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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-184/002

Pharmacology Review(s)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

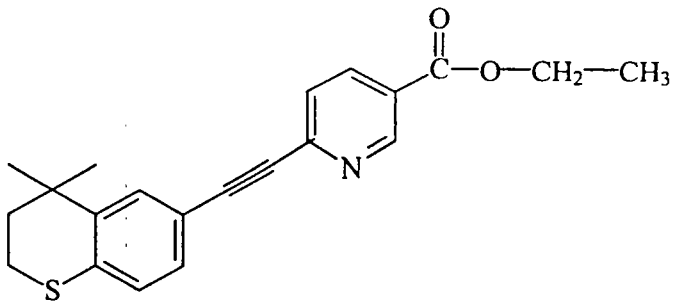
NDA number: 21-184
Review number: 4
Sequence number/date/type of submission: SE1 002
stamp date 6/29/01
efficacy supplement
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Allergan, Inc., Irvine, California
Manufacturer for drug substance: [redacted]

Reviewer name: Amy C. Nostrandt, D.V.M., Ph.D.
Division name: Division of Dermatologic and Dental Drug Products
HFD #: 540
Review completion date: 1/18/02

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
Mole file number:
Molecular Formula / Molecular Weight / Structure:

$C_{22}H_{25}NO_2S$
MW =



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
IND [redacted] tazarotene
IND [redacted] tazarotene
IND [redacted] tazarotene creams for acne vulgaris

Drug class: acetylenic retinoid

Indication:

Clinical formulation:

ingredient	%w/w 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		
carbomer 1342 NF		
sorbitan monooleate NF		
carbomer 934P NF		
sodium hydroxide NF		
purified water USP		
total:	100	100

pH approximately 6.4

Route of administration: topical to affected skin

Proposed use:

In clinical trials of 0.1% tazarotene cream in patients treated for signs of photoaging, the drug product was applied once daily for 24 weeks. The sponsor states that 0.1% tazarotene cream was significantly more effective than vehicle in reducing the severity of fine wrinkling and mottled hyperpigmentation. The sponsor reports that adverse events were primarily mild to moderate local irritation.

A pharmacokinetic study was performed in which patients with photoaging were treated over 15% of total body surface area with of 0.1% tazarotene cream. The mean Cmax was 1.75 ng/mL and the mean $AUC_{0\text{-}24\ h}$ in those patients was 23.8 ng*hr/mL. The maximum $AUC_{0\text{-}24\ h}$ seen in clinical patients was 43.971 ng*hr/mL. This value is used for interspecies comparisons below.

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

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. An efficacy supplement for the use of the 0.1% tazarotene cream formulation in the treatment of acne vulgaris was recently approved. The current submission is an efficacy supplement for the use of the 0.1% tazarotene cream formulation.

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 [redacted] for an oral tazarotene formulation. These studies were previously submitted to the efficacy supplement for treatment of acne vulgaris (SE1 001) and were reviewed under that submission.

Studies reviewed within this submission: none

Studies not reviewed within this submission:

The following studies were submitted to this supplement and to SE1 001. They have been reviewed under the previous supplement and are summarized only in this review.

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.

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.

Executive Summary

I. Recommendations

A. Recommendation on Approvability

From a pharmacology/toxicology standpoint, the application is approvable, with labeling revisions as detailed at the end of this review.

B. Recommendation for Nonclinical Studies

None

C. Recommendations on Labeling

Labeling should be consistent with the previously approved labeling for the drug product for the indications of treatment of psoriasis and acne vulgaris. Specific wording is recommended at the end of this review to include description of animal exposure as multiples of human exposure, based on pharmacokinetic data from clinical trials of the drug used for this indication.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings

There are no new nonclinical findings. Effects of tazarotene are typical of retinoid drugs. The target organs of toxicity are the skin, liver, skeleton, adrenal gland, kidney, testis and blood. Three-month topical studies of tazarotene creams were performed in rats and minipigs. Partial improvement of effects was seen after a one-month recovery period. Toxicokinetic monitoring revealed a dose-related linear systemic exposure to tazarotenic acid. Longer term studies of tazarotene gels were performed. Similar effects were seen that appeared to be time- and dose-related in incidence and severity. Oral studies in multiple species revealed signs typical of hypervitaminosis A.

Results of genetic toxicology tests and a dermal carcinogenicity study were negative. A study of photo co-carcinogenicity demonstrated enhancement at all concentrations tested of UV light-induced carcinogenesis.

