

Study Design & Dose Levels:

Group	UVB Dose (RBU/day)	Topical Treatment	UV A Dose (RBU/day)	Topical Treatment	Total UV Dose (RBU/week)
a	120	none	120	none	600
b	240	none	240	none	1200
c	120	vehicle	120	vehicle	600
d	120	0.001% (0.01 mg/ml)	120	0.001% (0.01 mg/ml)	600
e	120	0.005% (0.05 mg/ml)	120	0.005% (0.05 mg/ml)	600
f	120	0.01% (0.1 mg/ml)	120	0.01% (0.1 mg/ml)	600

RBU=Robertson-Berger Units (400 RBU + one minimal erythema dose in previously untanned skin).

Methods: Test articles were applied 5 days a week following (Monday, Wednesday, and Friday) or prior to (Tuesday and Thursday) UVR exposure (sunlight simulation). Animals were exposed to a xenon arc lamp with a Schott filter, and received a total of 120 RBU/day, except in the second untreated control group, which received 240 RBU/day to demonstrate that a change in tumor latency was measurable in the study design. Doses were chosen from the results of the dose-selection study.

The photocarcinogenicity of potential of compounds tested in this assay may be expressed in several formats:

Median Onset = the time that 1/2 of the group acquires a qualifying tumor

Mortality-free prevalence = the proportion of a group that exhibits one or more qualifying tumors as a function of time and adjusted for mortality

Tumor yield = the number of tumors divided by the number of surviving mice

Results:

Mortality: A significant increase in mortality was noted in groups b, d, e, and f males and females when compared to group a (low-dose UV only).

Clinical Observations: Clinical observations in areas other than the skin were not considered to

be related to treatment with Tazarotene, or were secondary to tumor appearance. In the skin, thickening, flaking, erythema, ulceration, and scab were noted in all groups. The severity of the findings, however, increased significantly with Tazarotene treatment or increase of the UV dose. A significant increase in incidence over group a (low-dose UV) was noted in grade 3 thickening (groups b, e, and f, but not group d), erythema (groups b, d, e, and f), and flaking (groups e and f). Ulceration and scabbing followed a similar pattern : significant increases over group a animals were noted in groups b, e, and f, and in groups d for scabbing only. Edema was noted only in the Tazarotene treated and high-dose UV groups. Significant increases in edema were noted in groups e and f. Note that the differences, although often significant, were of a lesser magnitude in the low-dose Tazarotene group d than in groups b, e, and f. For example, group d had a significant increase in grade 1 erythema, whereas group f had a significant increase in grades 1, 2, and 3.

Body Weight Values: Sporadic significant decreases were noted in total body weight values in all treated groups; these appeared most notably in the high-dose Tazarotene group (males in weeks 1, 11, 12, 13, 14, 15, 17, 24, 37, and 40; females in weeks 4, 9, 11, 12, 13, 14, 15, 17, 18, 21, 22, 24, 29, and 42). The differences were relatively slight, however, and generally represented less than 10% of body weight. A similar a pattern was noted in the body weight change values.

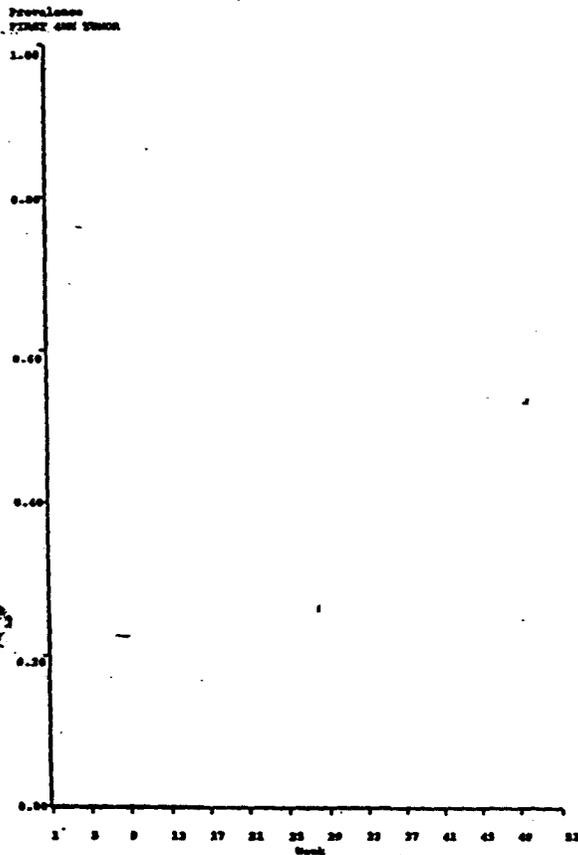
Necropsy Observations: In males, the number of enlarged spleens at necropsy was significantly greater than control (group a, 2 occurrences) values in groups b, e, and f (13, 11, and 10 occurrences, respectively). In females, large/mottled spleens were noted in 2, 6, or 7 animals for groups d, e, and f; the increase over group a (1 occurrence) was not significant. A significant decrease in ovarian cysts and uterus hydrometra were noted in groups b, d, e, and f. Other changes were noted sporadically in other organ systems and were not considered unusual for the age and strain of animal.

