CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-184/S-001

Pharmacology Review(s)

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION
Addendum to Review

NDA number: 21-184
Review number: second addendum to review no. 3
Serial number/date/type of submission: SE1 001
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Allergan, Inc., Irvine, California
Manufacturer for drug substance: [ ]

Reviewer name: Amy Nostrandt
Division name: Division of Dermatologic and Dental Drug Products
HFD #: 540
Review completion date: 9/19/01; addendum completion on 10/4/01

After a telephone conference to discuss FDA's revisions to the sponsor's proposed label, the following pharmacology/toxicology amendments to recommendations to the label were agreed upon. Comments to clarify specific changes are included below in italics, but are not meant to be included in revised labeling. The following is a revision of the label sent to the sponsor prior to the telephone conference.

1. Under CONTRAINDICATIONS:

Draft Labeling

7 pages redacted from this section of the approval package consisted of draft labeling

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION
Addendum to Review

NDA number: 21-184
Review number: 3
Serial number/date/type of submission: SE1 001
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Allergan, Inc., Irvine, California
Manufacturer for drug substance:

Reviewer name: Amy Nostrandt
Division name: Division of Dermatologic and Dental Drug Products
HFD #: 540
Review completion date: 9/19/01; addendum completion on 9/26/01

At an internal meeting to discuss labeling on 9/25/01, it was the consensus of the review team that exposure multiples for interspecies comparison should be based on maximal AUC values in the clinical pharmacokinetics studies rather than mean AUC values. In the original pharmacology/toxicology review of this supplement, exposure multiples were based upon the mean AUC (17.0 ng*hr/mL) seen in a study in which subjects applied tazarotene 0.1% cream to 15% total body surface area. The maximal AUC in that study was 26.6 ng*hr/mL; that figure was used to recalculate exposure multiples recommended for revised labeling below.

1. Under CONTRAINDICATIONS:

Draft
Labeling

2 pages redacted from this section of the approval package consisted of draft labeling

Draft Labeling

(FDA-approved text for tazarotene cream, psoriasis indication with modifications highlighted; see NDA 21-184.)

Reviewer signature: /S/ 10/1/01

Team leader signature [concurrence/non-concurrence]:

/S/ 10/2/01

cc:
NDA
HFD-340
HFD-540
HFD-540/PHARM/Nostrandt
HFD-540/TLPHARM/Jacobs
HFD-540/MO/Ko
HFD-540/CHEM/Timmer
HFD-540/PMS/Bhatt

Concurrence Only:
HFD-540/DD/WILKIN

Memorandum of non-concurrence (if appropriate, attached):

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

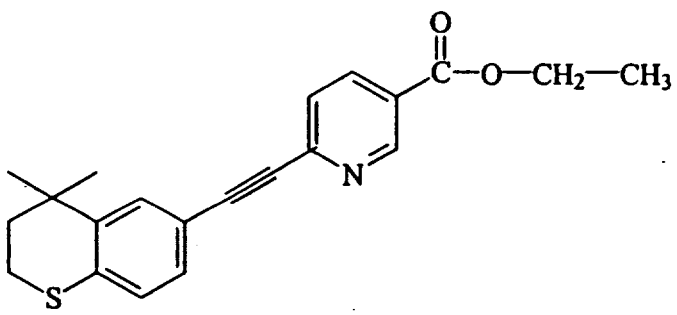
NDA number: 21-184
Review number: 3
Serial number/date/type of submission: SE1 001
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Allergan, Inc., Irvine, California
Manufacturer for drug substance: [redacted]

Reviewer name: Amy Nostrandt
Division name: Division of Dermatologic and Dental Drug Products
HFD #: 540
Review completion date: 9/19/01

Drug:

Trade name: Tazorac (tazarotene) cream 0.1%
Generic name (list alphabetically): tazarotene
Code name: AGN 190168
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 = 367.5



Relevant INDs/NDAs/DMFs: all from Allergan

IND [redacted]	tazarotene creams for psoriasis
IND [redacted]	tazarotene gels for psoriasis and acne
NDA 20-600	tazarotene 0.1 and 0.05% gels for psoriasis and acne
IND [redacted]	tazarotene oral capsules for a drug interaction study
IND [redacted]	tazarotene creams for facial photoaging
IND [redacted]	tazarotene oral capsules for severe psoriasis and nodulocystic acne
IND [redacted]	tazarotene creams for acne vulgaris

Drug Class: acetylenic retinoid

Indication: for the topical treatment of acne vulgaris

Clinical formulation:

	%w/w	
ingredient	0.05% (9103X)	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 EP		
carbomer 1342 NF		
sorbitan monooleate NF		
carbomer 934P NF		
5N sodium hydroxide NF		
purified water USP		
total:	100	100
pH approximately		

Route of administration: topical to affected skin

Proposed use:

In clinical trials of 0.1% tazarotene cream in acne patients, the drug product was applied once daily for 12 weeks. The sponsor states that 0.1% tazarotene cream was significantly more effective than vehicle in the treatment of acne.

A pharmacokinetic study was performed in which acne patients were treated over 15% total body surface area with 2 mg/cm^2 of 0.1% tazarotene cream. The mean Cmax was 1.2 ng/mL and the mean $AUC_{0\text{-}24\,h}$ in those patients was 17.0 ng*hr/mL. The latter figure is used for interspecies comparison data below.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

OVERALL SUMMARY AND EVALUATION:

Introduction: Tazarotene has been approved in a gel formulation for the treatment of psoriasis (0.05% and 0.1%) and acne (0.1%). The drug in a cream formulation has also been the subject of a recently approved NDA for the treatment of psoriasis (0.05% and 0.1%). The current efficacy supplement is for the use of 0.1% tazarotene cream in the treatment of acne vulgaris. The sponsor has included a number of extra reproductive/developmental toxicology studies.

