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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-184

Pharmacology Review(s)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:
Addendum to Review

DRAFT

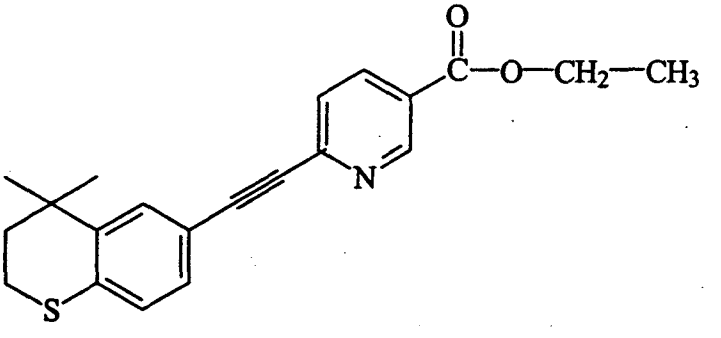
KEY WORDS: tazarotene, Tazorac cream, plaque psoriasis, retinoid
Reviewer Name: Amy Nostrandt
Division Name: Division of Dermatologic and Dental Drug Products
HFD# 540
Review Completion Date: 9/25/2000

Review number: second addendum to review no. 1
IND/NDA number: NDA 21-184
Serial number/date/type of submission: original submission, received 9/30/99
Information to sponsor: Yes ( ) No (X)
Sponsor (or agent): Allergan, Inc., Irvine, California
Manufacturer for drug substance: [redacted]

Drug:

Code Name: AGN 190168
Generic Name: tazarotene
Trade Name: Tazorac® (tazarotene) cream 0.05% and 0.1%
Chemical Name: ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate
CAS Registry Number: 118282-40-3
Molecular Formula/ Molecular Weight/Structure:

$C_{22}H_{25}NO_2S$
MW = [redacted]



Relevant INDs/NDAs/DMFs: all from Allergan

[redacted]

NDA 20-600 tazarotene 0.1 and 0.05% gels for psoriasis and acne

[redacted]

Drug Class: acetylenic retinoid

Indication: for the topical treatment of plaque psoriasis

Clinical formulation:

ingredient	%w/w 0.05% (9103X)	%w/w 0.1% (9087X)
tazarotene	0.050	0.10
benzyl alcohol NF	1.0	1.0
sodium thiosulfate USP (pentahydrate)		
edetate disodium USP		
mineral oil USP		
med. chain triglycerides		
carbomer 1342 NF		
sorbitan monooleate NF		
carbomer 934P NF		
sodium hydroxide NF		
purified water USP		
total:		
pH approximately		

Route of administration: topical to affected skin

Proposed clinical protocol or Use:

The label directions direct application of 2 mg of drug product per cm^2 of affected skin once daily.

Introduction

A minor change is recommended for the carcinogenicity section of the label. The results of the dermal carcinogenicity study in mice are described as they are in the label for tazarotene gel. It would be appropriate to specify in the label for tazarotene cream that the study was conducted using the gel formulation.

RECOMMENDATIONS:

The following wording is recommended for the carcinogenicity section of the tazarotene cream label:

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; untreated control animals were not completely evaluated. Systemic exposures (AUC_{0-12h}) at those doses were up to 3.9 times that (AUC_{0-24h}) seen in a human psoriatic patient treated with 0.1% tazarotene cream at 2 mg/cm^2 over 35% body surface area in a controlled pharmacokinetic study.

Amy C. Nostrandt, D.V.M., Ph.D.
Pharmacologist/Toxicologist

cc:
NDA 21-184
HFD-340
HFD-540
HFD-540/PHARM/Nostrandt
HFD-540/TLPHARM/Jacobs
HFD-540/MO/Ko
HFD-540/CHEM/Timmer
HFD-540/PMS/Bhatt
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Draft date (# of drafts): 9/25/00 (1)

Concurrence Only:
HFD-540/DD/WILKIN

HFD-540/TLPHARM/JACOBS

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: tazarotene, Tazorac cream, plaque psoriasis, retinoid
Reviewer Name: Amy Nostrandt
Division Name: Division of Dermatologic and Dental Drug Products
HFD# 540
Review Completion Date: 6/5/2000

JUN 13 2000

Review number: 1
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Serial number/date/type of submission: original submission, received 9/30/99
Information to sponsor: Yes (X) No ( )
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Manufacturer for drug substance: [redacted]

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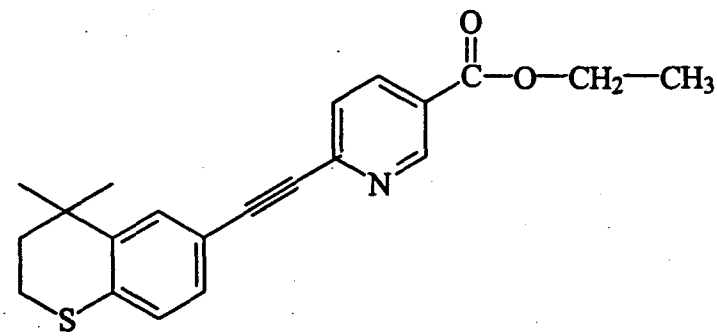

Relevant INDs/NDAs/DMFs: all from Allergan

IND [redacted]
IND [redacted]
NDA 20-600 tazarotene 0.1 and 0.05% gels for psoriasis and acne
IND [redacted]
IND [redacted]
IND [redacted]
IND [redacted]

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ingredient	%w/w 0.05% (9103X)	%w/w 0.1% (9087X)
tazarotene	0.050	0.10
benzyl alcohol NF	1.0	1.0
sodium thiosulfate USP		
edetate disodium USP		
mineral oil USP		
med. chain triglycerides		
carbomer 1342 NF		
sorbitan monooleate NF		
carbomer 934P NF		
sodium hydroxide NF		
purified water USP		
total:		
pH approximately		

Route of administration: topical to affected skin

Proposed clinical protocol or Use:

The label directions direct application of 2 mg of drug product per cm^2 of affected skin once daily. *Reviewer's comment: There is no wording limiting application to nighttime use (positive results were seen in photo co-carcinogenicity studies, and other retinoid products limit application to nighttime, including tazarotene gel) or to indicate the duration of use, although use in clinical trials was limited to 12 weeks. The sponsor indicates in the application that the drug may be used on unlimited percentage of total body surface area, which may have implications for systemic exposure to the drug and its comparison to that in animal studies.*

Previous clinical experience:

Two multicenter double-blind, randomized, vehicle-controlled phase 3 studies of tazarotene creams 0.1% and 0.05% in patients with plaque psoriasis were performed. Tazarotene cream was applied once daily for 12 weeks. The sponsor states that superior efficacy relative to the vehicle was noted as early as one week with the 0.1% formulation. Clinical improvement was reported to have been maintained during a 12-week follow-up period after discontinuation of treatment. The higher concentration was associated with earlier and greater efficacy and increased incidence of local adverse effects. Studies included patients with 2% to 95% total body surface area involvement, with a mean of 10.6% TBSA involved (*It is not clear how many trial subjects had a high percentage of body surface area involvement*). Adverse events most frequently involved the skin, including pruritus, erythema, burning skin, irritation, desquamation, rash, irritant contact dermatitis, stinging skin, dermatitis, worsening of psoriasis, skin pain, and eczema. Hypertriglyceridemia was seen in control and treated groups, and joint disorder was reported in treated groups in one study.

The application states that systemic bioavailability was 2-3% in a controlled clinical pharmacokinetic study of tazarotene cream 0.1% at clinical (2 mg/cm^2) and exaggerated (10 mg/cm^2) rates (*Reviewer's comment: It is interesting to note that in early in vitro and animal studies, the systemic availability of tazarotene and/or tazarotenic acid from these cream formulations was equal to or greater than that seen with tazarotene gel formulations. An initial controlled pharmacokinetic study was performed, but the results were not reported in this submission. A second controlled pharmacokinetic study that is reported here found systemic exposure that appears to be considerably less than that from comparable gel formulations.*) The maximum Cmax for subjects treated with 0.1% cream at 2 mg/cm^2 was 6.85 ng/ml and the maximum AUC was 88.3 ng•hr/ml, both at 15 days after the start of treatment. *Reviewer's comment: The exaggerated rate (10 mg/cm^2) is not relevant, as the thickness of the applied cream may limit the amount of drug substance available to the skin for absorption; application to larger body surface areas would have been more informative than application of larger amounts of drug product to a small area of skin.* The pharmacokinetic parameters for tazarotenic acid for the five patients treated with 0.1% tazarotene cream at the clinical rate of 2 mg/cm^2 for 14 days are shown in the table below.

Patient number	psoriatic involvement % TBSA on day 0	Dose on day 0 (g cream)	$AUC_{0\text{-}24h}$ (ng•hr/ml)	$AUC_{0\text{-}24h}$ extrapolated for 20% BSA (ng•hr/ml)	Cmax (ng/ml)	Cmax extrapolated for 20% BSA (ng/ml)
003	5	1.81	8.67	34.68	0.515	2.06
004	35	15.4	88.3	50.46	6.85	3.91
007	6	2.59	0.96	3.2	0.131	0.44
008	14	6.16	40.7	58.14	3.05	4.36
011	20	6.73	17.5	17.5	1.02	1.02
Mean				32.8		2.4

Reviewer's comment: The percent body surface area of psoriatic involvement did not change appreciably over the course of the study, and in some instances increased. Exposures were dose-proportional in most of the patients, but that proportionality did not hold for patients 007 and 011. The means for AUC and Cmax extrapolated for 20% BSA are 47.8 ng•hr/ml and 3.4 ng/ml, respectively, if values for those two patients are omitted from the calculation. It is unclear what contribution the sites treated might have made to this variability, or if differences might be attributable to washing off of the material.

