 21184

## 2.3 Drug Formulation

Ingredient	Foam 0.1% (% w/w)
Tazarotene	0.1
Mineral oil	(b) (4)
Diisopropyl adipate	
Macrogol cetostearyl ether 12	
Potassium Sorbate	
Sorbic acid	
Potassium citrate, monohydrate	
Butylated hydroxytoluene	
Citric acid, anhydrous	
Purified water	
Total	

The container of the drug product is pressurized with a propane/butane propellant (b) (4) which is supplied as a (b) (4) of approximately (b) (4) propane, (b) (4) n-butane, and (b) (4) isobutane. The sponsor stated that there was no (b) (4) in the propellant as a (b) (4).

## 2.4 Comments on Novel Excipients

Macrogol cetostearyl ether 12 has other names as Cetareth-12 and Polyoxyl 12 cetostearyl ether and is an inactive Ingredient in other previously-approved drug products.

## 2.5 Comments on Impurities/Degradants of Concern

Two new impurities, (b) (4) were found during the drug development. The proposed acceptance criterion in the drug product specification for each of them is (b) (4). The CMC reviewer has evaluated (b) (4) (b) (4) and concluded that there are no structural alerts for genotoxicity and that the proposed acceptance criteria meet the Q3B(R2) Qualification Threshold. As discussed with CMC reviewer (see CMC Review), the impurities and some potential (b) (4) leachables in this drug product will add minimal risk to patients using this drug product, from a Pharmacology/Toxicology perspective.

## 2.6 Proposed Clinical Population and Dosing Regimen

Tazarotene Foam (0.1%) is proposed for the topical treatment of (b) (4) acne vulgaris in patients 12 years of age or older. It will be applied once daily in the evening after washing with a mild cleanser and fully drying the affected area with the maximum amount of 4 grams drug product.

## 2.7 Regulatory Background

Tazarotene Gel was approved for topical treatment of psoriasis (0.05% and 0.1%) and acne vulgaris (0.1%) under NDA 20600 in 1996. Tazarotene Cream (0.1%) was also approved for psoriasis and acne vulgaris under NDA 21184 in 2001. The sponsor of this NDA has obtained a full right of reference from Allergan to NDAs 20600 and 21184 to support this NDA for the treatment of acne vulgaris with a new formulation, Tazarotene Foam (0.1%).

# 3 Studies Submitted

## 3.1 Studies Reviewed

(1) Tazarotene Foam: 90-Day Dermal Toxicity Study in Rats followed by a 28-Day Recovery Period (OEE000129)

### 3.2 Studies Not Reviewed

The following studies were reviewed in IND 105564 by Dr. Jiaqin Yao:

- (1) Tazarotene Foam - W0290: In Vitro Human Skin Penetration Study (2008-337-MB)
- (2) Tazarotene Foam: 28-Day Dermal Toxicity Study in Minipigs (OEE00058)
- (3) Tazarotene Foam: 28-Day Dermal Toxicity Study in Rats (OEE00057)
- (4) Tazarotene Foam 0.1%: Acute Eye Irritation Study in Rabbits (OEE00055)
- (5) Tazarotene Foam 0.1%: Acute Dermal Irritation Study in Rabbits (OEE00056)
- (6) Tazarotene Foam 0.1%: Local Lymph Node Assay (515587)

### 3.3 Previous Reviews Referenced

Reviews for NDAs 20600 and 21184. Some information in this review was duplicated from the labeling of Tazorac Gel (NDA 20600) and/or Tazorac Cream (NDA 21184).

## 4 Pharmacology

Tazarotene is a pro-drug. It is rapidly metabolized to the active metabolite, tazarotenic acid, which binds to nuclear retinoic acid receptors and activates retinoid-responsive genes. Tazarotene has multiple effects on keratinocyte differentiation and proliferation, as well as on inflammatory processes.

## 5 Pharmacokinetics/ADME/Toxicokinetics

**5.1. Tazarotene Foam - W0290: In Vitro Human Skin Penetration Study** (Study No. 2008-337-MB): An in vitro skin penetration study was conducted to characterize the delivery of tazarotene from 2 prototype formulations of tazarotene foam with various amounts of oils (11% and 15% w/w), compared with Tazorac Gel (0.1%) and Tazorac Cream (0.1%). The results of the study showed that 1) there was no statistically significant difference in tazarotene delivery between the 2 tazarotene foam formulations; 2) delivery of tazarotene into the dermis and epidermis from tazarotene foam was similar to that of Tazorac Gel 0.1%; 3) compared with Tazorac Cream 0.1%, the delivery of tazarotene into the dermis and epidermis from tazarotene foam was 50% lower; and 4) tazarotene sulfoxide and tazarotenic acid were below the lower limit of quantitation (LLOQ, 50 pg/mL) in all samples.

Pharmacokinetic evaluations following topical application of Tazarotene Foam were performed in the 28-day studies in mini-pigs and rats and in the 90-day study in rats. In these studies, a dose-related increase in systemic exposure to tazarotenic acid was seen and the systemic exposure levels of tazarotenic acid from Tazarotene Foam 0.1% were less than or comparable to those from Tazorac Gel 0.1%.

One clinical pharmacokinetic study has been conducted in subjects with acne vulgaris (Trial W0260-105). Thirty subjects (11 male and 19 female, age range 12 - 33 years) were enrolled in the trial and twenty-nine subjects (13 tazarotene foam arm and

16 tazarotene gel arm) completed the trial. Approximately 5 grams of the study product was applied by the clinical staff once daily in late afternoon or early evening for 22 days to the face, upper chest, upper back and shoulders (~15% body surface area, BSA). The bioavailability of tazarotene and tazarotenic acid on Day 22 following administration of the foam formulation was lower than the gel formulation. The geometric mean value of  $AUC_{0-\tau}$  of tazarotenic acid following the administration of the foam formulation was 6.98 ng·hr/mL (see Clinical Pharmacology Review), which is used to calculate the animal multiples of human exposure.

## 6 General Toxicology

### 6.1 Single-Dose Toxicity

None

### 6.2 Repeat-Dose Toxicity

#### 6.2.1. Study title: Tazarotene Foam: 28-Day Dermal Toxicity Study in Minipigs

Study no.:	OEE00058
Study report location:	(b) (4)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 3, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Tazarotene Foam 0.05%, Lot 714/9/2, >99.1% Tazarotene Foam 0.1%, Lot 714/9/3, >98.2% Tazarotene Foam 0.2%, Lot 714/9/4, >99.5% Tazorac Gel 0.1%, 55066

#### Key Study Findings

There were no treatment-related effects on mortality, body weights, ophthalmoscopic findings, ECG, hematology, clinical chemistry, organ weights, and clinical signs except dermal observations. Treatment-related effects of dermal irritation consisted primarily of erythema, edema, and eschar, although there was generally no increase in incidence and severity with increasing concentration of tazarotene foam. Grossly visible flaking, scabbing, and cracking at the treatment site correlated with microscopic changes including hyperplasia, hyperkeratosis, acantholysis, and ulceration of the epidermis with accompanying chronic and chronic/active inflammation within the superficial dermis and accumulation of serocellular crust on the treatment site surface. Changes observed with Tazarotene Foam exposure, even at the highest concentration of 0.2%, were less severe than the findings associated with Tazorac Gel 0.1%. A no-observed-adverse-effect level (NOAEL) for dermal treatment of tazarotene foam for 28 days could not be determined because of the dermal findings.

## Methods

Doses: 0, 0.06, 0.13, and 0.25 mg/kg/day tazarotene, see the following table.

Frequency of dosing: Once daily for 28 days

Route of administration: Topical

Dose volume: 125  $\mu$ L/kg

Formulation/Vehicle: Not indicated

Species/Strain: Gottingen minipigs

Number/Sex/Group: 3/sex/group

Age: Approximately 11 weeks

Weight: Male 7.43 - 9.18 kg; Female 7.92 - 9.85 kg

Satellite groups: None

Unique study design: Approximately 10% body surface area was treated once daily for 28 days.