Safety evaluation: The new nonclinical information included in this submission does not present any significant changes in risk characterization of the drug.

Safety issues relevant to clinical use: New data presented indicates that tazarotene is a developmental toxicant at systemic exposures that are within the same order of magnitude as systemic exposures in acne patients treated over 15% total body surface area.

Other clinically relevant issues: Additional studies of orally administered tazarotene in dogs demonstrate adverse effects similar to those previously demonstrated in rats and monkeys.

Conclusions: From a pharmacology/toxicology standpoint, the application is approvable, with labeling revisions outlined below.

Communication review:

Labeling review:

Draft

4 pages redacted from this section of the approval package consisted of draft labeling

RECOMMENDATIONS:

Internal comments:

External recommendations (to sponsor)/Draft letter content for sponsor (if not same as above): None

NDA issues: None

/S/

Reviewer signature:

/S/

Team leader signature [concurrence/non-concurrence]:

cc:
NDA
HFD-340
HFD-540
HFD-540/PHARM/Nostrandt
HFD-540/TLPHARM/Jacobs
HFD-540/MO/Ko
HFD-540/CHEM/
HFD-540/PMS/Bhatt

/S/

Concurrence Only:
HFD-540/DD/WILKIN

HFD-540/TLPHARM/JACOBS

Memorandum of non-concurrence (if appropriate, attached):

Addendum to review (if necessary):

Studies reviewed within this submission:
Toxicology Studies:
1. Study 98-3377: A repeated dose comparative oral range-finding study of tazarotene, Accutane (isotretinoin) and Soriatane (acitretin) in beagle dogs.
2. Study 98-3378 (TX-99010): A 9-month oral toxicity study of tazarotene in beagle dogs.

Reproductive Toxicology Studies:
1. Study TX99103 Tazarotene: oral (gavage) fertility and general reproduction toxicity study in male rats.
2. Study TX99104 Tazarotene: oral (gavage) fertility and general reproduction toxicity study in female rats.
3. Study 98-4144 A comparative oral range-finding developmental toxicity study in rats on tazarotene, tretinoin, and adapalene.
4. Study TX99039 A comparative oral developmental toxicity and toxicokinetic/placental transfer study in the rat on tazarotene and tretinoin.
5. Study 98-4145 A comparative oral range-finding developmental toxicity study in rabbits on tazarotene, tretinoin, and adapalene.
6. Study TX99023 A comparative oral developmental toxicity study in the rabbit on tazarotene and tretinoin.
7. Study 98-4148 A toxicokinetic and placental transfer study of tazarotene and tretinoin in pregnant rabbits vial oral administration.

Studies not reviewed within this submission:
The sponsor has included three new *in vitro* metabolism studies, which are briefly summarized in the pharmacokinetics/toxicokinetics section. A number of journal articles were

submitted, but are not reviewed, as the sponsor had a full complement of GLP studies to support the use of their drug product.

Introduction and drug history:

Tazarotene gels were approved for topical treatment of psoriasis (0.05% and 0.1%) and acne vulgaris (0.1%) under NDA 20-600 in 1996. Cream formulations were investigated for use in psoriasis and were approved under NDA 21-184 in 2000. The current submission is an efficacy supplement for the use of the 0.1% tazarotene cream formulation in the treatment of acne vulgaris.

In the current submission, the sponsor has provided additional reproductive and developmental toxicology studies to support pregnancy category labeling. Also included are two general toxicity studies of oral tazarotene in dogs originally performed to support IND[ ]for an oral tazarotene formulation.

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APPEARS THIS WAY
ON ORIGINAL

PHARMACOLOGY:

No new nonclinical pharmacology data was provided. The submission cross-references NDA 20-600 for tazarotene gels and the original submission of NDA 21-184.

Pharmacology summary:

From the original review of NDA 21-184:

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 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:

No new safety pharmacology data were provided with this submission. The following is reproduced from the review of the original NDA.

Safety pharmacology summary:

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 500 ng/ml in mice and 10 ng/ml 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, 10 µg/ml 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:

The sponsor has performed three *in vitro* ADME studies of tazarotene.

1.

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

The following summary is reproduced from the original review of NDA 21-184:

PK/TK summary:

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:

1. Study Title: A repeated dose comparative oral range-finding study of tazarotene, Accutane (isotretinoin) and Soriatane (acitretin) in beagle dogs.

Study No: 98-3377 (Allergan study no. 20030040-1318)

Amendment #, Vol #, and page #: NDA 21-184 SE1-001, volume 6

Conducting laboratory and location:
Date of study initiation: 11 November 1998
GLP compliance: yes
QA- Report Yes (X) No ()
Methods:
Dosing:

- species/strain: beagle dogs
- #/sex/group or time point: 2
- age: approximately 6 months
- weight: 6.4-10.0 kg
- satellite groups used for toxicokinetics or recovery: Main group test animals were used for toxicokinetic sampling.
- dosage groups in administered units:

Group no.	Test article	Dose (mg/kg/day)	HED (mg/kg/day)	multiple of maximum clinical dose[a]
1	tazarotene vehicle capsules			
2	tazarotene	0.1	0.05	0.7
3	tazarotene	0.3	0.15	2.1
4	tazarotene	1.0	0.5	7.1
5	Accutane®	1.0	0.5	0.25
6	Accutane®	10	5	2.5
7	Accutane®	30	15	7.5
8	Soriatane®	1.0	0.5	0.6
9	Soriatane®	10	5	6
10	Soriatane®	30	15	18

[a]Maximum daily clinical doses are 4.2 mg (0.07 mg/kg) for tazarotene, 2 mg/kg for Accutane, and 50 mg (0.83 mg/kg) for Soriatane.