A segment I reproductive and developmental toxicity study of tazarotene gel in rats showed no impairment of fertility at doses up to 0.125 mg/kg. Segment II studies of topical or oral tazarotene demonstrated teratogenicity and/or fetal toxicity. A segment III study in rats of tazarotene gel at doses up to 0.125 mg/kg/day resulted in decreased pup survival, and developmental and behavioral delays.

B. Pharmacologic Activity

There is no new information regarding pharmacologic activity. Tazarotene is metabolized to tazarotenic acid, which is the active substance. Tazarotenic acid binds to nuclear retinoic acid receptors (RAR's) and activates retinoid-responsive genes. In nonclinical models, tazarotene formulations appeared to be more irritating and resulted in greater loss of skin barrier function, as measured by an increase in trans-epidermal water loss, than tretinoin creams.

C. Nonclinical Safety Issues Relevant to Clinical Use

There are no new nonclinical safety issues. Systemic exposure in rats and/or rabbits to tazarotenic acid at teratogenic doses of the drug were in the same order of magnitude as the maximum systemic exposure seen in patients in clinical trials treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for signs of photoaging.

III. Administrative

A. Reviewer signature: /S/

B. Supervisor signature: Concurrence - /S/

Non-Concurrence - _____
(see memo attached)

C. cc:
NDA 21-184
HFD-540/DD/WILKIN
HFD-540/SupPHARM/JACOBS
HFD-540/MO/Ko
HFD-540/CHEM/Turujman
HFD-540/PMS/Bhatt
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PHARMACOLOGY/TOXICOLOGY REVIEW

I. 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 [redacted](000), 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.

II. 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.

III. PHARMACOKINETICS/TOXICOKINETICS:

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

1.

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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 — 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.

IV. GENERAL TOXICOLOGY:

Study reports submitted with this supplement were previously reviewed and are summarized here.

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 weights, increased adrenal weight, and hematologic and serum chemistry changes typical of retinoids, such as decreased erythrocyte counts, decreased serum protein, and increased serum triglycerides and transaminase enzyme activities. 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 after a one-month recovery period.

A three-month topical study was performed in — 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 $mg/m^2/day$), split into two daily doses, 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 one-month bridging study in rats 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.

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. Hematological evaluation revealed decreased erythrocytes. 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 has previously reported no systemic effects in either study, 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 intravenous dose of up to 2 mg/kg in rats caused no drug-related effects after a 14-day observation period. Similarly, 0.075 mg/kg intravenous 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 intravenous bolus dose of 0.75 mg/kg in monkeys was reported to cause no drug-related adverse effects after a one-week observation period.

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, heart, and spleen and/or thymus 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. Systemic effects in theses species were seen at exposures that were less than or within the same order of magnitude as systemic exposures seen in acne patients treated over 15% TBSA.

In oral toxicology studies of tazarotene in rats, a NOEL was not identified. In a 90-day study, body weight decreases were seen at 0.05 mg/kg (HED=0.008 mg/kg). In a second rat study, at 0.05 mg/kg for 13 weeks, altered cholesterol levels were seen in males. At 0.025 mg/kg (HED=0.004 mg/kg) for 26 weeks, hematologic and serum chemistry changes included decreased total protein, albumin, cholesterol, neutrophils, and serum calcium, and increased serum glucose. In the latter study, "mean blood levels" were reported to be 0.5 ng/mL at that dose. At higher doses in the three rat studies, histopathological changes in bone, liver, heart, thymus, and lung were seen.

In oral toxicology studies in monkeys, the NOEL reported for the 4-week study was 1.0 mg/kg (HED=0.33 mg/kg). However, higher doses in that study were associated with fatality. When dosing was continued for a longer period of time, the NOEL dropped sharply. In a 13-week study in cynomolgus monkeys, a dose of 0.05 mg/kg (HED=0.017 mg/kg) was considered to be the NOEL. Decreased body weights were seen at the next highest dose (0.25 mg/kg, HED=0.08 mg/kg), and 50% fatality occurred at 1.0-1.6 mg/kg (HED=0.33-0.53 mg/kg). When administered for six months, a dose of 0.05 mg/kg (HED=0.017 mg/kg) produced spinal stiffness and epiphyseal growth plate changes in monkeys. In a 1-year monkey study, the NOEL was 0.0125 mg/kg (HED=0.004 mg/kg) which was associated with a Cmax of approximately 4 ng/mL and an AUC of approximately 25 ng*hr/mL. At 0.025 mg/kg (HED=0.008 mg/kg), one of four males had a rare ophthalmic lesion judged to be possibly related to treatment. Severe toxicity, including irreversible bone and articular degeneration, serum chemistry changes and death, was observed in that study at 0.125-0.25 mg/kg (HED=0.042-0.083 mg/kg) with Cmax of approximately 22 ng/mL or greater and AUC of approximately 128 ng*hr/mL or greater.