Deviation from study protocol: Two males in Group 1 and one male and one female in Group 4 stopped treatment for 2 -3 days due to ulceration (open lesions) within the test site.

Text Table 1: Experimental Design

Group No.	No. of Animals		Test Material	Total Dose Level (mg/kg/day)	Tazarotene Dose Level (mg/kg/day)	Dose Volume ( $\mu$ L/kg)	Dose Concentration (mg/mL)
	Male	Female					
1	3	3	Tazarotene Foam Vehicle	0	0	125	0
2	3	3	Tazorac® Gel, 0.1%	125	0.13	125	1
3	3	3	Tazarotene Foam, 0.05%	125	0.06	125	0.5
4	3	3	Tazarotene Foam, 0.1%	125	0.13	125	1
5	3	3	Tazarotene Foam, 0.2%	125	0.25	125	2

## Observations and Results

## Mortality

Checked twice daily. No deaths occurred.

## Clinical Signs

Cage-side observations were performed daily; detailed clinical observations were performed weekly; and dermal observations were performed prior to dosing during the treatment period (Days 1 - 28). There were no signs of systemic toxicity. There were treatment-related effects of dermal irritation consisted primarily of erythema, edema, and eschar, which were first noted on Day 3 or 4, although there was generally no increase in incidence and severity with increasing concentration of tazarotene foam.

Overall, the males had a greater incidence and severity of dermal findings compared to the females.

### **Body Weights**

Recorded weekly. There were no treatment-related effects.

### **Feed Consumption**

NA

### **Ophthalmoscopy**

Performed on Days -9/8 and 27/28. There were no treatment-related effects.

### **ECG**

Performed pre-test and on Day 24/25. There were no treatment-related effects.

### **Hematology**

Blood samples were collected pre-test and on Day 29. There were no treatment-related effects.

### **Clinical Chemistry**

Blood samples were collected pre-test and on Day 29. Although aspartate aminotransferase (AST) was 2-fold higher in the Tazarotene Foam 0.2%-treated females (0.25 mg/kg/day) than that in the Vehicle-treated females, AST was only 20% higher in the Tazarotene Foam 0.2%-treated females as compared to the pre-test values.

### **Urinalysis**

NA

### **Gross Pathology**

Treatment-related gross necropsy findings were limited to changes in the skin including flaking, scabbing, and cracking at the tazarotene-treated sites.

### **Organ Weights**

Adrenal gland, brain, epididymis, heart, kidney, liver, lung, ovary, pituitary gland, prostate gland, salivary gland, spleen, testis, thymus, thyroid gland, and uterus were weighed. There were no treatment-related effects.

### **Histopathology**

The tissues and organs collected at necropsy (see the next table) from all animals were processed and examined microscopically.

**Text Table 11: Tissue Collection and Preservation**

Adrenal gland (paired)	Mammary gland
Animal identification	Nerve, optic <sup>b</sup>
Aorta	Nerve, sciatic
Bone, femur	Ovary (paired)
Bone, sternum	Pancreas
Bone marrow, sternum	Parathyroid gland <sup>c</sup>
Bone marrow smear <sup>a</sup>	Pituitary gland
Brain (cerebrum, cerebellum, brain stem, medulla)	Prostate gland
Cervix	Salivary gland (paired)
Epididymis (paired)	Seminal vesicle (paired)
Esophagus	Skeletal muscle (thigh)
Eye (paired) <sup>b</sup>	Skin (mammary)
Harderian gland (paired)	Skin (treated-entire site collected)
Heart	Skin (untreated-hip region)
Intestine, cecum	Spinal cord (cervical, thoracic, lumbar)
Intestine, colon	Spleen
Intestine, duodenum	Stomach (nonglandular and glandular)
Intestine, ileum with Peyer's patch <sup>c</sup>	Testis (paired)
Intestine, jejunum	Thymus
Intestine, rectum	Thyroid gland (paired)
Kidney (paired)	Tongue
Liver	Trachea
Lung	Urinary bladder
Lymph node, mandibular	Uterus
Lymph node, mesenteric	Vagina
	Gross lesions/masses
<sup>a</sup> Bone marrow smears were collected from the femur at scheduled necropsies only (for possible examination).	
<sup>b</sup> Preserved in Davidson's fixative and then transferred to 10% neutral buffered formalin.	
<sup>c</sup> Examined only if present in the routine section.	

Grossly visible flaking, scabbing, and cracking at the treatment site correlated with microscopic changes including hyperplasia, hyperkeratosis, acantholysis, and ulceration of the epidermis with accompanying chronic and chronic/active inflammation within the superficial dermis and accumulation of serocellular crust on the treatment site surface. Epithelial hyperplasia was minimal in three of the six Vehicle-treated animals (2 males and 1 female), while all of the Tazorac Gel 0.1% (0.13 mg/kg/day)-treated animals displayed mild (1 male and 2 females) to moderate (2 males and 1 female) hyperplasia. Animals within the three Tazarotene Foam-treated groups (0.06, 0.13, and 0.25 mg/kg/day) had minimal to moderate hyperplasia in a pattern suggesting dose proportionality. Minimal to mild hypergranulosis was observed only in the Tazarotene Foam-treated groups. Minimal hyperkeratosis was noted in all of the Vehicle-treated animals. In the Tazorac Gel 0.1%-treated animals, all but one male displayed mild (one male and one female) to moderate (one male and two females) hyperkeratosis of the treated skin. Hyperkeratosis in the treated skin of Tazarotene Foam-treated animals was generally mild in severity. Acantholysis and epidermal ulceration was limited to the Tazorac Gel 0.1% and Tazarotene Foam-treated animals. Tazorac Gel 0.1%-treated animals displayed minimal to moderate acantholysis, while the severity in Tazarotene Foam-treated animals was minimal to mild. Ulceration due to these treatments was minimal to mild in severity. Serocellular crust accumulation on the skin surface ranged from minimal to severe in Tazorac Gel 0.1%-treated animals and from minimal to moderate in Tazarotene Foam-treated animals. Inflammation associated with the above

findings most common in Tazorac Gel 0.1%- and Tazarotene Foam-treated animals, was chronic or chronic/active in nature, and was minimal to mild in severity. Chronic/active lesions were common in areas of ulceration. Changes observed with Tazarotene Foam exposure, even at the highest concentration of 0.2%, were less severe than the findings associated with Tazorac Gel 0.1%.

### Special Evaluation

NA

### Toxicokinetics

Blood samples were collected at 0, 2, 4, 6, 8, and 24 hour on Days 1 and 28. Plasma tazarotene concentrations were either low or below LLOQ (25 pg/mL). The exposure of its metabolite, tazarotenic acid, increased as the dose increased (see the next table). Accumulation of tazarotenic acid was observed in both sexes following 28-day repeated dermal administration at all dose levels from either tazarotene foam or Tazorac Gel 0.1%. The exposure of tazarotenic acid at 0.13 mg/kg/day dose from the gel formulation was approximately twice that of the foam formulation after 28 once-daily administrations.

**Table 3 Toxicokinetics of Tazarotenic Acid in Study OEE00058**

Vehicle/Formulation:	Tazorac Gel, 0.1%		Tazarotene foam, 0.05%		Tazarotene foam, 0.1%		Tazarotene foam, 0.2%	
Dose (mg/kg):	0.13		0.06		0.13		0.25	
Gender (M/F)/Number	M/3; F/3		M/3; F/3		M/3; F/3		M/3; F/3	
PK parameters:	Male	Female	Male	Female	Male	Female	Male	Female
Day 1								
C <sub>max</sub> (pg/mL)	39.2	0	13.5	12.5	44.8	51.7	95.8	88.6
T <sub>max</sub> (h)	24	ND	6	6	16	6	6	6
AUC (pg·h/mL)	506	0	250	206	805	886	1,740	1,460
Day 28								
C <sub>max</sub> (pg/mL)	758	1,010	167	263	468	507	1,350	876
T <sub>max</sub> (h)	6	4	4	4	6	4	2	2
AUC (pg·h/mL)	11,300	13,200	2,670	3,540	6,930	6,170	20,000	12,600

AUC: area under the curve, C<sub>max</sub>: highest recorded concentration, PK: pharmacokinetic, T<sub>max</sub>: time to maximum recorded concentration.