Because of the small number of patients in the controlled pharmacokinetic study, and because the drug is to be used over an unlimited percentage of body surface area, the values determined for patient 004 (highest BSA psoriatic involvement, 35%) for AUC and Cmax are used below to calculate multiples of exposure for comparison between human use and animal studies.

Phototoxicity and photoallergy studies in human subjects were reported to have been negative, although they were performed using UVA irradiation only. The sponsor states their intention to repeat the photoallergy study using UVB and UVA irradiation. In cumulative irritation studies, irritation scores consistent with effects of other retinoids and with tazarotene gels were seen. Irritation was greater with higher concentrations of tazarotene. Results of the repeat-insult patch test were negative.

Disclaimer : Note that some information may come directly from the sponsor's submitted material.

Introduction and drug history:

Tazarotene gel formulations are currently approved for topical treatment of stable plaque psoriasis (0.05% and 0.1%) and moderate facial acne vulgaris (0.1%). The sponsor has developed the cream formulation that is the subject of the current NDA as an alternative to the approved drug.

Studies reviewed within this submission:

Pharmacology studies:

1. Study BIO-96-116: Evaluation of tazarotene creams in the rhino mouse.

Pharmacokinetics/Toxicokinetics:

1. Wester RC and Maibach HI. In vivo animal models for percutaneous absorption. In Models in Dermatology, vol.2, HI Maibach and FN Marzulli, eds. Karger, Basel, 1985, pp 159-169.
2. Study PK-98-P009: Skin distribution of 0.1% (w/w) ^{14}C-tazarotene cream in the Hanford minipig after daily topical application to the skin for 1, 5, and 7 days.

Toxicology studies:

3. Study TX99008: Tazarotene cream containing 0.1% sodium thiosulfate or ascorbic acid: A 1-month comparative topical skin toxicity study in Sprague-Dawley rats.

Special Toxicology studies:

5. Study TX99018: Tazarotene cream: A single dose ocular irritation study in New Zealand White rabbits

Studies <u>not</u> reviewed within this submission:

The following studies have been reviewed previously and/or are summarized or the reviews reproduced in the appropriate sections below:

Pharmacokinetics/Toxicokinetics:

- The screening of tazarotene (AGN190168) cream formulations by determining the *in vitro* skin penetration of tazarotene through human cadaver skin.

Toxicology studies:

Previously reviewed under [redacted]

1. Study 1643C-3526-6: Tazarotene cream: A three month topical skin toxicity study in Sprague-Dawley rats with a one month recovery period.
2. Study 575A-601-234-97: A three-month topical skin and systemic safety study of tazarotene cream in Sinclair miniswine with a 1-month recovery period.

Special Toxicology studies:

Previously reviewed under [redacted]

1. Study #0424XA08.001: Tazarotene cream: Delayed contact hypersensitivity in guinea pigs (Buehler method)
2. Study #0432GA08.001: Tazarotene cream: Phototoxicity test in guinea pigs
3. Study # 0458XA08.002: Tazarotene cream: Photoallergy study in guinea pigs

Previously reviewed under [redacted]

4. Study #TX97011: Tazarotene cream: comedogenicity study in rabbits

PHARMACOLOGY:

The drug substance, tazarotene, is a prodrug. It is rapidly metabolized to the active metabolite, tazarotenic acid (AGN 190299). Tazarotenic acid, but not the parent drug, binds to nuclear retinoic acid receptors (RAR's) and activates retinoid-responsive genes. Nuclear retinoic acid receptors are members of the nuclear receptor gene superfamily which includes steroid hormone receptors. The sponsor states that tazarotenic acid is relatively selective for RAR_β and RAR_γ relative to RAR_α. Neither tazarotene nor tazarotenic acid bind significantly to retinoid X receptors (RXR's).

In the hairless mouse, retinoids block induction of ornithine decarboxylase (ODC) activity induced by 12-O-tetradecanoylphorbol 13-acetate (TPA). The sponsor claims that tazarotene is more potent in this function than tretinoin or tazarotenic acid. (*Reviewer's comment: This claim was made for the parent drug, and it was claimed that tazarotene was 10 times more potent than tazarotenic acid in eliciting this effect. This may indicate that the effect is not RAR-mediated. The sponsor attributes this difference to greater penetration of the prodrug into the skin with rapid activation by ester hydrolysis in the skin.*) The sponsor states that ornithine decarboxylase activity is elevated in psoriatic plaque and is presumably responsible for epidermal hyperplasia in psoriasis.

The efficacy of tazarotene creams in reduction in size of keratin-filled utriculi in female rhino mice was evaluated (Study #BIO-96-116). Tazarotene cream formulations of 0.01%, 0.05%, and 0.1% were compared to tazarotene gel and cream vehicle. Doses were 50 µl/animal of the respective formulation. Most experiments involved topical application three times per week for one to two weeks. The report states that efficacy and irritation (flaking and abrasion at the treated site) of tazarotene creams were equivalent to that of tazarotene gels of the same concentration. Effects on skin smoothing, utriculus diameter reduction, and skin irritation were concentration-dependent.

Tazarotene was reported to be more irritating to the skin than equivalent doses of tretinoin in the hairless mouse. As noted in the review of IND ——— , splenomegaly was observed in hairless mice after treatment with either 0.1% tazarotene gel or one of the 0.1% tazarotene creams.

In the Yucatan minipig, daily topical application of tazarotene cream under occlusion resulted in a loss of barrier function, as evidenced by trans-epidermal water loss (TEWL). The effect was first seen one to two weeks after the start of treatment, and was somewhat greater than the effect of Retin A® cream at the same concentration.

The sponsor states that tretinoin is more potent than tazarotene in the induction of epidermal hyperplasia, and that binding to RAR receptors is required for this effect.

In cell culture and *in vitro* models of skin, tazarotene is reported to suppress expression of MRP-8 (macrophage inhibitory factor related protein-8) and skin-derived antileukoproteinase (SKALP), markers of inflammation in skin that are present in high levels in the epidermis of psoriasis patients. The sponsor also cites a study where this marker was reduced in psoriatic plaque of patients treated with tazarotene gel. In human keratinocyte cultures, tazarotene inhibits cornified envelope formation.

The sponsor reports that three tazarotene-induced genes (TIG 1 through 3) have been identified *in vitro*. TIG1 is reported to be a putative transmembrane protein that is upregulated by tazarotene and tretinoin in skin fibroblasts and keratinocytes. TIG2 is a protein expressed in epidermis that is up-regulated by tazarotene in skin raft cultures and in psoriatic plaque. TIG3 is reported to be homologous to the class II tumor suppressor gene *H-rev* 107, and to have been shown to inhibit proliferation in cultured cells. After psoriasis patients were treated for two weeks with topical tazarotene, induction of TIG3 was seen in psoriatic plaque, as was decreased

expression of the inflammatory markers, HLA-DR and ICAM-1 in the epidermis (by an unknown mechanism).

The sponsor reports that tazarotene and tazarotenic acid inhibit activity of nuclear factor AP-1, as does tretinoin. AP-1 binding to DNA is involved in induction of inflammatory and hyperproliferative events. The sponsor states that RAR-mediated inhibition of this factor is expected to have anti-inflammatory and anti-proliferative effects (*Reviewer's comment: The sponsor has demonstrated that the parent drug does not bind or activate RAR's, and should not be able to inhibit AP-1 activity by that mechanism directly).* Other targets for tazarotene inhibition are stromelysin-1, a protease involved in inflammation and tissue remodeling, keratin 6, an intermediate filament protein highly expressed in hyperproliferative epidermis, and transglutaminase 1, which is over-expressed in psoriasis.

SAFETY PHARMACOLOGY:

The sponsor states that tazarotene was inactive in assays of physiological function in animal models of CNS, circulatory, respiratory, renal and GI tract function after subcutaneous injection of up to 2.5 mg/kg, resulting in serum levels of tazarotenic acid up to ——— mice and —— in dogs. After a 12-day topical exposure in hairless mice, tazarotene induced splenomegaly and uterine atrophy (the sponsor states that tretinoin results in similar effects.)

In isolated guinea pig ileum, —— tazarotenic acid produced a small but significant (24%) inhibition of serotonin-induced contraction and 95% inhibition of nicotine-induced contraction. The sponsor states that this concentration is approximately four orders of magnitude higher than those recorded in patients receiving topical tazarotene.

PHARMACOKINETICS/TOXICOKINETICS:

Most nonclinical pharmacokinetic information is cross-referenced from studies performed to support applications for tazarotene gels.

Absorption:

The sponsor studied the *in vitro* skin penetration of tazarotene creams through human skin mounted in Franz diffusion cells relative to the penetration of gel formulations. The cream formulations chosen for continued development demonstrated equivalent or slightly greater skin penetration than the respective gel formulations. The sponsor states that percutaneous absorption results in prolonged drug retention in the skin, supporting a once daily dosing regimen.

The following literature reference was provided:

Wester RC and Maibach HI. In vivo animal models for percutaneous absorption. In Models in Dermatology, vol.2, HI Maibach and FN Marzulli, eds. Karger, Basel, 1985, pp 159-169.