- route, form, volume, and infusion rate: Capsules were administered per os once daily for four months.

Drug, lot#, radiolabel, and % purity: tazarotene lot nos. 11331 and 11446 for 0.2 mg capsules, 11332, 11201, and 11447 for 0.7 mg capsules; purity for all was reported to be 100%.
Formulation/vehicle: clinical formulation (see above)
Observations and times:

- Clinical signs: daily, once before and once after test article administration. Gait and posture evaluations were made once daily for the first 20 days and twice weekly thereafter. Physical examinations were performed pre-test and once weekly during the study.
- Body weights: Animals were weighed pre-test and weekly during the study. Terminal fasted body weights were obtained just prior to necropsy.
- Food consumption: Visual estimation of daily food consumption was made four times per week.
- Ophthalmoscopy: Indirect ophthalmoscopy was performed after administration of Mydriacyl 1% pre-test, at week 9, and at termination.

- EKG: not performed
- Hematology: Fasting blood samples were collected pre-test, at weeks 4 and 9, and at termination from all animals for hematology and coagulation studies.
- Clinical chemistry: Fasting blood samples were collected pre-test, at weeks 4 and 9, and at termination from all animals for serum chemistry evaluations.
- Urinalysis: Urine samples were collected for a six-hour period pre-test and at week 4 for urinalysis. At termination, urine samples were collected by cystocentesis. Urine volume was measured over a 16-hour period pre-test, at weeks 4 and 8, and at termination.
- Organ weights: performed at necropsy
- Gross pathology: Animals were sedated with Acepromazine, anesthetized with sodium pentobarbital, and then euthanized by exsanguination. A statement on page 33 of the report indicates that 16 animals were terminated, but the study included 40 animals.
- Organs weighed: brain, adrenals, heart, kidneys, liver, ovaries, pituitary, spleen, testes, thymus.
- Histopathology: performed on tissues identified in the table Addendum 1
- Toxicokinetics: Blood was collected at 0 (pre-dose), 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose on days 7, 8, 57, 58, 125, and 126 for toxicokinetic analysis. Samples were centrifuged and plasma was removed and stored at -15°C until analysis. The sensitivity of the assay for tazarotenic acid ranged from ng/mL.

Results:

- Deaths: none
- Clinical signs: Slight erythema, primarily on the ears, was seen in 1/4 and 4/4 dogs in the mid- and high dose tazarotene groups, respectively. Erythema on the ears, abdomen, or paws was seen at all isotretinoin doses and at the mid- and high doses of acitretin. Erythema was first noted during week 3 in tazarotene-treated dogs.

One male in the mid-dose tazarotene group presented with a limp during week 16 (day 111 examination) involving the right foreleg and the left hind leg. Physical examination findings for this animal were not recorded for the previous week. The report states that the limp was not present during weeks 17 and 18, and that there were no corresponding histopathological signs at termination (*Reviewer's comment: It is unclear whether or not histopathological examination included the bones of the affected legs or joints.*). However, no radiographic examination was performed. (*Reviewer's comment: In the 9-month study in beagles at this same dose, long bone alterations were confirmed radiographically as early as 1 month after the beginning of treatment.*)

Although not included in the tabular summaries, there is a note on pages 49 and 112 of the report that animal no. 7905 (female, 30 mg/kg isotretinoin) had an irregular gait and posture from days 114 through 125.

- Body weights: Dose-related decreases in body weight gains were observed for all three drugs and were most evident at the mid- and high doses. Body weights appeared lower in tazarotene-treated animals than controls, particularly in the mid- and high dose groups during treatment, but too few animals were included in the study for statistical comparison to be performed.
- Food consumption: Visual estimations were considered to be similar to controls and to exhibit "normal variability".

- Ophthalmoscopy: No drug-related effects were reported after 9 weeks or after 4 months.
- Electrocardiography: not performed
- Hematology: No drug-related effects were reported.
- Clinical chemistry: Decreases were seen in serum phosphorus concentrations at the high doses of tazarotene and acitretin, and at the mid- and high doses of isotretinoin. However, all values were within normal limits for this species, and the differences were not biologically significant.
- Urinalysis: No drug-related effects were reported.
- Organ Weights: Relative adrenal weights were reported to be increased at the mid- and high doses of tazarotene (also in Accutane and Soriatane-treated dogs and in monkeys in 6-12 month studies of tazarotene). The report states that "adrenal weight changes ... are likely class effects of retinoids and are not considered toxicologically significant." Absolute adrenal weights were not provided, but were reported to be low in the previously submitted interim report. Low testis weights were reported at the high doses of isotretinoin and acitretin.
- Gross pathology: Skin redness was noted, consistent with the in-life observations of erythema in treated animals. This finding was reported for one tazarotene-treated male (high dose), one male treated with the mid-dose of acitretin and for 50% of the animals at the high doses of isotretinoin and acitretin.
- Histopathology: Skin from high dose isotretinoin- and acitretin-treated dogs with a necropsy finding of skin redness had subacute/chronic inflammation, squamous cell hyperplasia and/or hyperkeratosis. These findings were minimal to moderate in severity.

Delayed ossification of the costo-chondral junction was noted in 50-100% of animals treated with 10-30 mg/kg isotretinoin or acitretin.