### Stability and Homogeneity

It appears that Tazarotene Foams were stable after 3-month storage at 25 °C.

**6.2.2. Study title: Tazarotene Foam: 28-Day Dermal Toxicity Study in Rats**

Study no.:	OEE00057
Study report location:	(b) (4)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 3, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Tazarotene Foam 0.05%, Lot 714/9/2, >99.1% Tazarotene Foam 0.1%, Lot 714/9/3, >98.2% Tazarotene Foam 0.2%, Lot 714/9/4, >99.5% Tazorac Gel 0.1%, 55066

**Key Study Findings**

There were no treatment-related effects on mortality, ophthalmoscopic findings, urinalysis, and clinical signs except dermal observations. Dermal irritation increased in incidence and severity as the dose concentration increased. Ulceration (open lesion) was observed in the Tazarotene Foam 0.2% (0.6 mg/kg/day)-treated animals that resolved when the animals affected stopped treatment for 1 to 4 days. The severity of the dermal irritation (erythema and edema) was less in the Tazorac Gel 0.1 %-treated animals than that in the Tazarotene Foam 0.5%, 0.1%, or 0.2%-treated animals. Compared to the vehicle-treated group, the statistically significant increase of alkaline phosphatase was 80% and 236% in the Tazarotene Foam 0.2%-treated males and females, respectively. Statistically significant decreases in thymus weights (up to 42.8%) were also seen in the 0.3 or 0.6 mg/kg/day tazarotene-treated females. Minimal to moderate epidermal hyperplasia and hyperkeratosis were associated with exposure to Tazarotene Foam Vehicle, while mild to severe hyperplasia was seen in the Tazarotene Foam-treated animals. Although acantholysis, ulceration, inflammation, and serocellular crust were observed in a few Vehicle-treated animals, these findings occurred with greater incidence and severity in the tazarotene-treated animals. The severity of these parameters in the Tazarotene Foam 0.05%-treated rats was comparable to those in the Tazorac Gel 0.1%-treated animals. A no-observed-adverse-effect level (NOAEL) for dermal treatment of tazarotene foam for 28 days could not be determined because of the dermal findings.

## Methods

Doses: 0, 0.15, 0.3, and 0.6 mg/kg/day tazarotene, see the following table.

Frequency of dosing: Once daily for 28 days

Route of administration: Topical

Dose volume: 300  $\mu$ L/kg

Formulation/Vehicle: Not indicated

Species/Strain: Crl:CD(SD) rats

Number/Sex/Group: 10/sex/group

Age: Approximately 8 weeks

Weight: Male 242 - 288 g; Female 173 - 211 g

Satellite groups: TK: 9/sex/group

Unique study design: Approximately 10% body surface area was treated once daily for 28 days.

Deviation from study protocol: A few animals treated with Tazarotene Foam 0.2% stopped treatment for some days due to ulceration within the test site.

**Text Table 1: Experimental Design for the Toxicity and Toxicokinetic Phases**

Group No.	No. of Animals				Dose Material	Total Dose Level (mg/kg/day)	Tazarotene Dose Level (mg/kg/day)	Dose Volume ( $\mu$ L/kg)	Dose Concentration (mg/mL)
	Toxicity		Toxicokinetic						
	Males	Females	Males	Females					
1	10	10	9	9	Tazarotene Foam Vehicle	0	0	300	0
2	10	10	9	9	Tazorac <sup>®</sup> Gel, 0.1%	300	0.3	300	1
3	10	10	9	9	Tazarotene Foam, 0.05%	300	0.15	300	0.5
4	10	10	9	9	Tazarotene Foam, 0.1%	300	0.3	300	1
5	10	10	9	9	Tazarotene Foam, 0.2%	300	0.6	300	2

**Observations and Results****Mortality**

Check twice daily. No deaths occurred.

**Clinical Signs**

Cage-side observations were performed daily; detailed clinical observations were performed weekly; and dermal observations were performed prior to dosing during the treatment period (Days 1 - 28). There were no treatment-related effects on clinical signs, except dermal observations. Dermal irritation (erythema, eschar, eschar exfoliation, fissuring, and desquamation) increased in incidence and severity as the dose concentration increased. Ulceration (open lesion) was observed in the Tazarotene Foam 0.2% (0.6 mg/kg/day)-treated animals that resolved when the animals affected stopped treatment for 1 to 4 days. Dermal irritation (erythema, eschar, and desquamation) was noted in the Tazarotene Foam Vehicle-treated animals during the study at a lower incidence and severity compared to the tazarotene-treated animals.

Overall, females had greater incidence and severity of dermal findings compared to males. The severity of the dermal irritation (erythema and edema) was less in the Tazorac Gel 0.1%-treated animals than that in the Tazarotene Foam 0.05%, 0.1%, or 0.2%-treated animals.

### **Body Weights**

Recorded weekly. There were treatment-related decreases in body weight gain in tazarotene-treated animals, particularly in females. Compared to the vehicle-treated females, the difference of body weights in tazarotene-treated females was less than 10%.

### **Feed Consumption**

Recorded weekly. Slight decreases in food consumption were also seen in tazarotene-treated animals.

### **Ophthalmoscopy**

Performed on Days -3 and 27. There were no treatment-related effects.

### **ECG**

NA

### **Hematology**

Blood samples were collected on Day 29. Compared to the Vehicle control group, statistically significant changes in hematology and coagulation parameters for males or females treated with tazarotene included decreased hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and mean corpuscular volume (MCV) and increased activated partial thromboplastin time (APTT), leukocytes, monocytes, and segmented neutrophils. Overall the changes were relatively minor and within the historical control ranges. No significant differences were noted between Groups 2 and 4.

### **Clinical Chemistry**

Blood samples were collected on Day 29. Test article-related changes in serum chemistry parameters in males or females included increased alanine aminotransferase (ALT) and alkaline phosphatase, and increased globulin accompanied by decreased albumin and A/G ratio in some tazarotene-treated groups. Compared to the vehicle-treated group, the increase of alkaline phosphatase was 80% and 236% in the Tazarotene Foam 0.2%-treated males and females, respectively.

### **Urinalysis**

Urine was collected overnight on Day 29. There were no treatment-related effects.

### **Gross Pathology**

Treatment-related gross necropsy findings were limited to changes in the skin including flaking, scabbing, and cracking at the treatment sites.

### Organ Weights

Adrenal gland, brain, epididymis, heart, kidney, liver, lung, ovary, pituitary gland, prostate gland, salivary gland, seminal vesicle, spleen, testis, thymus, thyroid gland, and uterus were weighed. Statistically significant decreases in thymus weights (up to 42.8%) were seen in the 0.3 or 0.6 mg/kg/day tazarotene-treated females.

### Histopathology

All tissues and organs collected at necropsy (see the next table) from animals in Groups 1, 2, and 5 and gross lesions from all animals in all groups were processed and examined microscopically.