Percutaneous absorption was reviewed in various laboratory species in comparison to man. While absorption through the skin was often greater in the rabbit, rat and guinea pig than in man, it was similar between man and minipigs and monkeys (squirrel and rhesus). One study cited in the review was performed in dogs. In that study, percutaneous absorption characteristics in the skin of the dog was such that less material was absorbed than in man. At least one study comparing human skin to that of the hairless mouse *in vitro* showed "remarkable similarities in absorption for the skin of the two species for many compounds." An additional conclusion of the review was that relative permeability depended not only on species, but also on skin location and method of hair removal.

Distribution:

Tazarotenic acid is bound extensively (over 99%) to plasma proteins. The Vd is approximately 0.5 L/kg for the mouse, rat, hamster, rabbit, and monkey. ^{14}C-tazarotene was studied in tissue distribution studies in rats. The highest radioactivity was found in adrenals, liver, ovary, and spleen after iv dosing. By 48 hours post dose, tissue to plasma concentration ratios for those organs were 14-94. After topical application, liver, skin and gastrointestinal tract had significantly higher radioactive concentrations than plasma. In monkeys, 10 days after a single topical dose, the highest percent of the dose was found in liver. After a single oral dose to pregnant rabbits, the greatest fetal concentrations were seen at 8 hours, with maximal concentrations in fetal heart (*Reviewer's comment: The localization of tazarotenic acid in the fetus may be somewhat dependent on gestation time. Since retinoid receptors are important in developmental signaling, their concentration in a particular tissue at a given point in gestational time may influence the sites in the fetus where tazarotene or its derivatives may be found at that stage.*) When administered to pregnant rats, a single dose resulted in tazarotenic acid concentrations in the fetus. The drug was also secreted in the milk of treated rats.

Study PK-98-P009 was a pharmacokinetic study of "Skin distribution of 0.1% (w/w) ^{14}C-tazarotene cream in the Hanford minipig after daily topical application to the skin for 1, 5, and 7 days." Single and multiple topical administration of 0.07% tazarotene cream was made to seven 5-cm^2 dosing sites on each of three male minipigs. Doses were applied for 1, 5, and 7 days, and each daily dose removed at 24 hours. Additional sites were treated for 7 days, then sampled after weekly washout periods for up to four weeks. Twenty-four hours after a single dose, 11.8%, 4.69% and 4.58% of the administered radioactivity was found in stratum corneum, epidermis and dermis, respectively (82.8% of total radioactivity was recovered), and tissue concentrations were 80.6, 10.5, and 0.412 µg-eq/g, respectively. Drug accumulation occurred in each skin layer over time. Tissue concentrations at the timepoints sampled and their decline during the washout period are shown in the table below:

Timepoint	Stratum corneum (µg-equiv/g)	Epidermis (µg-equiv/g)	Dermis (µg-equiv/g)
Day 1	80.6 ± 51.7	10.5 ± 4.5	0.412 ± 0.460
Day 5	316 ± 177	48.3 ± 4.22	0.206 ± 0.086
Day 7	573 ± 200	76.8 ± 38.7	0.732 ± 0.370
Day 7 – 1 week washout	94.3 ± 46.9	9.63 ± 4.64	0.119 ± 0.036
Day 7 – 2 week washout	42.1 ± 13.8	5.54 ± 7.27	0.0474 ± 0.0548
Day 7 – 4 week washout	13.7 ± 1.9	0.962 ± 0.040	0.0174 ± 0.0042

The rate of decline of tissue concentrations was greatest in the first week after the end of treatment. The apparent half-life of radioactivity in the skin layers was 5 days. Radiolabel was found in skin tissues located between the dosing sites, outside of the protective rings that had been applied to keep the administered dose in place, indicating lateral movement of the material within the skin layers.

Metabolism: The sponsor reports that the metabolism of tazarotene is similar in animals and man. Metabolism of ^{14}C-AGN 190168 was evaluated in a number of studies in mouse, rat, pig,

monkey and human, after topical, iv, and/or oral administration. Metabolism was qualitatively similar across species. Tazarotene undergoes ester hydrolysis to form tazarotenic acid, the active form of the drug. The parent compound and tazarotenic acid also undergo oxidation to form sulfoxide and sulfone metabolites. The major urinary metabolite in most animal species was the sulfoxide of tazarotenic acid. Metabolites found in feces were tazarotenic acid, the sulfone of tazarotenic acid, and a polar metabolite identified as an oxygenated derivative of tazarotenic acid. In studies in rats and humans, there was no apparent induction of hepatic drug metabolizing enzymes.

Elimination: The parent drug is not excreted unchanged. The major excretion pathway in the rat was biliary, but urinary and fecal excretion pathways appeared to be equally important in monkeys and man.

TOXICOLOGY:

Two three-month toxicology studies of topically applied tazarotene cream were performed in support of the use of tazarotene cream formulations. Reviews of these studies are reproduced below from the reviews of [redacted] serial #000, 008, and 012. A one-month bridging study was performed in rats to support a change in the cream formulation and is reviewed as study #3 below.

1. **Study title:** Tazarotene cream: A three month topical skin toxicity study in Sprague-Dawley rats with a one month recovery period.
Study number: 1643C-3526-6
Performing organization: Allergan, Irvine, CA
Drug lot and batch: vehicle cream, formulation 8918X, lot no. 454;
0.025% tazarotene cream, formulation 9067X, lot no. 453;
0.05% tazarotene cream, formulation 8880X, lot no. 456;
0.1% tazarotene cream, formulation 8881X, lot no. 455.
Date of study: 2/25/97-6/26/97
GLP compliance: yes
Study design:
Dosing: once daily, topical to shaved skin on the back (10% body surface area) for 91-92 days; remaining test material was removed with a gauze wipe at the end of the 6 hour exposure period. Animals were collared during the exposure period to prevent ingestion of the test material.
Dose groups: untreated control, vehicle control, 0.025%, 0.05%, and 0.1% cream (0.05, 0.125, 0.25 mg/kg/day, or 0.3, 0.75, and 1.5 mg/m^2/day, respectively)
Formulation: see above
Test animals: Sprague-Dawley rats, 15/sex/group, 5 of which underwent a 4 week recovery period, plus 16/sex/group designated as toxicokinetic satellite animals. All were approximately 8 weeks old at the initiation of dosing.
Findings:
Deaths: none related to treatment.
Clinical signs: Dose-dependent skin irritation, consisting of erythema and edema was observed in tazarotene-treated animals at the application site. Severity ranged from very slight to severe for erythema and very slight to moderate for edema. There was a dose-related incidence of scabs, fissures, and flaking/scaling at the treatment site and hardening of the

treatment site. Males appeared slightly more affected than females. Improvement was documented during the 4 week recovery period. After day 116, daily clinical observations of females revealed no apparent abnormalities.

The mean body weights for mid- and high dose males were significantly less than control beginning weeks 11 and 9, respectively, through the end of treatment. Both groups tended to be lower than control beginning day 21. Mean body weight for high dose females was significantly lower than controls during the last two weeks of the treatment period, although a tendency toward lower body weights in that group was evident as early as day 42. No significant differences were seen in recovery period body weights. No biologically significant differences were seen in food and water consumption.

Ophthalmologic findings: (examinations performed pre-test, week 13, and week 17)
No significant test article-related effects were noted upon ophthalmological examination.

Clinical chemistry and hematology: (urine samples collected during week 4, week 13, and week 17; blood samples collected at week 13 and week 17)

Hematologic changes included decreased RBC counts, hemoglobin, and hematocrit in high dose males at the end of the treatment period. Neutrophils were increased in mid- and high dose males (absolute and %) and in high dose females (%). The percent lymphocyte count was decreased mid- and high dose males. No treatment-related hematologic changes were seen after the recovery period.

Serum chemistry changes included dose-dependent decreases in albumin and cholesterol at all tazarotene doses. Serum protein was decreased in high dose animals and the mean albumin/globulin ratio was decreased in mid and high dose males and all tazarotene-treated female groups. Alkaline phosphatase was increased in the mid and high dose groups. In high dose males, serum ALT and AST activities were significantly increased. The mean BUN and BUN/creatinine ratio were significantly increased in high dose males. Most of these alterations appeared to be reversible after the recovery period. Mean serum ALT, AST, and LDL were high in mid-dose males, but variability in that group was so high that the differences were not significant. Mean serum phosphorus was significantly increased in that group as well, but was within normal limits.

No adverse effect was noted on urinalysis at any time point.

Pharmacokinetics: (blood samples collected at 0 (pre-dose), 3, 6, 9, 12 and 24 hours post dose from 8 rats/sex/group during weeks 2 and 12), separate reports PK-97-021 and PK-97-039, analysis by —— quantitation range ———— of tazarotenic acid (AGN 190299).

A dose dependent increase in systemic exposure to tazarotenic acid was seen after topical application. There were no apparent gender differences. No tazarotenic acid was detected in control animals. Values obtained in this study were comparable to or higher than those obtained in repeat-dose rat studies of tazarotene gels, reviewed under NDA 20-600.

Formulation:		0.025% cream	0.05% cream	0.1% cream
Dose:	Week	0.05 mg/kg/day	0.125 mg/kg/day	0.25 mg/kg/day
Cmax (ng/ml)[a]	2	1.59 ± 0.66	4.42 ± 2.43	10.5 ± 7.0
	12	1.22 ± 0.74	2.89 ± 4.02	11.4 ± 10.9
Tmax (hr)	2	12	9	6
	12	12	6	6
$AUC_{0\text{-}24hr}$ (ng• hr/ml)[b]	2	21.2 ± 1.9	53.1 ± 4.8	96.8 ± 12.1
	12	20.1 ± 2.3	49.1 ± 5.2	111 ± 15
half-life (hr)	2	6.32	7.84	7.37
	12	NC[c]	NC[c]	8.34

[a]mean ± SD
[b]mean ± SEM
[c]not calculable, no discernible decline in terminal phase
Reviewer's note: No discernible decline in the terminal phase was also noted in the 3-month study in miniswine at the later time point.