Testicular degeneration was reported in one of two mid-dose and both high dose isotretinoin-treated males. Degeneration was slight at 10 mg/kg and severe at 30 mg/kg. One acitretin-treated dog had focal atrophy of the germinal epithelium and low testis weight; this was considered to be related to the lack of sexual maturity in the young animal.

- Toxicokinetics: All three test articles were well absorbed and were metabolized to active metabolites. Systemic exposures to the parent drugs, tazarotenic acid, and 4-oxo-isotretinoin were dose dependent. Data for 13-cis-acitretin was provided, but exposures were low and were reported differently in different sections of the report (see note after table below). For tazarotene, steady state appeared to have been achieved between weeks 9 and 18, as compared to week 2 for isotretinoin and acitretin. Five values in the high dose tazarotene group were above the upper LOQ and were extrapolated. The samples were not diluted appropriately and re-analyzed.

The following data are from samples collected at the week 18 sampling.

Dose (mg/kg/day)	Cmax (ng/mL)	Tmax (hours)	AUC_{0-t} (ng•hr/mL)
TAZAROTENE			
0.1	5.54	2.63	6.47
0.3	23.4	1.63	28.9
1	42.8	1.00	77.4
TAZAROTENIC ACID			
0.1	44.7	2.75	161

0.3	183	1.75	473
1	466	1.5	1240
	ISOTRETINOIN		
1	386	4.75	2770
10	2190	6.25	16500
30	6670	4.00	38700
	4-OXO-ISOTRETINOIN		
1	4.11	6.67	40.6
10	72.8	10.0	737
30	200	6.00	2390
	ACITRETIN		
1	127	3.00	302
10	376	3.50	1280
30	357	4.25	2020
	13-CIS-ACITRETIN[a]		
1	0	Not calculable	not calculable
10	7.17	2.0	18.8
30	0	4.0	68.3

[a]13-cis acitretin data was reported differently throughout the report; transposition of numbers between columns is a possible explanation. The data included in the above table was from the toxicokinetics report in appendix K. It is unclear how Tmax was determined for a Cmax of 0 for 13-cis-acitretin.

Reviewer's comment: In other species, including man, tazarotene concentrations are rarely measurable due to rapid metabolism to the active moiety, tazarotenic acid. In an earlier submission, the sponsor noted that the dog was chosen for additional studies because the species is less sensitive to the adverse effects of retinoids. In the case of tazarotene, this relative lack of sensitivity may be in part due to slower metabolism of the drug to the active metabolite. There is no discussion of ADME in dogs relative to humans in order to support the relative value of the canine model. There does appear to be accumulation of active drug in these animals over time, particularly at the higher doses.

Key Study Findings:

Slight erythema, initial body weight loss, decreased weight gain, and increased absolute and relative adrenal weights were seen at the mid and high doses (0.3 and 1.0 mg/kg) of tazarotene. At the mid-dose of tazarotene, a limp was observed in one dog, which may be indicative of adverse effects on the bones or joints. The NOEL was 0.1 mg/kg/day tazarotene po for 4 months (HED=0.05 mg/kg/day). Tazarotene appeared to accumulate over time, with steady state plasma concentrations not being reached until after nine weeks of treatment. The AUC_{0-t} for tazarotenic acid at the NOEL was 161 ng•hr/mL.

2. Study Title: A 9-month oral toxicity study of tazarotene in beagle dogs
Study No: 98-3378 (sponsor study no. TX99010)
Amendment #, Vol #, and page #: NDA 21-184 SE1-001, volumes 9-12
Conducting laboratory and location:
Date of study initiation: 12 April 1999

GLP compliance: yes
QA- Report Yes (X) No ()
Methods:
Dosing:

- species/strain: beagle dogs
- #/sex/group or time point: 6/sex/group
- age: 6.5 – 7.5 months
- weight: 6.7-11.6 kg
- satellite groups used for toxicokinetics or recovery: 2/sex/group continued for a 2-month recovery period
- dosage groups in administered units: vehicle, 0.3, 1, 3, 10, or 30 mg/kg/day tazarotene
- route, form, volume, and infusion rate: oral, once daily. Doses were missed on several occasions in all groups. On one occasion, animals in the 3 mg/kg group were administered 0.3 mg/kg.

Drug, lot#, radiolabel, and % purity: tazarotene solution lot numbers 11524 (preparation # 9226X), 11525 (preparation # 9235X), 11526 (preparation # 9236X), 11527 (preparation # 9237X), 11521 (preparation # 9239X)
Formulation/vehicle: tazarotene solutions, 0.025% (preparation # 9226X), 0.1% (preparation # 9235X), 0.25% (preparation # 9236X), 1.0% (preparation # 9237X), 2.0% (preparation # 9239X)
Observations and times:

- Clinical signs: Cageside observations were made twice daily, once before and once after test article administration. Posture and gait observations were made pretest and twice weekly during treatment and recovery periods. Physical examinations were performed pretest and once weekly during the study.

Radiographs were taken pretest, after 1, 4, 7, and 9 months of treatment, and at the end of recovery period. Films included lateral and cranio-caudal views of both forelegs, and a lateral view of the left hind leg from the distal third of the femur to the tarsus. Films of the spine and skull were taken at approximately 8 months of treatment and at the termination of the treatment and recovery periods.