**Text Table 11: Tissue Collection and Preservation**

Adrenal gland (paired)	Mammary gland
Animal identification	Nerve, optic <sup>b</sup>
Aorta	Nerve, sciatic
Bone, femur	Ovary (paired)
Bone, sternum	Pancreas
Bone marrow, sternum	Parathyroid gland <sup>c</sup>
Bone marrow smear <sup>a</sup>	Pituitary gland
Brain (cerebrum, cerebellum, brain stem, medulla)	Prostate gland
Cervix	Salivary gland (paired)
Epididymis (paired)	Seminal vesicle (paired)
Esophagus	Skeletal muscle (thigh)
Eye (paired) <sup>b</sup>	Skin (mammary)
Harderian gland (paired)	Skin (treated-entire site collected)
Heart	Skin (untreated-hip region)
Intestine, cecum	Spinal cord (cervical, thoracic, lumbar)
Intestine, colon	Spleen
Intestine, duodenum	Stomach (nonglandular and glandular)
Intestine, ileum with Peyer's patch <sup>c</sup>	Testis (paired)
Intestine, jejunum	Thymus
Intestine, rectum	Thyroid gland (paired)
Kidney (paired)	Tongue
Liver	Trachea
Lung	Urinary bladder
Lymph node, mandibular	Uterus
Lymph node, mesenteric	Vagina
	Gross lesions/masses
<sup>a</sup> Bone marrow smears were collected from the femur at scheduled necropsies only (for possible examination).	
<sup>b</sup> Preserved in Davidson's fixative and then transferred to 10% neutral buffered formalin.	
<sup>c</sup> Examined only if present in the routine section.	

Grossly visible flaking, cracking, and scabbing at the treatment sites correlated with microscopic changes including hyperplasia, hyperkeratosis, acantholysis, and ulceration of the epidermis with accompanying chronic and chronic/active inflammation within the superficial dermis, and accumulation of serocellular crust. Minimal to moderate epidermal hyperplasia and minimal to mild hyperkeratosis were associated with exposure to Tazarotene Foam Vehicle, while a slight increase in severity of hyperplasia

and hyperkeratosis was seen in tazarotene-treated animals. Although acantholysis, ulceration, inflammation, and serocellular crust were observed in a few Vehicle-treated animals, these findings occurred with greater incidence and severity in the tazarotene-treated animals. The severity of these parameters in the Tazarotene Foam 0.05%-treated rats was comparable to those in the Tazorac Gel 0.1%-treated animals. There was a slight trend of increased severity of dermal findings with increasing concentration of the Tazarotene Foam.

## Special Evaluation

NA

## Toxicokinetics

Blood samples were collected at 0, 3, 6, 9, 12, and 24 hour on Days 1 and 28. Plasma tazarotene concentrations were either low or below LLOQ (25 pg/mL). The exposure of its metabolite, tazarotenic acid, increased as the dose increased (see the next table). Tazarotenic acid exposure levels were slightly higher in females than in males following single dosing of tazarotene, but after repeated treatment exposure levels of tazarotene acid were slightly higher in males in the low- and mid-dose groups (0.15 and 0.3 mg/kg/day for both gel and foam formulations). Tazarotenic acid exposure levels were generally lower following 28-day repeated dermal treatment at all dose levels from either tazarotene foam or gel in both sexes when compared with those after single-dose treatment. The exposure levels of tazarotene acid from the gel formulation were approximately 50% higher than those from the foam formulation after a single dose, but were comparable following 28-day treatment.

**Table 2 Toxicokinetics of Tazarotenic Acid in Study OEE00057**

Vehicle/Formulation:	Tazorac Gel, 0.1%		Tazarotene foam, 0.05%		Tazarotene foam, 0.1%		Tazarotene foam, 0.2%	
Dose (mg/kg):	0.3		0.15		0.3		0.6	
Gender (M/F)/Number	M/9; F/9		M/9; F/9		M/9; F/9		M/9; F/9	
PK parameters:	Male	Female	Male	Female	Male	Female	Male	Female
Day 1								
C <sub>max</sub> (pg/mL)	19,800	28,400	3,510	10,800	12,300	15,100	13,000	40,500
T <sub>max</sub> (h)	3	3	3	3	3	3	3	3
AUC (pg·h/mL)	146,000	155,000	63,200	70,600	126,000	103,000	143,000	224,000
Day 28								
C <sub>max</sub> (pg/mL)	9,170	2,880	4,300	1,710	5,250	3,140	4,900	5,220
T <sub>max</sub> (h)	3	3	3	3	3	3	9	3
AUC (pg·h/mL)	67,800	51,200	47,800	29,100	69,600	43,000	54,500	71,300

AUC: area under the curve, C<sub>max</sub>: highest recorded concentration, PK: pharmacokinetic, T<sub>max</sub>: time to maximum recorded concentration.

## Stability and Homogeneity

It appears that Tazarotene Foams were stable after 3-month storage at 25 °C.

The sponsor stated that based on the 28-day dermal toxicity studies in rats and in minipigs, dermal irritation was the primary treatment-related effects and topical treatment with tazarotene foam resulted in more findings in rats than in minipigs. Therefore, the sponsor conducted a 3-month dermal toxicity study in rats (the more sensitive species) instead of minipigs.

### 6.2.3. Study title: Tazarotene Foam: 90-Day Dermal Toxicity Study in Rats followed by a 28-Day Recovery Period

Study no.:	OEE000129
Study report location:	(b) (4)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 20, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Tazarotene Foam 0.025%, Lot LBR-NA-0018/01, Purity 99.2%-100.4%; Tazarotene Foam 0.05%, Lot LBR-NA-0019/01, Purity 100.0%-101.0%; Tazarotene Foam 0.1%, Lot LBR-NA-0020/01, Purity 100.8%-101.1%

### Key Study Findings

Topical treatment with Tazarotene Foam at concentrations of 0.025%, 0.05%, or 0.1% for 90 days resulted in a variety of treatment-related effects, including dermal irritation, decreased body weight gain, alterations in hematology and clinical chemistry parameters, organ weight changes, and microscopic findings in the skin of males and females and in the adrenal gland, thymus, and liver of females. Dermal irritation was generally less severe in Tazorac Gel 0.1%-treated animals compared to Tazarotene Foam-treated animals, and generally increased in incidence and severity with increasing concentrations of Tazarotene Foam. The systemic changes in the adrenal gland, thymus, and liver in the Tazarotene Foam 0.05% -treated group were comparable to those observed in the Tazorac Gel 0.1% -treated group. Changes at the treatment site and thymus were reversible, while some adrenal changes remained in the females following recovery. A no-observed-adverse-effect level (NOAEL) could not be determined for Tazarotene Foam in this study.

## Methods

Doses: 0, 0.075, 0.15, and 0.3 mg/kg/day tazarotene, see the following table.

Frequency of dosing: Once daily for 90 days

Route of administration: Topical

Dose volume: 300 µL/kg

Formulation/Vehicle: Not indicated

Species/Strain: Crl:CD(SD) rats

Number/Sex/Group: 10/sex/group

Age: Approximately 7 weeks

Weight: Male 221 - 255 g; Female 167 - 196 g

Satellite groups: TK: 9/sex/group; Recovery (28 days): 5/sex/group

Unique study design: Approximately 10% body surface area was treated once daily for 90 days.

Deviation from study protocol: A few animals treated with Tazarotene Foam 0.1% stopped treatment for some days due to ulceration/eschar within the treatment site.

Text Table 1 Experimental Design for the Toxicity and Toxicokinetic Phases

Group No.	No. of Animals				Test Material	Total Dose Level (mg/kg/day)	Tazarotene Dose Level (mg/kg/day)	Dose Volume (µL/kg)	Dose Concentration (mg/mL)
	Toxicity (Recovery)		Toxicokinetic						
	Male	Female	Male	Female					
1	10(5)	10(5)	--	--	Untreated	0	0	0	0
2	10(5)	10(5)	3	3	Tazarotene Foam Vehicle	0	0	300	0
3	10(5)	10(5)	9	9	Tazorac® Gel, 0.1%	300	0.3	300	1
4	10(5)	10(5)	9	9	Tazarotene Foam, 0.025%	300	0.075	300	0.25
5	10(5)	10(5)	9	9	Tazarotene Foam, 0.05%	300	0.15	300	0.5
6	10(5)	10(5)	9	9	Tazarotene Foam, 0.1%	300	0.3	300	1

## Observations and Results

## Mortality

Checked twice daily. One male in the Tazorac Gel 0.1% group was found dead on Day 31.