Organ weights: Mean adrenal weight relative to body weight was significantly increased in mid- and high dose males (absolute adrenal weight in high dose males was increased but not statistically significant), and mean relative heart, kidney, and pituitary weights in high dose males at the end of treatment were increased. These changes were not evident at the end of the recovery period; the sponsor attributed these changes to the stress of skin irritation.
Pathological examination: No treatment-related gross necropsy lesions were seen at the end of the treatment or recovery periods.

Complete histopathological examination was performed for the vehicle and high dose groups. Additionally, liver and stomach from mid and low dose were examined at the end of the treatment period and from all tazarotene-treated and vehicle groups at the end of recovery. No histopathological examination was performed for untreated controls.

Microscopically, local skin effects consisting of acanthosis, parakeratosis, erosion, ulceration, and edema/hemorrhage were noted in all treated animals. The severity was dose-dependent ranging from minimal to moderate, with one high dose female exhibiting marked edema/hemorrhage. At the end of the recovery period, acanthosis was observed in some low dose and most mid and high dose animals, and was dose-related in severity (minimal to mild). Mild irritation was reported in one rat each at the mid- and high dose. One high dose female had minimal parakeratosis.

Acanthosis of squamous epithelium of the non-glandular stomach in several mid- and high dose animals was reported and presumed to be due to ingestion of the test material. This finding reversed after the recovery period. Vacuolization of hepatocytes was observed in most animals, including vehicle controls. Patterns of this lesion included both periportal and centrilobular distribution. The former pattern was slightly higher in incidence in high dose

animals relative to vehicle controls. Similar changes were observed in recovery animals, but the significance is uncertain, due to the low numbers of animals examined at that time point.

The NOEL for systemic toxicity was reported to be 0.05 mg/kg/day, using 0.025% cream (0.3 mg/m^2/day), but changes were seen at that dose in serum albumin and cholesterol. The NOEL for cutaneous effects was not determined. Most effects seen at all topical doses appeared to be reversible.

2. **Study title:** A three-month topical skin and systemic safety study of tazarotene cream in Sinclair miniswine with a 1-month recovery period.
Study number: 575A-601-234-97
Performing organization: [redacted]
Drug lot and batch: 454 and 461 (vehicle), 453 and 462 (0.025%), 456 and 463 (0.05%), 455 and 464 (0.1%)
Date of study: 3/6/97-7/8/97
GLP compliance: yes
Study design:
Dosing: topically, twice daily (at least 7 hours between doses) to clipped areas of the back (10% body surface area); remaining test material was removed with a gauze wipe prior to the morning dose. Dosing was for 91 (non-recovery males and all recovery animals) or 92 (non-recovery females) consecutive days.
Dose groups: vehicle, 0.05 (0.025% cream), 0.125 (0.05% cream), and 0.25 (0.1% cream) mg/kg/day (0, 1.75, 4.375, 8.75 mg/m^2/day); half of the dose was applied in the morning and the other half was applied approximately 7 hours later.
Formulation: tazarotene creams, vehicle (8918X), 0.025 % (9067X), 0.05% (8880X), and 0.1% (8881X).
Test animals: Sinclair miniswine, 5-8 months of age at the start of the study, 6/sex/group. Physical exams were performed pretest, at week 5, at the end of treatment, and at the end of the recovery period. Skin irritation scoring was performed daily. At the end of the treatment period, 4/sex were euthanized by sodium pentobarbital injection and necropsied; the remaining 2/sex were euthanized after a 1-month recovery period and necropsied. Histological examination was performed of normal and treated skin and lesions from all groups, and of tissues and organs from vehicle and high dose groups.
Findings:
Deaths: none
Clinical signs: Skin irritation was noted in all tazarotene-treated groups, and was progressive and dose-dependent. Severity ranged from slight to severe skin irritation. Local signs included erythema, papules by week 2, followed by serum exudation and scabbing by week 3, cracks, and fissures. The numbers of papules and scabs were higher at higher doses. At the end of 4 weeks, animals in 0.025% concentration group had slight to moderate irritation, most animals in the 0.05% and 0.1% concentration groups had moderate to severe irritation in which scabs covered most of the application area, with cracks and fissures present. Lesions were more severe in females at the low dose, and there was no gender difference in severity at the mid- or high doses. By week 7, all high dose animals exhibited severe skin irritation that persisted through the end of treatment. Most mid-dose animals at that time had skin irritation that was graded as severe, and the rest in that group were graded as marked. Skin reactions in the low dose group continued to progress through week 8 or 9 at which time most were graded as marked, with a few graded as moderate irritation. No signs of irritation were seen in vehicle-treated animals. After discontinuing treatment, rapid improvement in skin reactions was seen in

all groups. At the end of the recovery period, low dose animals had no (2/4) or only slight (2/4) skin irritation. Mid dose animals had slight (3/4) or moderate (1/4) irritation. In the high dose group, skin irritation scores were slight (1/4), moderate (1/4), or marked (2/4). No signs of systemic toxicity were seen.

Clinical chemistry and hematology: (samples collected pretest and during week 4, week 13, and week 17)

No biologically significant treatment-related effects were seen on hematology, serum chemistry, or urinalysis at week 4.

At week 13, WBC counts in mid and high dose females were significantly increased, with percent neutrophils increased and percent lymphocytes decreased for high dose females. The sponsor hypothesizes that these effects were treatment-related and compensatory for secondary bacterial infection of treated and irritated skin. Platelets were increased in high dose females. WBC and platelets were also increased for high dose males, but the difference from control was not significant. The absolute counts for these values were within normal limits for domestic swine and do not appear to be biologically significant.

Serum chemistry changes at week 13 included decreased serum alkaline phosphatase activity in high dose females, increased total protein and globulin with decreased albumin:globulin ratio in mid and high dose females, decreased albumin:globulin ratio in low dose females (this was thought to be due to loss of serum and electrolytes through skin damaged by the test article), and increased potassium and decreased albumin:globulin ratio in high dose males. Other significant findings included decreased total bilirubin in high dose males and increased sodium in mid-dose males, but these values were within normal limits for domestic swine.

At week 17, WBC counts in mid-dose females were still higher than, but more near to control, and the percent neutrophil count in high dose females was greater than control. Serum chemistry evaluation revealed persistent effects on total protein, globulin and albumin:globulin ratio in mid- and high dose males and females. Total bilirubin was increased in high dose males. There were no biologically significant urinalysis findings.

Pharmacokinetics: (blood samples collected on days 14 and 89 at 0 (pre-dose), 2, 4, 7 (pre-second dose), 10, 16, and 24 hours post dose, from 11-12 animals/group), separate report PK-97-027, analysis by: _____

No gender differences were noted. Analysis revealed dose-related systemic exposures to tazarotenic acid. No tazarotenic acid was detected in samples from control animals. The sponsor states that pharmacokinetic profiles were consistent with those of the gel formulation. Pharmacokinetic parameters for tazarotenic acid (AGN 190299) are summarized below:

Formulation:		0.025% cream	0.05% cream	0.1% cream
Dose:	Day	0.05 mg/kg/day	0.125 mg/kg/day	0.25 mg/kg/day
Cmax (ng/ml)	14	0.259 ± 0.104	1.30 ± 0.70	1.72 ± 0.92
	89	0.386 ± 0.066	1.57 ± 0.73	3.74 ± 2.11
Tmax (hr)	14	5.05 ± 3.99	1.67 ± 1.88	1.91 ± 3.42
	89	5.20 ± 4.13	NC	NC
$AUC_{0\text{-}24hr}$ (ng• hr/ml)	14	4.78 ± 2.15	20.8 ± 12.0	29.9 ± 16.1
	89	7.12 ± 1.30	27.6 ± 11.8	61.5 ± 31.2

NC=not calculable due to lack of decline in terminal phase

Organ weights: At the end of the 3 month treatment period, low and high dose females had significantly lower body weights, and low dose females had a significantly higher mean relative heart weight. Absolute and/or relative heart, kidney, and liver weights in treated groups appeared to be greater or less than control, but there was no apparent dose-relationship or statistical significance.

Pathological examination: No systemic effects were reported at any dose level. No dermal effects were seen in the vehicle control group. Tazarotene creams caused minimal to marked irritation of the skin with acanthosis, dermal inflammatory cell infiltrate, cellular debris on the surface, neutrophilic cellular infiltration, and focal erosion, ulceration, and/or dermal fibrosis in a dose-related manner. After recovery, skin histopathology was reported as not remarkable for all low dose and 1/4 mid-dose animals. Residual skin effects were reported for 3/4 mid-dose and 4/4 high dose animals, but some improvement was evident.

The NOEL for systemic toxicity was reported to be 0.25 mg/kg/day (8.75 mg/m^2/day) with tazarotene 0.1% cream. A NOEL for local toxicity was not determined.

3. Study Title: Tazarotene cream containing 0.1% sodium thiosulfate or ascorbic acid: A 1-month comparative topical skin toxicity study in Sprague-Dawley rats.