- Body weights: Animals were weighed pretest and weekly during treatment. Terminal fasted body weights were obtained just prior to necropsy.
- Food consumption: Food consumption was visually estimated weekly throughout the study.
- Ophthalmoscopy: Eyes were examined visually and by indirect ophthalmoscopy pretest, on day 9 in the two high dose groups, at weeks 5, 18, 26, and 39 for the surviving treatment groups, and on day 341 for recovery animals. Mydriasis was induced by Mydriacil 1%.
- EKG: not performed
- Hematology: Fasting blood samples were taken from all study animals pretest, at months 1, 4, 6, and 9, and at the end of the recovery period. Terminal samples were taken from animals in the high dose groups when euthanized early in the study for humane reasons. Hematology and coagulation parameters were evaluated.
- Clinical chemistry: Serum was obtained from clotted blood samples collected at the timepoints described above for hematology determinations.

- Urinalysis: Urine samples were collected in ice-chilled containers overnight, using metabolism pans under the cages. Samples were obtained pretest, at months 1, 4, 6, and 9, and at the end of the recovery period. Urine volume was measured over a 16-hour period at the same intervals from food- and water-deprived animals. Samples were collected, where possible, from animals in the 10 mg/kg group by cystocentesis at termination on day 29.
- Organ weights: obtained at necropsy
- Gross pathology: Animals were euthanized by exsanguination following anesthesia with acepromazine and sodium pentobarbital. All six animals/sex in the 30 mg/kg dose group were terminated on day 9, and all six animals/sex in the 10 mg/kg dose group were terminated on day 29. One male in the 3 mg/kg dose group was terminated on day 188 (6 months). Up to 4/sex/group in groups 1-4 were sacrificed at the end of the 9-month treatment period, and the remaining 2/sex/group were sacrificed at the end of the recovery period. All animals were subjected to a complete gross necropsy.
- Organs weighed: adrenals, brain, heart, kidneys, liver (without gall bladder), ovaries, pituitary, spleen, and testes.
- Histopathology: performed on tissues identified in the table under Addendum 1
- Toxicokinetics: Blood was collected at 0 (pre-dose), 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose on days 20 (week 3), 190 (6-months), and 274 (termination of treatment) for toxicokinetic analysis. Samples were collected from dogs in the 30 mg/kg group on day 8 at all but the 12 hour timepoint, just prior to early termination of that group. Samples were centrifuged and plasma was removed and stored at -15°C until analysis. The sensitivity of the assay for tazarotenic acid ranged from ` ng/mL.
- Other: Mean body and organ weights and clinical laboratory parameters were analyzed statistically. The methods used were changed mid-study without clear explanation. Protocol amendment #7 documented the change "to reflect current procedures, used for report," but did not explain why data from the first half of the study were not re-analyzed using the second set of procedures.

First, Bartlett's test for homogeneity of variance (two-tailed, 1% significance level) was applied. If variances were equal, then one-way ANOVA (parametric test) was performed followed by Dunnett's test to determine which values were different from control. If not, then the Kruskal-Wallis test (nonparametric) was performed, followed by Dunn's summed rank test. A statistical test for trend (standard regression techniques in the parametric case and Jonckheere's test for monotonic trend in the nonparametric case) also was performed. Analyses were made at the 5% and 1%, two-sided significance levels.

After week 21 for body and organ weights, and beginning month 9 for clinical pathology data, the statistical methodology was altered. For all parameters except organ weights, the above methodology was altered by addition of Williams' test as an optional alternative to Dunnett's test, and addition of Shirley's test as an optional alternative to Dunn's test. Pairwise comparisons with Bonferroni correction were stated to be used to determine differences of treatments from control. For organ weights, the original methodology was modified such that one-way ANOVA was performed whether or not variances were equal, and for variances that were not equal, Cochran and Cox's modified t-test was substituted for Dunn's test.

Results:

- Deaths: All six animals/sex in the 30 mg/kg dose group were terminated on day 9, all six animals/sex in the 10 mg/kg dose group were terminated on day 29, and one male in the 3 mg/kg dose group was terminated on day 188 (6 months), all for humane reasons due to adverse effects of the test article. The latter dog was euthanized, at least in part, because of skull and spinal abnormalities. Therefore, radiographs of the spine and skull were added to the protocol at 8 and 9 months and at the end of recovery.
- Clinical signs: At 3, 10 and 30 mg/kg, observations included decreased activity, thin appearance, dehydration, and irregular gait and posture that were dose-related in severity. At 3 mg/kg, one male presented with a persistently irregular gait hunched appearance, unthrifty coat, and progressive weight loss; that animal was euthanized after six months. Irregular gait or posture was observed occasionally in the rest of the animals at 1 and 3 mg/kg. On two occasions, apparent gait abnormalities were observed in animals at 0.3 mg/kg. Erythema, rashes, otitis, and red gums were noted at all treatment doses; some persisted through the recovery period. Gait abnormalities were not observed during the recovery period.