## Clinical Signs

Cage-side observations were performed daily; detailed clinical observations were performed weekly; and dermal observations were performed during the treatment and recovery periods on Days 1, 8, 12, 15, 19, 22, 26, 29, 33, 36, 40, 43, 47, 50, 54, 57, 61, 64, 68, 71, 75, 78, 82, 85, 90, 91 (scheduled euthanasia animals only), 94, 97, 101,

104, 108, 111, 115, 118, and 119. There were no treatment-related effects on clinical signs, except dermal observations.

Dermal irritation primarily consisted of erythema, desquamation, and eschar and was observed through the treated groups. The severity of the erythema increased with increasing concentration of Tazarotene Foam. Edema was noted in a dose-related manner in Tazarotene Foam-treated groups. Desquamation was noted throughout the treated groups, including Foam Vehicle-treated animals. Eschar of minimal severity was observed in all treated groups, whereas increases in eschar severity were observed only in Tazarotene Foam-treated animals. Eschar exfoliation was also observed in the test article-treated female groups. Overall, female animals had a greater incidence and severity of dermal findings compared to the males. Dermal irritation was generally less severe in Tazorac Gel-treated animals, and generally increased in incidence with increasing concentrations of Tazarotene Foam. Dermal irritation persisted throughout the recovery phase in the majority of the animals, although a reduction in the severity of the findings was observed.

### **Body Weights**

Recorded weekly. Treatment-related decreases in body weight gain resulted in lower body weights of up to 11% to 20% less than untreated controls in Tazorac Gel 0.1%-treated females, Tazarotene Foam 0.025%-treated males, Tazarotene Foam 0.05%-treated males and females, and Tazarotene Foam 0.1%-treated males and females during the dosing phase. During the recovery phase, body weight gains in tazarotene-treated groups were generally larger than those of untreated controls, resulting in smaller body weight differences by the end of the recovery phase.

### **Feed Consumption**

Recorded weekly. Slight decreases in food consumption were seen in test article-treated males. However, during the recovery phase, food consumption was slightly higher in some tazarotene-treated groups.

### **Ophthalmoscopy**

Performed on Days -6/7 and 88/89. There were no treatment-related effects.

### **ECG**

NA

### **Hematology**

Blood samples were collected on Day 91 from those animals scheduled for euthanasia and on Day 119. Compared to the Vehicle control group, statistically significant changes in hematology and coagulation parameters for males or females treated with tazarotene included decreased hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and mean corpuscular volume (MCV) and increased activated partial thromboplastin time (APTT), leukocytes,

monocytes, and segmented neutrophils. Overall the changes were relatively minor and within the historical control ranges. Most of these changes were not seen at the end of the recovery period on Day 119.

### **Clinical Chemistry**

Blood samples were collected on Day 91 from those animals scheduled for euthanasia and on Day 119. Treatment-related changes in Tazarotene Foam and Tazorac Gel groups on Day 91 included increased alkaline phosphatase in males and females, decreased total protein in females, and decreased albumin, A/G ratio, and cholesterol in males and females compared to untreated or Tazarotene Foam Vehicle controls. The magnitude of these changes was generally reduced at the end of the recovery period.

### **Urinalysis**

Urine was collected overnight on Day 91 from those animals scheduled for euthanasia and on Day 119. There were no treatment-related effects.

### **Gross Pathology**

Treatment-related gross necropsy findings were seen at the treatment site including scabbing (eschar) and flaking. In addition, increased adrenal size in the females treated with Tazarotene Foam 0.05% or 0.1% and small thymus in Tazorac Gel-treated or Tazarotene Foam 0.1%-treated females were also noted.

### **Organ Weights**

Adrenal gland, brain, epididymis, heart, kidney, liver, lung, ovary, pituitary gland, prostate gland, salivary gland, seminal vesicle, spleen, testis, thymus, thyroid gland with parathyroid gland, and uterus were weighed. Treatment-related increases in adrenal weights (up to 104%) and liver weights (up to 40%) and decreases in thymus weights (up to 59%) were observed in females treated with Tazarotene Foam or Tazorac Gel. These changes were smaller or not seen in the recovery animals at the end of the recovery period.

### **Histopathology**

All tissues and organs collected at necropsy (see the next table) from all animals in Groups 1, 2, 3, and 6 and gross lesions and treated and untreated skin sites from all Group 4 and 5 animals were processed and examined microscopically. In addition, the adrenal gland, thymus, and liver from the Group 4 and 5 females were processed to slides and examined microscopically. Slides were examined microscopically by a board-certified veterinary pathologist.

Text Table 12 Tissue Collection and Preservation

Adrenal gland (paired)	Nerve, optic <sup>b</sup>
Animal identification	Nerve, sciatic
Aorta	Ovary (paired)
Bone, femur	Pancreas
Bone, sternum	Parathyroid gland <sup>c</sup>
Bone marrow, sternum	Pituitary gland
Bone marrow smear <sup>a</sup>	Prostate gland
Brain (cerebrum, cerebellum, brain stem, medulla)	Salivary gland (paired)
Cervix	Seminal vesicle (paired)
Epididymis (paired)	Skeletal muscle (thigh)
Esophagus	Skin (inguinal)
Eye (paired) <sup>b</sup>	Skin (treated – entire site collected)
Harderian gland (paired)	Skin (untreated – hip region)
Heart	Spinal cord (cervical, thoracic, lumbar)
Intestine, cecum	Spleen
Intestine, colon	Stomach (nonglandular and glandular)
Intestine, duodenum	Testis (paired) <sup>d</sup>
Intestine, ileum with Peyer's patch <sup>c</sup>	Thymus
Intestine, jejunum	Thyroid gland (paired)
Intestine, rectum	Tongue
Kidney (paired)	Trachea
Liver	Urinary bladder
Lung	Uterus
Lymph node, mandibular	Vagina
Lymph node, mesenteric	Gross lesions
Mammary gland	
<sup>a</sup> Bone marrow smears were collected from the femur at scheduled necropsies only (for possible examination).	
<sup>b</sup> Preserved in Davidson's fixative and then transferred to 10% neutral buffered formalin.	
<sup>c</sup> Examined only if present in the routine section.	
<sup>d</sup> Preserved in modified Davidson's fixative and then transferred to 10% neutral buffered formalin.	

Grossly visible flaking and scabbing at the treatment sites correlated with microscopic changes including hyperplasia, hyperkeratosis, acantholysis, and ulceration of the epidermis with accompanying chronic and chronic/active inflammation within the superficial dermis, and accumulation of serocellular crust. Minimal to moderate epidermal hyperplasia and minimal to mild hyperkeratosis were associated with exposure to Tazarotene Foam Vehicle, while a slight increase in severity of hyperplasia and hyperkeratosis was seen in tazarotene-treated animals. Although acantholysis, ulceration, inflammation, and serocellular crust were observed in a few Vehicle-treated animals, these findings occurred with greater incidence and severity in the tazarotene-treated animals. The severity of these parameters in the Tazarotene Foam 0.05%-treated rats was comparable to those in the Tazorac Gel 0.1%-treated animals. There was a slight trend of increased severity of dermal findings with increasing concentration of the Tazarotene Foam.

In addition to the skin, Tazorac Gel 0.1% and Tazarotene Foam caused microscopic changes in the adrenal gland (cortical hypertrophy, cystic degeneration, and congestion), thymus (lymphoid depletion), and liver (periportal vacuolation) in females, with a slight trend of increased severity with increased dose of Tazarotene Foam, which correlated with changes in the weights of these organs. The non-dermal effects were most similar between the Tazorac Gel 0.1% and Tazarotene Foam 0.05% groups. The

sponsor stated that the findings in adrenal and thymus may have been associated with experimental stress.