Studies of oral tazarotene in dogs were undertaken. Preliminary results were first reported in IND [redacted] serial #007, where the sponsor stated that this animal model is less sensitive to the toxic effects of retinoids and has been used in the evaluation of isotretinoin and acitretin. In a 4-month range-finding oral toxicology study in dogs, the NOEL was 0.1 mg/kg (HED=0.05 mg/kg). At doses of 0.3 mg/kg (HED=0.15 mg/kg) and higher, effects were seen on body weight and adrenal weights, as well as erythema of the skin. One (of four) animal at 0.3 mg/kg did present with a limp at week 16, which was dismissed by the sponsor as not drug-related, although the drug is known to cause skeletal and articular abnormalities at sufficiently high doses for extended durations. Toxicokinetic evaluation indicated dose-related systemic exposure to the drug and its active metabolite, and accumulation over time.

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 (*Reviewer's comment: This is consistent with the finding of a limp in one dog at 0.3 mg/kg/day at the end of the 4-week study.*) 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. The sponsor states that systemic drug exposures in dogs were one order of magnitude greater than those seen in clinical acne patients treated over 15% BSA.

V. GENETIC TOXICOLOGY:

Genetic toxicology summary:

Tazarotene was negative in a standard battery of genotoxicity 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/HGPRT mammalian cell forward gene mutation assay. Tazarotene was negative for clastogenicity in the *in vivo* mouse micronucleus assay.

Labeling recommendations: Recommendations have been made previously for reporting of negative results in the mutagenicity section of the labels for existing tazarotene drug products. The same wording would be appropriate for the label for this clinical indication.

VI. CARCINOGENICITY:

Carcinogenicity summary:

Dietary (doses up to 0.125 mg/kg/day) and dermal (doses up to 1 mg/kg/day as a 0.1% gel) carcinogenicity studies in rats and mice, respectively, were negative, but all concentrations of tazarotene tested (0.001% - 0.01%) 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.

Labeling Recommendations: Recommendations have been made previously for reporting of results of carcinogenicity and photo co-carcinogenicity studies in the labels for existing tazarotene drug products. The same wording would be appropriate for the label for this clinical indication.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Study reports submitted with this supplement were previously reviewed and are summarized here.

Reproductive and developmental toxicology summary:

In a dermal segment I study of tazarotene gel in rats, no impairment of fertility was seen at doses up to 0.125 mg/kg/day (0.25 mL/kg of 0.05% gel; HED=0.02 mg/kg). Oral fertility studies were performed in male and female rats separately. In males, at doses of 0.3, 1.0, and 3.0 mg/kg, accessory sex organ weights were decreased. At 3.0 mg/kg (AUC=325 ng*hr/mL), sperm count and density were decreased, and the animals were severely affected as evidenced by decreased body weight and long bone fractures. There were no significant effects on parameters related to mating performance and fertility, but the high dose group was discontinued early due to severe toxicity and was mated to females selected in proestrus, so comparison of results in that group to the others in that study was inappropriate. In females, the high dose of 2 mg/kg (AUC=296 ng*hr/mL) resulted in decreased estrous cycling, decreased litter size and implantations, decreased fetal body weights and increased malformations. However, there were no significant effects on mating or fertility parameters.

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, eschar, and skin thickening, with no change in body weight or food consumption. Pup survival was significantly less in the high dose group at lactation days 6 and 21. Decreased pup body weight was seen at 0.05 mg/kg. There was no effect on the reproductive capability of the offspring. Postnatal developmental and behavioral delays were observed.

Tazarotene was teratogenic in oral studies in rats and rabbits and appeared to be teratogenic in a dermal developmental study in rabbits performed to support the gel formulation. The following table summarizes segment II studies of oral and topically applied tazarotene in rats and rabbits. Exposure comparisons are made to patients in clinical pharmacology studies of tazarotene cream.