Study No: TX99008
Amendment #, Vol #, and page #: NDA 21-284, original submission, vol. #8, page #8 284
Conducting laboratory and location: Allergan, Irvine, CA
Date of study initiation: 2/23/99
GLP compliance: yes
QA- Report Yes (X) No ( )
Methods: -
Dosing:

- species/strain: Sprague-Dawley (Crl:CD®(SD) IGS BR)rats
- #/sex/group or time point: Six groups of 10/sex/group
- age: approximately 9 weeks
- weight: 271-341 g (males), 185-240 g (females)

- satellite groups used for toxicokinetics or recovery: An additional four (vehicle-treated) or eight (tazarotene-treated) rats per group were used for pharmacokinetic determinations.
- dosage groups in administered units: 0.125 or 0.25 mg/kg/day tazartotene cream formulations (0.05% or 0.1% tazarotene, respectively) containing either 0.1% sodium thiosulfate or ascorbic acid. Control groups were treated with vehicle creams containing either 0.1% sodium thiosulfate or ascorbic acid. All groups received equivalent volumes of test material (0.25 g/kg/day).
- route, form, volume, and infusion rate: The test article was applied topically to shaved areas of the back (approximately 20% BSA) daily for 6 hours for 28 days. Animals wore Elizabethan collars during the exposure period. At the end of each daily exposure period, residual material was removed using water and gauze.

Drug, lot#, radiolabel, and % purity:
- vehicle cream containing 0.1% sodium thiosulfate, formulation 9104X, lot #11350
- 0.05% tazarotene cream containing 0.1% sodium thiosulfate, formulation 9103X, lot #11345
- 0.1% tazarotene cream containing 0.1% sodium thiosulfate, formulation 9087X, lot #11346
- vehicle cream containing 0.1% ascorbic acid, formulation 8918X, lot #461
- 0.05% tazarotene cream containing 0.1% sodium thiosulfate, formulation 8880X, lot #463
- 0.1% tazarotene cream containing 0.1% sodium thiosulfate, formulation 8881X, lot #464

Formulation/vehicle: see above

Observations and times:
- Mortality: Observations were made at least once daily.
- Clinical signs: Main study group rats were observed for clinical signs at least once daily and were graded for skin irritation once daily at the time of collar removal.
- Body weights: Body weights were determined prior to randomization, on day 1 prior to treatment and weekly thereafter. Body weights for main study group animals were also determined on the day prior to sacrifice.
- Food consumption: Food consumption was determined weekly for main study group animals only.
- Ophthalmoscopy: Both eyes of main study group animals were examined by direct opthalmoscopy after application of a topical mydriatic (1% tropicamide) prior to the start of the study and during week 4.
- EKG: not performed
- Hematology: Blood samples were collected from the abdominal aorta from overnight fasted main study animals under surgical anesthesia immediately prior to necropsy for hematology evaluation.
- Clinical chemistry: Blood samples were collected from the abdominal aorta from overnight fasted main study animals immediately prior to necropsy for serum chemistry evaluation.
- Urinalysis: not performed
- Organ weights: Absolute and relative organ weights were determined at necropsy.
- Gross pathology: Main study group animals were euthanized by exsanguination and subjected to gross necropsy after 4 weeks of treatment.
- Organs weighed: adrenal glands, brain, heart, kidneys, ovaries, spleen, testes, and liver
- Histopathology: Preserved tissues were examined from vehicle and high dose groups only. Tissues were collected from low dose groups and retained. Tissues collected were: adrenal glands, aorta, bone/bone marrow (femur, tibia, knee joint), brain,

cervix, diaphragm, epididymides, eyes, gastrointestinal tract (esophagus, stomach, duodenum, jejunum, ileum, cecum, colon), heart, kidneys, liver, lungs, lymph nodes (cervical, mesenteric), mammary gland area (with skin), ovaries, pancreas, pituitary gland, prostate gland, salivary glands (parotid, submaxillary), sciatic nerve, seminal vesicle, skeletal muscle (thigh), skin (treatment site), spinal cord (thoracic), spleen, sternum, testes, thymus, thyroid gland with parathyroids, tissues with lesions, tongue, trachea, urinary bladder, uterus, and vagina.

- Toxicokinetics: Blood samples were drawn from the retroorbital sinus in toxicokinetic satellite group animals on days 22 and 23 of the treatment period. Vehicle treated animals were bled at 0 (pre-dose), 6 and 9 hours post-dose. Treated animals (4 rats/time point) were bled at 0, 3, 6, 9, 12, and 24 hours post-dose. Blood was analyzed for tazarotenic acid using a validated [redacted] of tazarotenic acid (AGN 190299). Cmax, Tmax, and AUC were determined.
- Other: Statistical evaluations (means, standard deviations, ANOVA, and Duncan's test) were performed on body weight, food consumption, hematology, serum chemistry, and organ weight data for main study group animals.

Results:

- Deaths: none
- Clinical signs: Treatment-related observations were limited to skin irritation. Both tazarotene formulations resulted in dose-dependent irritation, consisting of slight to moderate erythema in all tazarotene-treated groups and and slight edema in both high dose groups. Signs of irritation were first observed in the middle of the first week of treatment, increased in severity through the second and third weeks, and remained stable over the fourth week. No irritation was noted with either vehicle cream. Animals treated with 0.05% creams exhibited very slight erythema that progressed to mild erythema by weeks 2 and 3. Some diminution of erythema was seen in the fourth week. Flaking, scaling, and scabs were also noted at the treatment sites. In groups treated with 0.1% cream, erythema was initially very slight to mild and progressed to moderate in some animals by week 2. Slight edema was observed in week 2. Flaking, scaling and scabs were noted at the treatment sites in both high dose groups, and abrasions were observed at the treatment sites in the high dose group treated with sodium thiosulfate-containing cream. At the high dose, males seemed to be more severely affected.
- Body weights: The sponsor reports no significant drug-related effects. However, the ANOVA for female body weights on day 28 indicated a treatment difference ($p<0.05$). There appeared to be a dose-dependent decrease in body weight. Statistical evaluation of terminal body weight in the organ weight section of the report indicated that terminal body weight was decreased in females treated with both 0.1% tazarotene formulations relative to their respective controls.
- Food consumption: The sponsor reports no significant drug-related effects. However, the ANOVA for feed comsumption in females on day 7 indicated a treatment difference ($p<0.05$). Duncan's test was not performed.
- Ophthalmoscopy: No drug-related effects were reported. One male (animal #302) and one female (animal #351) treated with 0.05% tazarotene cream containing ascorbic acid were reported to have corneal opacities in both eyes at the end of treatment. *(Reviewer's comment: The location and nature of the lesions in these two animals were identical, and both animals were the third in their respective groups; it is unclear whether or not this is a mistake in recording of lesions. Corneal opacities are a typical finding in rats treated with retinoids.)*

- Electrocardiography: not applicable
- Hematology: Dose-dependent increases in mean neutrophil counts and decreases in mean lymphocyte counts were seen in rats treated with both formulations relative to the respective vehicle controls. These changes were comparable between the two formulations. The sponsor speculates that these effects were due to skin irritation and inflammation. (*Reviewer's comment: These changes may also be consistent with stress.*)
- Clinical chemistry: The sponsor reports that all effects were seen in animals treated with both tazarotene cream formulations relative to their respective vehicle controls. Dose-dependent increases in serum alkaline phosphatase activity and decreased serum albumin levels were seen in both males and females. Serum glucose and triglycerides were increased in females (*Reviewer's comment: Serum triglycerides appeared to be increased in males treated with ascorbic acid containing formulae, but the difference was not statistically significant*). Cholesterol was decreased in males. Total protein in males treated with 0.1% tazarotene cream containing thiosulfate was decreased. Although the changes noted were statistically significant, many of them did not appear to be biologically significant.
- Urinalysis: not applicable
- Organ Weights: Absolute spleen weights were decreased in females treated with both tazartone cream formulations at both concentrations. Relative liver weights were increased in females treated with both formulations of 0.1% tazarotene cream and in females treated with 0.05% tazarotene cream containing ascorbic acid.
- Gross pathology: There were no drug-related findings other than skin irritation at the treatment site.
- Histopathology: Both tazarotene formulations at both concentrations produced irritation to the skin at the application site. Acanthosis, parakeratosis, ulceration, inflammation, atrophy, and/or hemorrhage were present. Those findings were dose-related in severity and comparable between the two formulations. Irritation was minimal to mild in the low dose group and minimal to marked in the high dose group. Hepatic vacuolization was seen in females at the high dose treated with both formulations and in vehicle groups. Vacuolization was microvesicular with periportal zonal distribution in tazarotene-treated rats, and was macrovesicular, with no zonal pattern in vehicle-treated animals. Reactive hyperplasia in cervical lymph nodes secondary to skin irritation was seen in animals treated with 0.1% tazarotene cream containing 0.1% sodium thiosulfate.

Additionally, minimal subacute liver necrosis was found in 2/10 high dose males dosed with the sodium thiosulfate formulation. Testicular tubular atrophy was reported in one animal in each of the two groups treated with ascorbic acid-containing tazarotene formulations. Two of the ten females treated with the high dose ascorbic acid-containing formulation had a pituitary cyst. In the group treated with the high dose sodium thiosulfate-containing formulation, one of nine females had minimal parathyroid atrophy and three of ten had minimal thymus atrophy.

- Toxicokinetics: Tazarotenic acid concentrations were detected at all time points for which blood was sampled. Those concentrations increased with increasing dose, and were not significantly different for treatment with the two cream formulations. Values for Cmax and AUC were somewhat lower than in the previous three-month study in rats.