At the end of the recovery phase, microscopic findings at the treatment site were limited to minimal to mild hypergranulosis, hyperkeratosis, and epithelial hyperplasia, which were similar to those observed in the untreated group; no adverse microscopic findings were noted in the thymus of treated animals. However, microscopic adrenal findings persisted in two females treated with Tazorac Gel 0.1%, and one female treated with Tazarotene Foam 0.05% at the end of the recovery phase.

### **Special Evaluation**

NA

### **Toxicokinetics**

Blood samples were collected from 3 TK animals/sex/group (Groups 3-6) at 0, 3, 6, 9, 12, and 24 hour and from the 3 TK animals/sex in Group 2 at 3 and 9 hour post-treatment on Days 1 and 90.

All pre-dose samples on Day 1 for all groups treated with Tazarotene Gel or Foam had no quantifiable plasma concentrations of tazarotene or tazarotenic acid (LLOQ 25 pg/mL). However, tazarotenic acid at concentration ranging from 35.2 pg/mL to 51.7 pg/mL was found in 4 out of 6 samples collected from the 3 control females on Day 90.

The exposure of its metabolite, tazarotenic acid, increased as the dose increased (see the next table). Tazarotenic acid exposure levels were slightly higher in females than in males and generally lower following 90-day repeated dermal treatment when compared to single dose administration. The overall exposure of tazarotenic acid from Tazorac Gel (0.1%) was slightly higher than Tazarotene Foam (0.1%) after single dosing. Following 90 daily administrations, the exposure from Tazorac Gel (0.1%) was slightly higher than Tazarotene Foam (0.1%) in males and was comparable in females.

**Table 9**  
Summary of Plasma TK Parameters of Tazarotenic Acid in Rats Following Tazarotene Administration in Tazarotene Foam in a 90-Day Dermal Toxicity Study

Day	Gender		Male			Female	
	Group	4	5	6	4	5	6
	Tazarotene Dose, mg/kg/day	0.075	0.15	0.3	0.075	0.15	0.3
1	C <sub>max</sub> , pg/mL	5,900	10,500	22,400	11,000	13,100	18,800
	T <sub>max</sub> , h	3.00	3.00	3.00	6.00	3.00	3.00
	AUC <sub>(0-24)</sub> , pg·h/mL	49,800	88,900	187,000	96,300	94,300	164,000
	C <sub>max</sub> Female/Male Ratio	-	-	-	1.86	1.25	0.839
	AUC Female/Male Ratio	-	-	-	1.93	1.06	0.877
90	C <sub>max</sub> , pg/mL	5,530	1,730	3,690	2,290	3,430	4,920
	T <sub>max</sub> , h	3.00	3.00	9.00	12.0	3.00	12.0
	AUC <sub>(0-24)</sub> , pg·h/mL	31,000	23,400	35,600	36,600	45,100	73,300
	C <sub>max</sub> Female/Male Ratio	-	-	-	0.414	1.98	1.33
	AUC Female/Male Ratio	-	-	-	1.18	1.93	2.06
	C <sub>max</sub> Day 90/Day1 Ratio	0.937	0.165	0.165	0.208	0.262	0.262
	AUC Day 90/Day1 Ratio	0.622	0.263	0.190	0.380	0.478	0.447

**Table 10**  
Comparison of Tazarotenic Acid Plasma TK Parameters in Rats Following Single and 90 Daily Dermal Doses of 0.3 mg/kg Tazarotene in Tazorac Gel 0.1% and Tazarotene Foam 0.1% Formulation

Day	Gender		Male		Female	
	Group	3	6	3	6	
	Tazarotene Formulation	Tazorac Gel 0.1%	Tazorac Foam 0.1%	Tazorac Gel 0.1%	Tazorac Foam 0.1%	
1	C <sub>max</sub> , pg/mL	26,000	22,400	29,000	18,800	
	T <sub>max</sub> , h	3.00	3.00	3.00	3.00	
	AUC <sub>(0-24)</sub> , pg·h/mL	182,000	187,000	178,000	164,000	
	C <sub>max</sub> Female/Male Ratio	-	-	1.12	0.839	
	AUC Female/Male Ratio	-	-	0.978	0.877	
	C <sub>max</sub> Gel/Foam Ratio	1.16	-	1.54	-	
	AUC Gel/Foam Ratio	0.973	-	1.09	-	
90	C <sub>max</sub> , pg/mL	9,050	3,690	5,120	4,920	
	T <sub>max</sub> , h	3.00	9.00	6.00	12.0	
	AUC <sub>(0-24)</sub> , pg·h/mL	57,700	35,600	68,000	73,300	
	C <sub>max</sub> Female/Male Ratio	-	-	0.566	1.33	
	AUC Female/Male Ratio	-	-	1.18	2.06	
	C <sub>max</sub> Gel/Foam Ratio	2.45	-	1.04	-	
	AUC Gel/Foam Ratio	1.62	-	0.928	-	
	C <sub>max</sub> Day 90/Day 1 Ratio	0.348	0.165	0.177	0.262	
	AUC Day 90/Day 1 Ratio	0.317	0.190	0.382	0.447	

### Stability and Homogeneity

No information on the stability and homogeneity was provided in this study report. However, previous study reports stated that Tazarotene Foams were stable after 3-month storage at 25 °C.

## 7 Genetic Toxicology

The following was duplicated from the labeling for Tazarotene Cream 0.1% and also proposed for the Tazarotene Foam label by the sponsor:

“Tazarotene was non-mutagenic in the Ames assays (b) (4) and did not produce structural chromosomal aberrations in a human lymphocyte assay. Tazarotene was also non-mutagenic in the CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in the in vivo mouse micronucleus test.”

## 8 Carcinogenicity

No carcinogenicity study has been conducted with Tazarotene Foam. The following was duplicated from the labeling for Tazarotene Cream 0.1%:

“A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter-term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to 1.4 times the maximum  $AUC_{0-24h}$  in patients treated with 2 mg/cm<sup>2</sup> of tazarotene cream 0.1% over 15% body surface area (b) (4)

In evaluation of photo co-carcinogenicity, median time to onset of tumors was decreased, and the number of tumors increased in hairless mice following chronic topical dosing with intercurrent exposure to ultraviolet radiation at tazarotene concentrations of 0.001%, 0.005%, and 0.01% in a gel formulation for up to 40 weeks.

A long-term topical application study of up to 0.1% tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1.0 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals; (b) (4) (b) (4)

*Reviewer comments: The maximum  $AUC_{0-24}$  in patients treated with 2 mg/cm<sup>2</sup> of tazarotene cream 0.1% over 15% body surface area for fine wrinkling and mottled hyperpigmentation used in the Tazarotene cream label was 44 ng·hr/mL (tazarotenic acid).*

## 9 Reproductive and Developmental Toxicology

No reproductive and development toxicology study has been conducted with tazarotene foam. The following was duplicated from the labeling for Tazarotene Cream 0.1%:



(b) (4)

No effect on parameters of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through day 7 of gestation with oral doses of tazarotene up to 2.0 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose

(b) (4)

Reproductive capabilities of F1 animals, including F2 survival and development, were not affected by topical administration of tazarotene gel to female F0 parental rats from gestation day 16 through lactation day 20 at the maximum tolerated dose of 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat would be equivalent to (b) (4) times the (b) (4)

(b) (4)

Under **Pregnancy:** (b) (4) **Pregnancy Category X:**

(b) (4) The possibility that a (b) (4) of childbearing potential is pregnant at the time of institution of therapy should be considered. (b) (4)

(b) (4) There are no adequate and well-controlled studies in pregnant women. (b) (4)

(b) (4)

## 10 Special Toxicology Studies

**10.1. Tazarotene Foam 0.1%: Acute Eye Irritation Study in Rabbits (OEE00055):** Each of 3 male rabbits received a single dose of 0.1 mL Tazarotene Foam 0.1% (Lot 714/9/3) in the conjunctival sac of the right eye. The contralateral eye of each animal remained untreated and served as the control. Treated and control eyes were examined for signs of irritation at 1, 24, 48, and 72 hours following dosing. Treatment with Tazarotene Foam 0.1% caused conjunctivitis (redness) in 2 of 3 treated eyes at the 1 hour scoring interval. Complete resolution of the conjunctivitis occurred by the 24-hour scoring interval. According to the Kay and Calandra Evaluation Criteria, Tazarotene Foam (0.1%) was considered to be a non-irritant to the ocular tissue of the rabbit.