Radiographic alterations were seen in all surviving treatment groups. These included a dose-related incidence of early epiphyseal closure in all dose groups at 1 and 4 months that was more pronounced in females than males. Physes were closed in all but one male control group dog at nine months, and all physes were closed at the end of the recovery period in all animals. Abnormal shape and/or density of the long bones were seen at 4 and 9 months in the 1 and 3 mg/kg groups and at 9 months in the 0.3 mg/kg group. A finding of medullary opacity/increased cortical margins was noted at one month in groups receiving 3 or 10 mg/kg, at four months in groups receiving 1 or 3 mg/kg, and at nine months in the 0.3 mg/kg dose group. Abnormalities of the skull and spine were seen in all dose groups at 8 and 9 months (dose-related in incidence and severity, again more pronounced in females). Changes in the skull included thinning of the dorsal cranium, decreased prominence of the occipital protuberances, and cloudy appearance of the frontal sinuses. In the spine, abnormal shape was noted of the vertebral bodies (mid-body thinning), spinous processes, and the neural canal (widening). Spondylosis was seen at L7-S1 in three tazarotene-treated dogs at 8 or 9 months. Apparent mineralization of the intervertebral disks was noted in two dogs dosed at 1 mg/kg. Mineralization of the epiglottis was seen at 3 mg/kg at 8 and 9 months. At the end of the recovery period, the report states that there was neither progression nor regression of radiographic lesions.
- Body weights: Marked body weight loss was reported for the 10 and 30 mg/kg groups. High dose animals lost up to 15% of their body weight in the first week of treatment, and the 10 mg/kg group exhibited up to 36% body weight loss during the first four weeks. In the 3 mg/kg group, body weights decreased by up to 26% in the first three to six months. Some recovery was noted after that time in surviving animals, but body weights and cumulative weight gains remained lower than controls for the remainder of the treatment period. During the recovery period, lower body weights persisted in females, but weight gains in many animals in the 3 mg/kg group were similar to controls. Recovery was more evident in males than in females. There were no apparent effects on body weight in the 0.3 and 1 mg/kg groups.
- Food consumption: Food consumption was decreased at 10 and 30 mg/kg. Supplementation with canned dog food was attempted, but with varying success. At 3 mg/kg, food consumption was decreased through week 7, and supplementation with canned food was also used for this group. After week 8, food consumption was similar to

or slightly lower than controls for the rest of the study (with the exception of the one male that was euthanized at six months.) For the 0.3 and 1 mg/kg groups, the report states that food consumption was similar to control values or exhibited "normal variability."
- Ophthalmoscopy: There were no test article-related findings. However, there is reference in protocol amendment #1, in which an ophthalmic examination at 8 days for the 10 and 30 mg/kg groups is added to the methods, to "ocular observations suggestive of an effect of the test article." These observations are not detailed in the report.
- Electrocardiography: not performed
- Hematology: Hematological effects were seen in the first month of treatment at 3, 10 and 30 mg/kg. These included increased erythrocyte counts, hemoglobin and hematocrits, possibly indicative of dehydration. Prothrombin times were increased in those three groups. Neutrophilia was reported in animals in the 30 mg/kg group that were euthanized at 8 days.

After the first month, red blood cell parameters in the 3 mg/kg group were decreased and persisted as such through the end of the recovery period, but the differences were not statistically significant.
- Clinical chemistry: At 10 and 30 mg/kg, clinical chemistry alterations seen in blood samples obtained at termination included increased serum alkaline phosphatase, SAST, and SALT, hypercalcemia, hyperphosphatemia, and increased BUN and creatinine. Serum protein alterations seen in those groups included slight increases in globulin and/or total protein and absolute or relative decreases in albumin, with corresponding decreases in the A/G ratio. Additional alterations seen at 30 mg/kg at 8 days included increased cholesterol, triglyceride, GGT, and LDH values.

At 1 month, BUN and serum calcium concentrations were increased in the 3 mg/kg group. SAST values were increased at 1 and 3 mg/kg for the duration of the treatment period, but were comparable to controls at the end of the recovery period. SALT values were increased for males at 0.3, 1, and 3 mg/kg at months 4 and 9, but were comparable to controls at the end of the recovery period. Serum alkaline phosphatase activity was increased at 1 and 3 mg/kg at months 1, 4, 6, and 9. With the exception of one animal in each of the 0.3, 1 and 3 mg/kg groups, alkaline phosphatase values were mostly comparable to controls by the end of the recovery period. Serum protein and triglyceride alterations were seen at 1 and 3 mg/kg throughout the treatment period, but were not evident at the end of the recovery period, with the possible exception of persistently decreased albumin in females at 3 mg/kg.
- Urinalysis: No urinalysis was performed on animals in the 30 mg/kg group. At 10mg/kg, specific gravity was decreased, but urine volume was not measured. Animals treated with 3 mg/kg tazarotene had decreased urine specific gravity and increased urine volume at one and four months, apparently indicating a decrease in renal ability to concentrate urine. Values were similar to control at other timepoints.
- Organ Weights: At the end of the treatment period, ovarian weights were decreased and liver weights were increased in females at 3 mg/kg. Absolute ovarian weights were lower and relative liver weights were considerably higher than controls in the 10 and 30 mg/kg groups as their termination, as well. Also in females, absolute and/or relative adrenal weights were increased at all tazarotene doses, but were only considered by the sponsor to be significant at 3 mg/kg. Absolute and relative spleen weights were lower in treated females than in controls (e.g., by nearly 25% in the 0.3 mg/kg group), but were not

considered significant. The report states that there were no corresponding microscopic changes in the spleen.

In males, absolute and relative adrenal weights were increased at all doses (except for absolute adrenal weight at 10 mg/kg, due to markedly decreased body weights), absolute and/or relative liver weights were increased at 1 mg/kg and above, and absolute and relative spleen weights were decreased at 10 and 30 mg/kg. These findings in males were not considered by the sponsor to be significant. Testis weights were decreased in males at 3 mg/kg and above, but were only considered significant in the 3 mg/kg group. There were corresponding microscopic changes in the testes at 3 and 10 mg/kg.

The sponsor reported that there were no organ weight differences from controls at the end of the recovery period. However, testis weights at 1 and 3 mg/kg appeared low.
- Gross pathology: At 10 and 30 mg/kg, discoloration of the long bones of the fore and hind limbs was seen, corresponding to the microscopic finding of highly vascularized or hemorrhagic periosteal granulation tissue. Enlarged kidneys, correlating with tubular dilation on histopathological examination, were seen in the 10 and 30 mg/kg groups. Discoloration of the gingiva was seen at both doses. Discoloration of lymph nodes was seen in males treated with 30 mg/kg tazarotene, corresponding to the histological finding of erythrophagocytosis.