Formulation:	0.05% cream containing 0.1% ascorbic acid	0.05% cream containing 0.1% sodium thiosulfate	0.1% cream containing 0.1% ascorbic acid	0.1% cream containing 0.1% sodium thiosulfate
Dose:	0.125 mg/kg/day	0.125 mg/kg/day	0.25 mg/kg/day	0.25 mg/kg/day
Cmax (ng/ml) mean ± SD	2.27 ± 0.88	3.04 ± 1.80	5.16 ± 3.10	4.43 ± 2.76
Tmax (hr)	12	9	9	12
$AUC_{0\text{-}24hr}$ (ng• hr/ml) mean ± SE	34.2 ± 2.9	40.2 ± 3.5	61.3 ± 4.8	61.1 ± 7.9

Key Study Findings:

Effects of the two formulations of tazarotene cream were similar in this study and were consistent with results of previous studies of tazarotene and other retinoids. It is notable that some findings seen in the three-month rat study described above, e.g. decreases in red blood cell parameters, were absent in this study., and that exposures to tazarotenic acid appeared to be slightly less than those seen in the 12-week study reported earlier.

Overall Toxicology Summary:

A three-month topical study was performed in rats, using tazarotene creams at concentrations of 0.025, 0.05, and 0.1%, once daily for 6 hours. Dose-dependent irritation at the treatment site was seen. Systemic effects at the mid- and high dose included decreased body weights and hematologic and serum chemistry changes typical of retinoids, such as decreased erythrocyte counts and changes serum protein, lipids, and liver enzymes. Albumin and cholesterol were decreased at all tazarotene doses. Histological examination of treated skin revealed dose-related acanthosis, parakeratosis, erosion, ulceration, edema and hemorrhage in all tazarotene-treated animals. Acanthosis was also seen in stomach epithelium in mid and high dose animals, presumably as a result of ingestion of the test material. Hepatocyte vacuolization was seen in vehicle and tazarotene-treated animals, with a higher incidence of periportal distribution at the high dose. The NOEL for systemic toxicity was reported to be 0.05 mg/kg/day, using 0.025% cream (0.3 mg/m^2/day), but changes were seen at that dose in serum albumin and cholesterol. The NOEL for cutaneous effects was not determined. Most effects seen at all topical doses appeared to be reversible.

A three-month topical study was performed in Sinclair miniswine, using tazarotene creams at concentrations of 0.025, 0.05, and 0.1%. Dosing was twice daily to 10% of body surface area. Progressive, dose-dependent irritation was evident in all treated groups. Irritation was severe in the mid- and high dose groups, but improvement was evident in all groups after a one-month recovery period. Laboratory tests revealed leukocyte and serum protein alterations at the mid- and high dose. Microscopic examination of treated skin revealed dose-related acanthosis, inflammatory cell infiltration of the dermis, focal erosion, ulceration and/or dermal fibrosis. Partial improvement was noted after recovery. The NOEL for systemic toxicity was

reported to be 0.25 mg/kg/day (8.75 mg/m^2/day), using the 0.1% tazarotene cream, and a NOEL for local toxicity was not determined.

Pharmacokinetic evaluations of the three month studies in miniswine and rats were performed. In both studies, a dose-related linear increase in systemic exposure to tazarotenic acid was seen. Parameters indicated similar or greater systemic exposures than those calculated from similar studies of tazarotene gel formulations.

A on-month bridging study was performed to compare tazarotene cream formulations containing ascorbic acid to those containing sodium thiosulfate as an antioxidant. Treatment with the two formulations resulted in comparable dermal and systemic effects and in similar systemic exposure with the two formulations containing equal concentrations of tazarotene.

The sponsor cross-referenced applications for tazarotene gel formulations in support of the current submission. Studies performed to support those applications are summarized below. Oral toxicity studies have been performed in rats and monkeys for up to 6 and 12 months, respectively. Signs of toxicity were consistent with those typical of retinoids and included mortality, effects on bone, liver, kidney, spleen and/or thymus, and heart, and related serum chemistry alterations. Effects were dose and time-dependent in incidence and severity. Some reversal of milder effects was seen after recovery periods, but the more severe effects, such as bone abnormalities did not improve. The sponsor states that systemic effects were seen at exposures that were one to four times in monkeys or slightly less in rats than maximal exposures in human patients extrapolated for topical treatment with 0.1% tazartoene cream over 20% TBSA.

Dermal toxicity studies of tazarotene gels were performed in rats and miniswine for up to 6 and 12 months, respectively. Effects on skin included erythema, edema, scabbing, flaking/scaling, ulceration, hyperkeratosis, acanthosis, and dermal inflammation and fibrosis. These were also time and dose-dependent. Serum chemistry findings were indicative of metabolic dysfunction related to liver and bone remodeling, with pathological findings in rats in the liver, adrenals and bone.

Topical studies of tazarotene gel were conducted for longer durations than those performed for the cream formulations. A six-month study in rats demonstrated retinoid effects similar to those seen at three months with tazarotene cream, with the added effects of significantly increased adrenal weight, adrenal cortical degeneration, and hepatic lipidosis (*Reviewer's comment: The distribution of the hepatic observation was periportal, as was vacuolization in the three-month study of tazarotene creams. There was also a subtle increase in adrenal weight after three-months treatment with the 0.1% cream.*) in animals treated with 0.05% tazarotene gel and above. Focal cortical bone necrosis was observed in animals treated with 0.1% tazarotene gel. (*Reviewer's comment: The sponsor states that these doses were 0.2 and 0.4 mg/kg/day, respectively, but the review of NDA 20-600, the doses are described as 0.05 ml, presumably per kg, of the respective concentrations BID, yielding doses of 0.05 and 0.1 mg/kg/day, respectively. In the review of NDA 20-600, it is noted that recovery from adverse effects seen in the 6-month rat study was incomplete, suggesting that increased duration of treatment may require longer recovery time from adverse events or that some adverse events may be irreversible.*) Studies were conducted in minipigs at 0.5 mg/kg/day of 0.1% tazarotene gel for 3 months or 0.25 mg/kg/day of 0.1% tazarotene gel for 1 yr. Findings included dose limiting dermal irritation. The sponsor reported no systemic effects, but the original review of those studies indicated that serum chemistry evaluation revealed increased serum hemoglobin, decreased albumin, increased total protein and globulin, and decreased A/G ratio; these changes

are consistent with serum chemistry findings in other species. Serum chemistry findings were not different from control after a recovery period.

In single dose studies conducted in support of tazarotene gels, the drug substance was found to be mildly irritating topically in rabbits and not irritating in rats. A single oral dose of 2 g/kg was nonlethal in rats, but produced signs of lethargy, piloerection, peri-anal soiling, paraphimosis, blood around the nose, hair loss and bloody tears. A single iv dose up to 2 mg/kg in rats caused no drug-related effects after a 14-day observation period. Similarly, 0.075 mg/kg iv infusions in rabbits and dogs resulted in no drug-related effects after a 14-day observation period, although it was later determined that a large portion of the dose may have adhered to the intravenous catheter during administration. A single iv bolus dose of 0.75 mg/kg in monkeys was reported to cause no drug-related adverse effects after a one-week observation period.

CARCINOGENICITY:

Oral and dermal carcinogenicity studies in rats and mice, respectively, were negative, but all concentrations of tazarotene tested in a photo co-carcinogenicity study in hairless mice did have a positive effect, increasing the number of tumors and shortening the median time to tumor onset. The results of the photo co-carcinogenicity study were not included in the proposed labeling and should be added.

IMMUNOTOXICOLOGY:

No immunotoxicology studies were submitted.

REPRODUCTIVE TOXICOLOGY:

In a segment I study in rats, no impairment of fertility was seen at doses up to 0.125 mg/kg/day (HED = 0.02 mg/kg). In a dermal segment III study in rats, the high dose of 0.125 mg/kg/day on gd 16 through lactation day 20 resulted in slight erythema and eschar, and skin thickening, with no change in body weight or food consumption. Pup survival was significantly in less in the high dose group at lactation days 6 and 21. There was no effect on the reproductive capability of the offspring.

Tazarotene was teratogenic in oral studies in rats and rabbits and appeared to be teratogenic in a dermal developmental study in rabbits. The following table summarizes segment II studies of oral and topically applied tazarotene gel in rats and rabbits.

study number	species	route	dose	AUC_{0-24h} of AGN 190299 (ng*hr/ml)[a]	adverse effects	multiple of human psoriatic exposure[b]
1643-SLS-3202.12	rat	oral	1.0 mg/kg/day (5.9 mg/m^2/day)	510	decreased litter size; decreased fetal/neonatal weight; malformations including cleft palate, skull anomalies, cephalocele, exencephaly, facial papilla anomaly, pinna anomaly; increased # early neonatal deaths; postnatal developmental and behavioral delays	6
			0.25 mg/kg/day (1.5 mg/m^2/day)	115	developmental delays external malformations	1.3
1643-SLS-3202.5	rat	topical	0.250 mg/kg/day (1.5 mg/m^2/day)	107	slight increase in number of dead pups; lower pup body weights; reduced skeletal ossification	1.2
			0.125 mg/kg/day (0.74 mg/m^2/day)		decreased fetal body weight	
1643-SLS-3202.14	rabbit	oral	0.200 mg/kg/day (2.2 mg/m^2/day)	2272	increased pre- and post-implantation loss; malformations, including pinna anomalies, cleft palate, spina bifida, heart anomalies, skiull anomalies, hyoid anomalies, tympanic ring anomalies	26
1643-SLS-3202.9	rabbit	topical	0.250 mg/kg/day (2.75 mg/m^2/day)	1160	single incidences (1/20 litters) each of hydrocephaly, heart anomaly, spina bifida	13

[a]Pharmacokinetic parameters were determined in dose-range finding studies for animal teratogenicity.
[b]This exposure multiple is based on the highest body surface area involvement treated topically in the controlled clinical pharmacokinetic study (35% bsa, AUC_{0-24h}= 88.3 ng•hr/ml).