**10.2. Tazarotene Foam 0.1%: Acute Dermal Irritation Study in Rabbits (OEE00056):**

Five hundred  $\mu\text{L}$  of Tazarotene Foam 0.1% (Lot 714/9/3) was applied to each of two test sites (approximately 1 inch x 1 inch) on each of 6 male rabbits. One of the two test sites was abraded prior to dosing. The test article was held in contact with the skin under a semi-occlusive binder for an exposure period of 24 hours. Test sites were then examined and scored for dermal irritation at 1 hour and 1, 2, 3, and 7 days following patch removal. Slight erythema at 1/6 abraded test sites and well-defined erythema at 6/6 intact and 5/6 abraded test sites were seen at the 1-hour scoring interval. The dermal irritation resolved completely at all test sites by Day 7. Additional dermal findings included desquamation (3/6 intact test sites and 4/6 abraded test sites). Under the conditions of the test, the mean Primary Irritation Index was 1.96, indicating Tazarotene Foam 0.1% was mildly irritating to the skin of the rabbit. No biologically significant differences were observed between the intact and abraded skin in severity and duration of irritation.

**10.3. Tazarotene Foam 0.1%: Local Lymph Node Assay (515587):**

Eight female CBA/Ca mice received 25  $\mu\text{L}$  of undiluted Tazarotene Foam 0.1% (Lot 714/9/3) onto the dorsum of each ear once daily for 3 consecutive days. A second group of 5 females received tazarotene foam vehicle and served as controls. Three days later each animal received an intravenous injection of [ $^3\text{H}$ ]-methyl thymidine into the lateral tail vein and 5 hours later the draining lymph nodes were collected and the incorporation of tritiated thymidine was assessed by scintillation counting as disintegrations per minutes (DPM). There were no signs of systemic toxicity and no effects on body weights. As seen from the next table constructed by the reviewer, the stimulation index (SI) for the group treated with Tazarotene Foam 0.1%, when compared with the control group, was 2.4, indicating that Tazarotene Foam 0.1% would not be considered a sensitizer. The sponsor further stated that "The stimulation indices in a recent positive control study were 1.7, 2.7 and 8.3 for 5%, 10% and 25% hexylcinnamaldehyde, respectively."

Treatment	DPM	DPM (mean $\pm$ SD)	SI
Vehicle control	17435, 11641, 19366, 16410, 20241	17019 $\pm$ 1506	-
Tazarotene Foam 0.1%	38456, 47234, 44978, 30350, 48090, 37105, 40309, 39632	40769 $\pm$ 2079	2.4

*(Review comments: The measurement of DPM in each vehicle control animal was high in this study. In other LLNA studies this reviewer has reviewed, the DPM in control animals was less than a couple of thousand.)*

Tazorac Gel and Tazorac Cream were not phototoxic when tested in guinea pigs. Dermal safety studies in human subjects indicate negative results in both sensitization and photosensitization tests of Tazorac Cream. No absorption peaks were observed at 290 - 900 nm for the tazarotene foam vehicle. Nonclinical photoirritation evaluation is

not recommended for tazarotene foam. Dermal safety studies with Tazarotene Foam 0.1% have been conducted in humans.

## 11 Integrated Summary and Safety Evaluation

Tazarotene has been marketed for the treatment of acne vulgaris for over 14 years as Tazorac Gel, and for over 10 years as Tazorac Cream. Tazarotene foam is intended for the same indication, route of administration and duration of use as the Tazorac products.

Tazarotene is a prodrug. It is rapidly metabolized to the active metabolite, tazarotenic acid, which binds to nuclear retinoic acid receptors and activates retinoid-responsive genes. Pharmacokinetic evaluations following topical application of Tazarotene Foam were performed in the 28-day studies in mini-pigs and rats and in the 90-day study in rats. In these studies, a dose-related increase in systemic exposure of tazarotenic acid was seen and the systemic exposure levels of tazarotenic acid following topical application of Tazarotene Foam 0.1% were less than or comparable to those following topical application of Tazorac Gel 0.1%.

In addition to the toxicology studies submitted within NDAs 20600 (Tazorac Gel) and 21184 (Tazorac Cream) that the sponsor 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 with some histopathological findings, in a dose-dependent manner. The toxic effects seen in the Tazarotene Foam 0.1%-treated minipigs were less severe than those seen in the Tazorac Gel 0.1%-treated minipigs. It appears that rats were more sensitive to tazarotene foam than minipigs. Besides 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 local and systemic changes in Tazorac Gel 0.1%-treated rats were less severe than those seen in the Tazarotene Foam 0.1%-treated rats and comparable to those in the Tazarotene Foam 0.05%-treated rats.

Tazarotene was not genotoxic and not a carcinogen in rats and mice. However, it is a teratogen in rats, rabbits, and humans. 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. In addition, the study using LLNA indicated that Tazarotene Foam 0.1% would not be considered a sensitizer.

## 12 Appendix/Attachments

As requested, the sponsor submitted the following table for the animal multiples of human exposure in the nonclinical sections of the label.

**Table 1 Comparative Exposure in Oral and Topical Carcinogenicity and Reproductive and Developmental Toxicity Studies of Tazarotene Gel in Rats and Rabbits to Topical Application of Tazarotene Foam in Humans**

Species	Study Type	Route	Dose (mg/kg/day)	AUC <sub>de</sub> (ng·h/mL)	Animal AUC <sub>de</sub> / Human AUC <sub>0-tau</sub> <sup>a</sup>
Mouse	Carcinogenicity (Study 1643-ALG/025)	Oral	1	344	49.3
Rat	Embryo/Fetal Development (Study TX99039)	Topical	0.25	207	29.7
Rabbit	Embryo/Fetal Development (Study PK-95-034)	Topical	0.25	1160	166.2
Rat	Male Fertility (Study TX99103)	Oral	1	164	23.5
Rat	Female Fertility and General Reproduction (Study TX99104)	Oral	2	296	42.4
Rat	Embryo/Fetal Development (Study TX99039)	Oral	0.5	94	13.5
Rabbit	Embryo/Fetal Development (Study TX99023)	Oral	0.25	5300	759.3

<sup>a</sup> The mean human AUC<sub>0-tau</sub> for tazarotenic acid following 22 days of tazarotene foam 0.1% administration was 6.98 ng·hr/mL (Study W0260-105; filed with original application, sequence no. 0000).

However, this reviewer made some corrections and clarifications for the systemic exposure data available for the nonclinical toxicity studies conducted with tazarotene. The calculations for the animal multiples of human exposure recommended in the label of this drug product are shown in the next table.