In surviving groups at the end of the treatment period, two 3 mg/kg females were noted to have thinning of the cranium. Discoloration of the intestinal mucosa was seen in all treated groups and in one control animal. Two 3 mg/kg males exhibited discoloration of the stomach, corresponding to severe ulcerative changes.

At the end of the recovery period, one female at 3 mg/kg was found to have small thin bones. One 3 mg/kg male had small testes and epididymides, corresponding histologically with atrophic tubules in both testes and reduced sperm in the epididymides.
- Histopathology: At 10 and 30 mg/kg, findings at early termination were primarily signs associated with increased bone resorption or toxicity secondary to excessive bone remodeling. Theses included periosteal thickening, vascularization and hemorrhage, periosteal granulation tissue, and increased subperiosteal osteoclastic activity that was most severe in long bones. Other skeletal findings included decreased cortical bone, exostosis, and partial physeal closure. Osteolysis, osteofibrosis, and periosteal granulation tissue were evident in the vertebrae. In the ribs, disorganization and osteolysis were noted at the costochondoral junciton, in addition to reduced cortical bone and periosteal granulation tissue.

Soft tissue mineralization was observed at many sites, especially in the kidney, heart, stomach, choroid plexus of the brain, blood vessels (including coronary vessels), intestinal tissue, and esophagus. In the heart, this was accompanied by myocardial degeneration and in the kidney by focal granulomatous inflammation. In the lungs, mineralization was associated with emphysema. The report describes necrotizing polyarteritis accompanied by mineralization, but states that arteritis "has been described as a treatment related finding with some retinoids." Mineralization and resulting secondary effects were seen to a greater degree in the 10 mg/kg group than in the 30 mg/kg group, probably due to duration of treatment prior to termination of the group.

Renal tubular dilation (primarily distal or collecting tubules) and degeneration were seen in animals in the 10 and 30 mg/kg groups. Mineralization was noted throughout the kidney, with the additional findings of interstitial nephritis or

granulomatous inflammation. At 10 mg/kg, cortical fibrosis was also noted and attributed to a progressive chronic condition.

At the highest dose, effects of the test article on the testes could not be determined fully, due to the relative immaturity of the animals. At both 10 and 30 mg/kg, there were findings consistent with testicular degeneration, tubular vacuolation, and germ cell depletion.

Additional findings in the two highest dose groups that were terminated early included erythrophagocytosis in lymph nodes, focal necrosis with inflammatory cell infiltrate and congestion in the liver, increased femoral bone marrow volume and cellularity, severe stomach ulceration with submucosal edema, hemorrhage, and inflammation, mucosal congestion and inflammation in the low colon, cysts in the parathyroid and pituitary, parafollicular cell hyperplasia and mineralization in the thyroid, atrophy of the thymus, and acanthosis of the skin with loss of hair follicles. At 30 mg/kg, increased basophilia was noted in the medulla of the adrenal gland.

In surviving animals at 0.3, 1, and 3 mg/kg:

In the one male at 3 mg/kg that was euthanized at six months, periosteal changes were noted. Because of radiographic skull findings in that animal and at later times in additional animals, the crania were collected at the month 9 necropsy for measurement and microscopic examination. A dose-related reduction in bone thickness was seen at all doses, and was more evident in females than males. Suture line fusion also was noted in some treated animals. Focal ossification of cartilaginous plates of the epiglottis was observed in 3 of 4 females and 1of 3 males at 3 mg/kg at the end of the treatment period.

Other skeletal effects included osteolysis, periosteal granulation tissue and increased osteoclastic activity (particularly in the long bones) to some degree at all tazarotene doses, and hypercellular marrow in most females at 3 mg/kg. Disorganization of chondrocytes and/or exostosis at the costochondral junction was observed in males at 3 mg/kg and females at 1 and 3 mg/kg. Chondroid disorganization and degeneration of the sternum was observed in all treated male groups and in females at 3 mg/kg. Osteolysis and fibrosis were noted in the vertebrae at 3 mg/kg.

Effects on the male reproductive system were seen at 3 mg/kg in all 3 males at the terminal sacrifice and in the one animal sacrificed early at six months. These included an increased incidence and severity of testicular degeneration and germ cell depletion correlating with decreased testis weights. Tubular vacuolation was seen. At 0.3 and 1 mg/kg, germ cell effects were reported to be similar to controls, but tubular atrophy and vacuolization were noted in the histopathology report in one male at 1 mg/kg.

Soft tissue mineralization was evident at 1 and 3 mg/kg. In the kidney, mineralization of the cortex and medulla was noted in males and females at both doses. Mineralized deposits in the bronchioles were noted in a 1 mg/kg female, and mineralization was reported in the spleen in a 3 mg/kg female, along with capsular fibrosis in the liver and spleen.

Congestion was reported in the liver (males) and gastrointestinal tract (both sexes). In the adrenal gland, the zona reticularis of the cortex was vacuolated in one 3 mg/kg male. In males and females at 1 and 3 mg/kg, and in one male at 0.3 mg/kg, increased incidence and/or severity of erythrophagocytosis was noted in the lymph nodes.

Atrophy of the thymus was reported at 1 and 3 mg/kg. The sponsor states that this may be due to tazarotene or to stress (*Reviewer's comment: Animals at these doses did*

not have a stress leukogram. Additionally, the thymus regresses in maturing dogs, and this may have been normal regression associated with the dogs' age.).