The sponsor states that systemic exposures at non-teratogenic doses of 0.05 mg/kg/day in rats and rabbits were 0.6 and 8 times human exposure extrapolated for 20% bsa. At 0.05 mg/kg/day administered orally to rats, there were no teratogenic effects and the AUC_{0-24h} was 60.1 ng•hr/ml in a prior range-finding study (0.7 times the exposure seen in the representative human subject). A dose of 0.05 mg/kg/day po was also not teratogenic in rabbits, but the pharmacokinetic data for that study is not available at this time.

Labeling Recommendations:

The systemic exposure for a clinical patient treated topically over 35% of total body surface area with 0.1% tazarotene cream was similar to or within one order of magnitude of the systemic exposure in animals treated orally in which teratogenic effects were seen. Non-teratogenic effects included decreased fetal weight, decreased survival, and postnatal

developmental and behavioral delays. It is recommended that this product be labeled Pregnancy Category X, as are the tazarotene gel formulations.

GENETIC TOXICOLOGY:

Tazarotene was negative in std battery of genotox tests. Tests performed included the Ames assay in Salmonella by plate incorporation and in E. coli WP2 uvrA by pre-incubation. No significant difference from negative control was seen in the in vitro chromosome aberration assay in human lymphocytes or in the CHO/HPRT mammalian cell forward gene mutation assay. Tazarotene was negative for clastogenicity in the mouse micronucleus assay.

SPECIAL TOXICOLOGY STUDIES:

The following three studies were previously reviewed in the original submission of IND

1. Study title: Tazarotene cream: Delayed contact hypersensitivity in guinea pigs (Buehler method)
Study number: 0424XA08.001
Performing organization: [redacted]
Drug lot and batch: 454 (vehicle), 453 (0.025%), 456 (0.05%), 455 (0.1%)
Date of study: 4/2/97-5/14/97
GLP compliance: yes
Study design:
Dosing: topically, three times for 6 hours at 7 day intervals for induction; challenged topically at a naive site at 14 days after final induction; rechallenged one week later.
Dose groups: vehicle, 0.025, 0.05, or 0.1% cream; DNCB as positive control; 0.3 ml/dose
Formulation: tazarotene creams, formulations 8918X, 9067X, 8880X, and 8881X, respectively.
Test animals: Hartley guinea pigs, 4 weeks of age, 10/sex/group plus 3/sex for positive control group; responses were evaluated at 24 and 48 hours after challenge.
Findings:

Positive reactions were seen in the DNCB group (scores of +1 to +3) and two minimal positive responses (scored as +1) were seen out of 20 animals at 48 hours in the 0.1% tazarotene cream group. No reaction was seen in the vehicle, 0.025, and 0.05% tazarotene groups.

Rechallenge was conducted in the vehicle and tazarotene cream groups after another week. Minimal to mild positive responses (+1 to +2) were seen in 1/20 animals in the 0.025% group and 6/20 animals in the 0.05% group at 48 hours and in 7/20 and 8/20 animals in the 0.1% group at 24 and 48 hours, respectively. (*Reviewer's comment: The two animals that had positive responses at the first challenge had no response to rechallenge. Therefore, it would seem possible that those positive responses may be due to sensitization or to irritation. No positive responses were seen during the induction phase, which would argue against irritation as a cause in the challenge phase. Additionally, scores of +2 were recorded for two of the high dose animals at rechallenge; these are consistent with scores in positive control animals.*)

At both challenges, tazarotene-induced animals were challenged with vehicle at a second site; vehicle-induced animals were challenged with 0.1% tazarotene at a second site. No reactions were seen at any vehicle-challenged site. However, at 48 hours after rechallenge, 4/20 vehicle control animals had minimal positive responses (scored as +1) at the 0.1% tazarotene site. (*Reviewer's comment: This positive response may be due to sensitization of these animals during the first challenge or due to irritation.*)

The sponsor states that the results of this study indicate that tazarotene cream has "no more than minimal" sensitization potential. However, due to the dose-related incidence and severity of responses seen at the second challenge, tazarotene in this cream vehicle may be a sensitizer. In a guinea pig sensitization test of tazarotene in a gel vehicle, no positive responses were seen in any tazarotene or vehicle-treated group (10 animals/group).

2. **Study title:** Tazarotene cream: Phototoxicity test in guinea pigs
Study number: 0432GA08.001
Performing organization: [redacted]
Drug lot and batch: 454 (vehicle), 453 (0.025%), 456 (0.05%), 455 (0.1%)
Date of study: 4/10-14/97
GLP compliance: yes
Study design:
Dosing: topically to duplicate symmetrical clipped sites on the back, 0.3 ml/site; half of the sites were irradiated with 164 J/cm^2 UVA (>320 nm) light over 60 minutes.
Dose groups: vehicle, 0.025, 0.05, and 0.1% tazarotene cream; positive control was 8-methoxypsoralen. Each of three groups was dosed with vehicle, one of the tazarotene creams, and the positive control to separate sites. An untreated site was also evaluated.
Formulation: tazarotene creams, formulations 8918X, 9067X, 8880X, and 8881X, respectively.
Test animals: Hartley guinea pigs, 5 weeks of age, 5/sex/group; evaluation at 24, 48, 72, and 96 hours after irradiation.
Findings:

No erythema or edema was seen at any tazarotene cream or vehicle-treated sites. Positive control sites had slight to moderate erythema and very slight to slight edema at 24 hours at irradiated sites only. Erythema at those sites increased with time, with some resolution of erythema and edema by 96 hours.

Tazarotene cream was not phototoxic in guinea pigs under the conditions of this study.

3. **Study title:** Tazarotene cream: Photoallergy study in guinea pigs
Study number: 0458XA08.002
Performing organization: [redacted]
Drug lot and batch: 454 (vehicle), 453 (0.025%), 456 (0.05%), 455 (0.1%)
Date of study: not stated; report date 6/20/97
GLP compliance: yes
Study design:
Dosing: topically, 0.3 ml/animal five times over 11 days in the induction phase to shaved and tape-stripped sites on the back of the neck, with irradiation with 30 J/cm^2 UVA light at 2 hours after each exposure; sixteen days after the final induction exposure, test materials were applied to symmetrical clipped sites on the back (0.2 ml each) on each animal and half of the sites were irradiated at 2 hours with 10 J/cm^2 UVA light. (*Reviewer's comment: It is unclear why the light dose was reduced for the challenge phase.*)
Dose groups: vehicle, 0.025, 0.05, and 0.1% tazarotene cream; positive control was TCSA. Animals in tazarotene-induced groups were challenged with all three tazarotene cream concentrations at three different duplicate sites.
Formulation: tazarotene creams, formulations 8918X, 9067X, 8880X, and 8881X, respectively.
Test animals: Hartley guinea pigs, 6 weeks of age, 5/sex/tazarotene cream or vehicle group, 3/sex for the positive control group, and 2/sex for the untreated control group; evaluation was made at 24 hours after challenge irradiation.

Findings:

Scores were 0 for irradiated and non-irradiated sites on untreated animals and animals administered vehicle, 0.025, or 0.05% tazarotene cream. In 1/10 animals administered 0.1% tazarotene cream, the irradiated site treated with 0.1% tazarotene cream was scored as +1 (minimal erythema). Responses in positive control animals ranged from +1 to +3 (minimal to considerable erythema). No evidence of contact allergy was noted at non-irradiated sites.

The sponsor states that tazarotene cream was considered to not be photoallergenic in guinea pigs. However, based on the positive response in the high dose group and the presence of responses of similar grade in the positive control group, it appears that tazarotene cream may be a positive photosensitizer under the conditions of this study.

Reviewer's comment: For both phototoxicity and photoallergy studies, solar simulation should be used, rather than UVA irradiation alone.

The following study review is reproduced from the review of IND ———

4. **Study title:** Tazarotene cream: comedogenicity study in rabbits
Study number: TX97011
Performing organization: Allergan, Irvine, CA
Drug lot and batch: vehicle cream, formulation 8918X, lot no. 454;
0.025% tazarotene cream, formulation 9067X, lot no. 453;
0.05% tazarotene cream, formulation 8880X, lot no. 456;
0.1% tazarotene cream, formulation 8881X, lot no. 455.
Date of study: 5/5-23/97
GLP compliance: yes
Study design:
Dosing: topical to the inner surface of the left ear pinna, 0.125 ml daily for 5 consecutive days/week for 3 weeks. The opposite ear served as an untreated control.
Dose groups: vehicle, 0.025%, 0.05%, and 0.1% cream.
Formulation: see above
Test animals: NZW rabbits, 3/sex/group, 21 weeks of age, specific pathogen free.
Findings:
Deaths: none
Clinical signs: Erythema was noted at the treatment site and was graded "very slight" (+1 on a 0-4 scale) for the vehicle cream group (1/3 males and 2/3 females), "very slight" to "well-defined" (+1 to +2) for the 0.025% group, and "very slight" to "moderate to severe" (+1 to +3) for the 0.05 and 0.1% groups. Reactions involved all animals in the three treated groups. Scratches, flaking, and yellowish discoloration were noted at the treatment site.
Pathological examination: On whole mount examination of the ear pinna, it appeared that all concentrations induced comedone-like lesions on the treated area. The epidermis of the treated ears was reported to be thicker than that of untreated ears. On histological examination, however, inflammatory responses were observed that were dose-related in incidence and severity, with no comedone formation.