Study Number	Species/ Study Type	Route	Dose (Tazarotene , mg/kg/day)	AUC (Tazarotenic acid, ng-hr/mL)	Reproductive / Developmental Toxicities	Multiple of Human Exposure *
1643-ALG/19/9 43062 <sup>a</sup>	Rat/ Carc	Oral (In Diet)	0.125 (NOAEL)	~13.9	NA	~2.0
1643-ALG/025	Mouse/ Carc	Topical	1 in Females (NOAEL)	344	NA	49
1643-SLS-3202.5 <sup>b</sup>	Rat / Segment II	Topical	0.25	107	Slight increase in number of dead pups; lower pup body weights; reduced skeletal ossification	15
1643-SLS-3202.9 (PK-95-0304)	Rabbit / Segment II	Topical	0.25	1160	Single incidences (1/20 litters) each of hydrocephaly, heart anomaly, spina bifida	166
98-4146	Rat / Segment II	Oral	2.0	207	Increased post-implantation loss; decreased live fetuses; malformations including exencephaly, pinna alteration, micro-/an-ophthalmia, microtia, facial papilla anomalies, cleft palate	30
			0.5	94	Increased skeletal alterations, including supernumerary ribs; two litters with cardiac anomalies	13
1643-SLS-3202.7 <sup>c</sup>	Rat / Segment I and III	Topical	0.125	53.1	No impairment of fertility; no effects on reproductive capabilities of F1 animals, including F2 survival and development	7.6
1643-SLS-3202.14 <sup>d</sup>	Rabbit / Segment II	Oral	0.2	2270	Increased pre- and post-implantation loss; malformations, including pinna anomalies, cleft palate, spina bifida, heart anomalies, skull anomalies, hyoid anomalies, tympanic ring anomalies	325
TX99103	Rat / Segment I - males	Oral	1	164	No impairment of mating performance or fertility	23

TX99104	Rat / Segment I - females	Oral	2	296	No effect on parameters of mating performance or fertility; decreased average number of estrous stages per 14 days; decreased number of implantation sites, decreased litter size, decreased number of live fetuses, and decreased fetal body weights; fetuses with exencephaly, open eyes, and/or meningocele in one litter	42
---------	---------------------------	------	---	-----	--	----

Carc: Carcinogenicity

\* This exposure multiple is based on the geometric mean value of  $AUC_{0-\tau}$  (6.98, ng-hr/mL) of tazarotenic acid in acne patients treated with 2 mg/cm<sup>2</sup> of tazarotene foam 0.1% over 15% body surface area.

<sup>a</sup> In the oral rat carcinogenicity study stated in the labeling, rats were treated with tazarotene in diet at the doses of 0.025, 0.05, or 0.125 mg/kg/day. A 3-month dietary study in rats (1643-ALG 18/920710) showed that AUC of tazarotenic acid was 10.7, 13.9, or 28.7 ng-hr/mL in rats treated with 0.05, 0.1, or 0.5 mg/kg/day, respectively. Therefore, the highest dose of 0.125 mg/kg/day in the long-term dietary study in rats was anticipated to give systemic exposure in the rat approximately 2 times the systemic exposure (AUC) in acne patients treated with 2 mg/cm<sup>2</sup> of tazarotene foam 0.1% over 15% body surface area (6.98 ng-hr/mL tazarotenic acid).

<sup>b</sup> Systemic exposure ( $AUC_{0-24h}$ ) to tazarotenic acid at topical doses of 0.25 mg/kg/day tazarotene in a gel formulation in rats was 107 ng-hr/mL (b) (4). (b) (4) 15 times the systemic exposure (AUC) in acne patients treated with 2 mg/cm<sup>2</sup> of tazarotene foam 0.1% over 15% body surface area. It is consistent with the labeling for Tazarotene Cream 0.1%: Systemic exposure ( $AUC_{0-24h}$ ) to tazarotenic acid at topical doses of 0.25 mg/kg/day tazarotene in a gel formulation in rats represented 2.4 times the maximum  $AUC_{0-24h}$  in patients treated with 2 mg/cm<sup>2</sup> of tazarotene cream 0.1% over 15% body surface area for fine wrinkling and mottled hyperpigmentation.

<sup>c</sup> In the fertility study and the pre- and post-natal developmental toxicity study, rats were treated with topical doses of tazarotene gel up to 0.125 mg/kg/day and the systemic exposure at 0.125 mg/kg/day was estimated from another study. Because the systemic exposure ( $AUC_{0-24h}$ ) to tazarotenic acid at topical doses of 0.25 mg/kg/day tazarotene in a gel formulation in rats was 107 ng-hr/mL (see above <sup>b</sup>), it was reasonable to estimate that the systemic exposure at 0.125 mg/kg/day was 53.5 ng-hr/mL, which was approximately 1.2 times of 44 ng-hr/mL, as stated in the label for Tazarotene Cream 0.1%, "the systemic drug exposure in the rat would be equivalent to 1.2 times the maximum  $AUC_{0-24h}$  in patients treated with 2 mg/cm<sup>2</sup> of tazarotene cream 0.1% over 15% body surface area for fine wrinkling and mottled hyperpigmentation." Actually, in a 3-month general toxicology study (1643C-3526-6) in rats treated topically with

tazarotene at 0.125 mg/kg/day in the cream formulation (0.05%), the systemic exposure ( $AUC_{0-24h}$ ) to tazarotenic acid was 53.1 ng·hr/mL, 7.6 times 6.98 ng·hr/mL. Therefore, the systemic exposure in the rat topically treated at 0.125 mg/kg/day would be equivalent to 7.6 times the systemic exposure in acne patients treated with 2 mg/cm<sup>2</sup> of tazarotene foam 0.1% over 15% body surface area.

<sup>d</sup> The developmental toxicities shown in the label of this drug product in rabbits treated orally with tazarotene were seen at the dose of 0.2 mg/kg/day [REDACTED] <sup>(b) (4)</sup> [REDACTED]. The AUC of tazarotenic acid was not 5300 ng·hr/mL as stated by the sponsor, but the AUC of tazarotenic acid at 0.2 mg/kg/day could be estimated from a dose-range study (SLS-3202.13), in which the AUC of tazarotenic acid was 77.9 or 2840 ng·hr/mL on Gestation Day 18 in rabbits treated with 0.05 or 0.25 mg/kg/day of tazarotene, respectively. The dose of 0.200 mg/kg/day was anticipated to give an AUC of tazarotenic acid of 2270 ng·hr/mL in the rabbit ( $2840 \text{ ng·hr/mL} \times 0.20 \text{ mg/kg/day} \div 0.25 \text{ mg/kg/day} = 2270 \text{ ng·hr/mL}$ ). It is 52 times the maximum  $AUC_{0-24h}$  in patients treated with 2 mg/cm<sup>2</sup> of tazarotene cream 0.1% over 15% body surface area for fine wrinkling and mottled hyperpigmentation (44 ng·hr/mL), as stated in the labeling for Tazarotene Cream 0.1%. Therefore, the multiple of human exposure in rabbits at the dose of 0.2 mg/kg/day was 325 times the AUC in acne patients treated with 2 mg/cm<sup>2</sup> of tazarotene foam 0.1% over 15% body surface area.

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

/s/  
-----

JIAQIN YAO  
02/29/2012

BARBARA A HILL  
02/29/2012  
I concur

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number:** 202428

**Applicant:** Stiefel  
Laboratories, Inc.

**Stamp Date:** July 29, 2011

**Drug Name:** Tazarotene  
Foam, 0.1%

**NDA Type:** 505(b)(1)

On initial overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		A right of reference letter is provided that allows the Agency to use the nonclinical toxicology data contained in NDA 20600 (Tazorac Gel) and NDA 21184 (Tazorac Cream) to support this NDA. Use of a right of reference letter makes this a 505(b)(1) NDA.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m <sup>2</sup> or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE?**     Yes    

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

N/A

Jiaqin Yao September 12, 2011  
 \_\_\_\_\_  
 Reviewing Pharmacologist Date

Barbara Hill See sign off date  
 \_\_\_\_\_  
 Team Leader/Supervisor Date

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

/s/  
-----

JIAQIN YAO  
09/12/2011

BARBARA A HILL  
09/19/2011