Recovery sacrifice:

The sponsor's report states that effects other than bone changes reversed after the two-month recovery period. Persisting effects included dose-related thinning of the cranium with suture line fusion all doses, which was more evident in females. At 3 mg/kg, both females had focal osteoid deposition in the epiglottis, and one male had focal dystrophy of the cartilaginous plates of the epiglottis. Females at 1 and 3 mg/kg had osteofibrosis at osteochondroid junctions.

Mineralization was evident in the medulla and cortex of the kidney, either alone or associated with cortical fibrosis in both 3 mg/kg males and in the medulla in one of the 3 mg/kg females, associated with chronic interstitial nephritis.

One male at 3 mg/kg had small testes and epididymides, corresponding histologically with multiple areas of atrophic tubules with Leydig cell hypertrophy in both testes and reduced sperm in the epididymides. Germ cell degeneration was noted in one of the two males at 1 mg/kg. Depletion of spermatocytes/spermatids was seen in one of the two recovery males in all tazarotene-treated groups, and occasional or scattered atrophic tubules were reported in one of the two recovery males in each of the 1 and 3 mg/kg groups.

Bone marrow was reported to be hypercellular in one of the 3 mg/kg males and one of the 1 mg/kg females. In the lymph nodes, erythrophagocytosis was noted in males and females in all tazarotene-treated groups and in one of the control females. One male at 0.3 mg/kg had optic nerve axonal degeneration and myelin vacuolation.

- Toxicokinetics: Oral tazarotene was well absorbed. Cmax and AUC were found to increase with dose.

		Tazarotene		Tazarotenic acid	
Tazarotene dose (mg/kg/day)	Day	Cmax (ng/mL)	AUC_{0-t} (ng•hr/mL)	Cmax (ng/mL)	AUC_{0-t} (ng•hr/mL)
0.3	20	4.12	18.6	54.5	271
	190	4.44	14.6	60	294
	274	4.28	15.1	66.1	340
1.0	20	15.7	58.1	190	680
	190	17.7	57.7	241	918
	274	13.2	50.7	192	891
3.0	20	36.3	176	526	2010
	190	34.1	153	512	1910
	274	43.2	177	593	1970
10[a]	20	135	488	1610	6490
30[b]	8	42.4	163	903	4500

[a]dogs euthanized after 29 days
[b]dogs euthanized after 8 days

Reviewer's comment: Values for the 0.3 and 1 mg/kg doses are substantially lower than those for the same doses in the 4-month study. Variability was high for Cmax and AUC at all doses. This raises questions about the relative bioavailability of the dose preparations used in the two studies (tazarotene in solution in the 9-month study vs. tazarotene clinical formulation in gel capsules in the 4-month study).

Key Study Findings:

In a 9-month study of oral tazarotene in beagle dogs, doses of 10 and 30 mg/kg/day resulted in severe skeletal effects and effects that appeared to be secondary to changes in bone metabolism, resulting in early termination of those groups. At 1 or 3 mg/kg/day, animals exhibited body weight loss, elevation of serum levels of liver enzymes, and skeletal changes. At 0.3 mg/kg/day and above, gait and/or postural abnormalities were noted, as was radiographic evidence of bone changes at all doses from early as one month. Radiographic signs included early epiphyseal closure, which was more pronounced in females, abnormal shape and density of long bones, and evidence of bone thinning and remodeling. These findings were dose-related in incidence, severity, and time of appearance. Soft tissue mineralization and skin changes (erythema, rashes, otitis and red gums) were evident in all groups. Body weights and food consumption were markedly decreased at doses of 3 mg/kg and above. Evidence of dehydration was apparent at 3, 10 and 30 mg/kg. After the first month, red blood cell parameters were decreased at 3 mg/kg. Serum levels of alkaline phosphatase, AST, and/or ALT were increased in all groups during treatment. At 10 and 30 mg/kg, additional findings included hypercalcemia, hyperphosphatemia, increased BUN and creatinine, alterations in total protein and A/G ratio, and increased cholesterol and triglycerides. After recovery, high alkaline phosphatase values persisted in some animals in all tazarotene-treated groups. At 3 mg/kg urine specific gravity was decreased and urine volume was increased. At necropsy, adrenal weights were increased, and spleen weights were decreased at all doses. Liver weights were increased at 1 mg/kg and above. Ovarian and testicular weights were decreased at 3 mg/kg and above. Gross and histopathological changes at 10 and 30 mg/kg included hemorrhagic periosteal granulation tissue, thinning of bones, exostosis, partial physeal closure, soft tissue mineralization, enlarged kidneys with corresponding microscopic lesions, and erythrophagocytosis in lymph nodes. At the end of the treatment period, skeletal effects were seen at all doses. Testicular changes were evident at as low as 1 mg/kg, and were associated with decreased testis weight at 3 mg/kg. Stomach ulceration was seen in 3 mg/kg males. At all tazarotene doses, there was discoloration of intestinal mucosa. Soft tissue mineralization and changes in the liver and spleen were evident at 1 mg/kg and higher. At the end of the recovery period, effects on the skeleton, testes, and kidney, as well as evidence of erythrophagocytosis in lymph nodes and soft tissue mineralization persisted.

Toxicology summary:

Toxicology studies of tazarotene in various formulations by various routes of administration in multiple species consistently have demonstrated effects typical of retinoids. Typical signs of retinoid toxicity seen in studies of tazarotene primarily affected the liver, skeleton, kidney, adrenal gland and the blood.

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