The sponsor concluded that the cream formulation of tazarotene at all concentrations was non-comedogenic, but that it did result in dose-dependent skin irritation.

The following study was submitted for the first time with the current NDA.

5. Study Title: Tazarotene cream: A single dose ocular irritation study in New Zealand White rabbits
Study No: TX99018

Amendment #, Vol #, and page #: NDA 21-284, original submission, vol. #1.10, p. #10 068
Conducting laboratory and location: Allergan, Irvine, CA
Date of study initiation: 4/6/99
GLP compliance: yes
QA- Reports Yes (X) No ( ):
Methods:
Dosing: A single dose of 0.1% tazarotene cream instilled into lower conjunctival sac of the left eye of each of three male and three female NZW rabbits. The right eye served as an untreated control.
Drug, lot#, radiolabel (if applicable), and % purity: 0.1% tazarotene cream, lot no. 11346
Formulation/vehicle: 0.1% tazarotene cream in clinical formulation containing 0.1% sodium thiosulfate (formula 9087X),
Observations and times: Observations for mortality and clinical signs were made at least once daily. Body weights were measured prior to the start of the study and on days 7 and 14. Gross ocular examination and scoring was performed at the time of treatment and once daily therafter. Slit lamp biomicroscopy was performed pre-test, 1, 24, 48 and 72 hours post-dose, and on days 7 and 14. Fluorescein and rose bengal stains were used for each slit lamp examination.
Results:

There were no deaths or drug-related clinical observations, other than ocular effects. Immediately following application of the test article, mild to severe ocular discomfort was observed, lasting up to two minutes, as was moderate ocular irritation. Slight to moderate hyperemia of the conjucntiva was observed in all six animals, and slight swelling of the conjunctiva was observed in 2/6 animals. Slit lamp examination revealed slight to mild congestion in all six treated eyes and mild swelling in one of six treated eyes at one hour post-dose. On day 2, one treated eye exhibited slight congestion and fluorescein staining of less than 25% of the cornea. No abnormal rose bengal staining was observed at any time point, indicating no effect on corneal epithelial cell vitality. Effects were reversed within 48 hours post dose.

Summary:

Tazarotene cream was found to have possible sensitization potential in guinea pigs. Tazarotene cream formulations were not phototoxic on exposure to UVA light in guinea pigs. The cream formulation containing 0.1% tazarotene appeared to be photoallergenic upon exposure to UVA light in guinea pigs. The sponsor considered all of these studies to be negative. Dermal safety studies in human subjects indicate negative results in both sensitization and photosensitization tests. The clinical photosensitization test was also performed using UVA alone, but will be repeated using both UVA and UVB irradiation.

In a rabbit comedogenicity study, tazarotene cream was found to be irritating, but not comedogenic when applied daily, 5 days per week for 3 weeks, at concentrations ranging from 0.025% to 0.1%.

Ocular irritation testing in rabbits revealed mild to severe ocular discomfort and moderate ocular irritation that was reversible within 48 hours after a single dose.

OVERALL SUMMARY AND EVALUATION:

Introduction: Tazarotene cream formulations have been developed as an alternative to the currently approved gel formulations.

Safety Evaluation: Much of the nonclinical safety data is cross-referenced from previous submissions in support of tazarotene gel formulations. Additional studies performed with the cream formulations resulted in similar findings to those of the gels.

Clinical Relevance of Safety Issues: The nonclinical safety profile of tazarotene creams is similar to that of tazarotene gels.

Other Clinically Relevant Issues: none

Conclusions: From a nonclinical standpoint, the safety profile of this product should be similar to that of the existing gel product and should have similar labeling.

Communication Review:

- Labeling Review (NDA):

1. Under **CLINICAL PHARMACOLOGY**, the sentence reading, " [redacted] has been changed to read "...cell proliferation and expression." The meaning is unclear, and it is recommended that the word "hyperplasia" be substituted for the word [redacted]

The word ' [redacted] ' has also been added to the end of the second sentence after that one, and it is recommended that it be removed.

The following has been added to the text contained in the label for tazarotene gel: "Tazarotene also induces the expression of TIG3 (tazarotene-induced gene 3), a tumor suppressor, which may inhibit epidermal hyperproliferation in treated plaques. Tazarotene, therefore, has multiple effects on keratinocyte differentiation and proliferation, as well as on inflammatory processes which contribute to the pathogenesis of psoriasis." This information was provided in the pharmacology summary in the current NDA, but the original supporting data or referenced publications do not appear to have been submitted for review; the review team may wish to consider striking the first sentence until supportive data have been submitted. It is recommended that the second of these two sentences be stricken, as an effect on expression of certain markers of inflammation may not constitute multiple effects on inflammatory processes contributory to the pathogenesis of psoriasis.

2. Since the cream product is not indicated for use limited to 20% total body surface area, it may be more appropriate to describe exposure in patients treated over maximum BSA at the clinical rate of application. For the patient treated in the controlled pharmacokinetic trial with 2 mg 0.1% tazarotene cream per cm^2 of skin over 35% TBSA, $AUC_{0\text{-}24h}$ was 88.3 ng•hr/ml. This value is used in recommended interspecies comparisons in the appropriate sections.

A study design in which subjects are treated with larger amounts of cream to the same surface area (10 mg/cm^2 instead of 2 mg/cm^2) as a means of increasing dose would be considered inappropriate in an animal study. The review team may wish to consider reporting only of values for patients treated at the clinical application rate (2 mg/cm^2) in the **Pharmacokinetics** section and wording to indicate proportional increase in systemic exposure with increased percentage of body surface area treated.

3. The following revisions are recommended to maintain consistency with the tazarotene gel label and to adjust multiples of exposure in interspecies comparisons for the reasons cited in

no. 2 above. Cmax values are removed, as retinoid toxicity correlates better with AUC values (and thus with doses normalized for total body surface area); AUC values are listed where available or are used for interspecies comparisons. Additionally, the results of the photo co-carcinogenicity study were omitted from the proposed label and should be included.

CONTRAINDICATIONS:

Retinoids may cause fetal harm when administered to a pregnant woman.

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 ($AUC_{0\text{-}24h}$) at topical doses of 0.25 mg/kg/day in rats and rabbits represented – 1.2 and – 13 times, respectively, that in a human psoriatic patients treated with 0.1% tazarotene cream at 2 mg/cm^2 over 35% body surface area in a controlled pharmacokinetic study;

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 seen in rats and rabbits at doses producing 1.3 and 26 times, respectively, the systemic exposure ($AUC_{0\text{-}24h}$) seen in a human psoriatic patient treated topically with 0.1% tazarotene cream at 2 mg/cm^2 over 35% body surface area in a controlled pharmacokinetic study

Under **PRECAUTIONS:**

Carcinogenesis, mutagenesis, impairment of fertility:

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% for up to 40 weeks.

Tazarotene was found to be non-mutagenic in — Ames— assays using Salmonella and E. coli and did not produce structural chromosomal aberrations in a human lymphocyte assay. Tazarotene was also non-mutagenic in the CHO/HPRT mammalian cell forward gene mutation assay and was non-clastogenic in the *in vivo* mouse micronucleus test.

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 of up to 0.125 mg/kg/day —

4. Under **Dosage and Administration**, the label states, '

- **Investigator's Brochure/Informed consent review (IND):** not applicable

RECOMMENDATIONS:

Internal comments: From a nonclinical standpoint, the NDA is approvable with the above revisions to the label.

External Recommendations (to sponsor)/Draft letter Content for Sponsor:

Please submit original study reports or copies of referenced literature to support label statements regarding effects of tazarotene on tazarotene-induced genes (TIG), i.e. DiSepio D et al, 1998, and Esgleyes-Ribot T. et al, 1994.

Clarification is requested for study TX99008. The ophthalmology reports are identical for animals 302 and 351. Both have a set of lesions that are unlikely to be exactly duplicated. Please recheck the ophthalmology reports for all animals in the study.

Future development or NDA issues: not applicable

/S/

Amy C. Nostrandt, D.V.M., Ph.D. 6/12/00
Pharmacologist/Toxicologist

cc:
NDA 21-184
HFD-340
HFD-540
HFD-540/PHARM/Nostrandt
HFD-540/TLPHARM/Jacobs
HFD-540/MO/Ko
HFD-540/CHEM/Timmer
HFD-540/PMS/Bhatt
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Draft date (# of drafts): 6/7/00 (2)

Concurrence Only:
HFD-540/DD/WILKIN

HFD-540/TLPHARM/JACOBS 6/13/00
2 DFS

/S/ 7/16/00

INFORMATION TO BE CONVEYED TO THE SPONSOR:

Please submit original study reports or copies of referenced literature to support label statements regarding effects of tazarotene on tazarotene-induced genes (TIG), i.e. DiSepio D et al, 1998, and Esgleyes-Ribot T. et al, 1994.

Clarification is requested for study TX99008. The ophthalmology reports are identical for animals 302 and 351. Both have a set of lesions that are unlikely to be exactly duplicated. Please recheck the ophthalmology reports for all animals in the study.