Study number	Species	Route	Dose (mg/kg/day)	AGN 190299 AUC (ng*hr/mL)	Adverse effects	Multiple of human exposure		
						psoriasis[a]	acne[b]	photo-aging[c]
1643-SLS-3202.12	Rat	Oral	1.0	510	Decreased litter size; decreased fetal/neonatal weight; malformations including cleft palate, skull anomalies, cephalocele, exencephaly, facial papilla anomaly, pinna anomaly, increased no. early neonatal deaths; postnatal developmental and behavioral delays	6	19.2	11.6
			0.25	115	Developmental delays; external malformations	1.3	4.3	2.6
98-4146	Rat	Oral	2.0	207	Increased post-implantation loss; decreased live fetuses; malformations including exencephaly, pinna alteration, micr-/an-ophthalmia, microtia, facial papilla anomalies, cleft palate.	2.3	7.7	4.7

			0.5 mg/kg	94	Increased skeletal alterations, including supernumerary ribs; two litters with cardiac anomalies	1.1	3.5	2.1
			0.1	20.6	Decreased fetal body weight	0.2	0.77	0.47
1643-SLS-3202.5	Rat	Topical	0.25	107	Slight increase in no. of dead pups; lower pup body weights; reduced skeletal ossification	1.2	4.0	2.4
			0.125		Decreased fetal body weight; increased variations, including supernumerary ribs			
1643-SLS-3202.14	Rabbit	Oral	0.200	2272	Increased pre- and post-implantation loss; malformations, including pinna anomalies, cleft palate, spina bifida, heart anomalies, skull anomalies, hyoid anomalies, tympanic ring anomalies	26	85	52
			0.05	779	NOAEL	8.8	29.3	17.7
98-4147	Rabbit	Oral	0.25	5300	Increased abortions; fetal alterations including microtia, cleft palate, exophtlamia, facial papilla anomaalies, heart and /or great vessel anomalies, skeletal alterations.	60	199	120
			0.1	2130	NOAEL	24	80	48
1643-SLS-3202.9	Rabbit	Topical	0.25	1160	Single incidences (1/20 litters) each of hydrocephaly, heart anomaly, spina bifida	13	43.5	26

[a] This exposure multiple is based on the highest body surface area involvement treated topically in the controlled clinical pharmacokinetic study of psoriasis (35% bsa, $AUC_{0\text{-}24h}$=88.3 ng*hr/mL).

[b] This exposure multiple is based on the maximum $AUC_{0\text{-}24h}$ (26.6 ng*hr/mL) seen in acne patients treated over 15% bsa in a controlled clinical pharmacokinetic study.

[c] This exposure multiple is based on the maximum $AUC_{0\text{-}24h}$ (44 ng*hr/mL) seen in patients treated over 15% bsa for photoaging in a controlled clinical pharmacokinetic study.

The two newest oral segment II studies, submitted in the current supplement, compared the developmental effects of tazarotene with those of tretinoin. Of the two, tazarotene was a more potent developmental toxicant; 10-fold lower doses on a mg/kg basis, resulted in similar developmental effects. Placental transfer of tazarotene was demonstrated in both the rat and the rabbit. Adapalene was not developmentally toxic at the doses tested in range-finding studies.

Reproductive and developmental toxicology conclusions:

The mean systemic exposure for photoaging patients treated topically over 15% of total body surface area with 0.1% tazarotene cream was 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.

Labeling recommendations:

It is recommended that this product be labeled Pregnancy Category X for the photoaging indication, as are the tazarotene gel formulations and this cream formulation as approved for psoriasis and acne vulgaris.

VIII. SPECIAL TOXICOLOGY STUDIES:

From the original review of NDA 21-184:

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.

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.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions:

From a pharmacology/toxicology standpoint, the supplement is approvable. However, the data provided do not justify a change of pregnancy category from X to C for the photoaging indication.

General Toxicology Issues:

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

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 patients treated over 15% total body surface area with 0.1% tazarotene cream. These data are consistent with information previously submitted.

Additional new studies of orally administered tazarotene in dogs demonstrate adverse effects similar to those previously demonstrated in rats and monkeys.

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

Labeling with basis for findings:

The following revisions are recommended for the label relative to the photoaging indication. Revisions have previously been recommended for the label relative to the

acne indication. It is anticipated that photoaging information will be added to the final approved label for the psoriasis and acne indications, so revisions made here are based upon the final approved labeling for the psoriasis and acne indications. Reviewer comments, not to be included in the label, are provided for clarification where necessary and are in italics.

1. Under **CONTRAINDICATIONS**:

[

]

2. Under **PRECAUTIONS**:

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

X. APPENDIX/ATTACHMENTS:

None

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

/s/

Amy Nostrandt
1/23/02 05:22:41 PM
PHARMACOLOGIST
Label recommendations are made based upon the approved label for Tazorac for psoriasis and acne. They can be found at the end of the review, beginning on page 12.

Abby Jacobs
1/24/02 07:17:29 AM
PHARMACOLOGIST

Jonathan Wilkin
2/15/02 11:03:18 AM
MEDICAL OFFICER