Cumulative Tumor Prevalence: No obvious sex differences were noted in tumor prevalence. Throughout the 48 weeks of tumor observation and evaluation, more tumors were noted earlier in the groups treated with Tazarotene and in the high-UV dose group. For example, by week 19, when the data from both sexes were combined, first perceptible tumors (i.e. new tumors) were noted in 0, 1, 0, 2, 3, and 5 mice in groups a-f, respectively. By week 22, a clear increase in tumor prevalence was noticeable in the same groups: 0, 211, 0, 11, 14, and 13, for groups a-f, respectively. Tumors appeared slightly earlier in the mid-dose, high-dose, and high-UV dose groups than in the low dose group, but this difference was only slight. The first tumors were noted in week 10. As expected, a tumor (1 incidence) was noted first in the high-dose Tazarotene group. Unexpectedly, an early (week 10) tumor was also noted in the low-UV dose group "a", although only one other tumor was than noted in that group until week 26, and thus the one early tumor does not appear to be biologically meaningful. The vehicle group "c", which was also treated with low-dose UV, was noted with only a few late-appearing tumors.

In addition to the observations of the first perceptible tumors (discussed above), group differences were noted in the appearance of progressively larger tumors (i.e. 1, 2, or 4 mm tumors). As the study progressed, and particularly beyond 30 weeks, the larger 4 mm tumors appeared less frequently in the low-dose Tazarotene group compared to the mid- and high-dose Tazarotene groups and the high-UV dose group. (See the figure below.) Using Peto analysis of time to tumor, significant differences were noted for groups b, d, e, and f for virtually all tumor size appearance when compared to the low-dose UV or the vehicle control group.

A 12-MONTH STUDY TO DETERMINE THE INFLUENCE OF AGN 190168 ON PHOTOCARCINOGENESIS IN HAIRLESS MICE

Sexes combined



Median Latent Periods: The median onset of tumors (to 1 mm) was longest (i.e. more time was required to induce tumors) in the low-dose UV and the vehicle control group: 35 and 37 weeks respectively. The median onset of tumors in the high-UV group was 25 weeks, and the median onset for the low-, mid-, and high-dose Tazarotene groups was 26, 23, and 24 weeks respectively. A similar pattern of median latent period was noted for larger tumors, and no sex differences were detected.

The sponsor performed Peto analysis of the onset to tumor (table below). A clear and statistically significant increase in tumor onset was noted in all Tazarotene treated groups.

Group Comparisons (Peto Analysis) of Tumor Onset
for Tumors ≥ 1 mm

Sexes Combined

Dosage Group	a	b	c	d	e	f
Test Article Concentration (%)	None	None	0 (Vehicle)	0.001	0.005	0.01
UVR Exposure (RBU/Week)	600	1200	600	600	600	600
		+++	(-)	+++	+++	+++
		C	-	(-)	++	N.S.
			C	+++	+++	+++
				C	+++	++
					C	N.S.

Codes relate to level of statistical significance based on two-tailed p-values. Note that the comparison group is indicated by a C on the same line. Where C is not given, the comparison is with Group a. Plus signs indicate the group specified has a risk greater than that with which it is being compared; minus signs indicate the group specified has a risk less than that with which it is being compared.
 +++ = P<0.001
 ++ = P<0.01
 (-) = P<0.1
 N.S. = Not Significant

Tumor Yield: The number of tumors in surviving animals increased as expected in the Tazarotene treated groups compared to the low-dose UV and vehicle control group. These data mirror the cumulative tumor prevalence noted above. In general, the first perceptible tumors appeared first in the Tazarotene and high-UV treated groups. By week 24, the differences were profound: 2, 204, 1, 110, 251, and 171 total tumors in groups a-f, respectively.

**13-week oral toxicity study in rats; Study no.1643- /18-920710;
10/92**

Animal Strain: Sprague Dawley rats Crl:CD (SD) BR

No. of Animals: 10/sex/group

Route: Orally through the diet

Duration: Daily for at least 90 days

Study Design & Dose Levels:

Group	Dose level (mg/kg/day)
1-control	0
2-low	0.05
3-mid	0.10
4-high	0.50

Results:

Mortality: No animals died prior to scheduled euthanasia.

Clinical Observations: No treatment-related clinical signs were noted.

Body Weights/Food & Water Consumption: Week-to-week body weights were comparable between the treated and the control group values. Body weight gains over weeks 2-13 were significantly decreased (<10%) in high-dose males and females. Food and water consumption values were comparable between the control and treated groups.

Ophthalmic Observations: No treatment-related effects were noted.

Hematology (13 parameters): All treated females had significantly decreased hemoglobin and increased MCHC (mean corpuscular hemoglobin concentration). High-dose males females had significantly decreased MCV (mean corpuscular volume), total white blood cells, and lymphocytes. High-dose females also had significantly decreased platelets. Other values were comparable between treated and control groups.

Clinical Chemistry (16 parameters): Mid-and high-dose females and males had significantly

decreased albumin levels, and high-dose animals had significantly decreased total protein when compared to control values. All treated males and high-dose females had significantly decreased total cholesterol levels when compared to control values. High-dose males also had significantly different alkaline phosphatase, chloride, and calcium (also noted in the mid-dose) when compared to control values. High-dose females also had significantly different glucose, creatinine, alkaline phosphatase, alanine aminotransferase, sodium, and calcium when compared to control values.

Urinalysis: High-dose female pH was significantly increased and mid- and high-dose female specific gravity was significantly decreased when compared to control values.

Gross Necropsy Observations: No treatment-related observations were noted.

Organ, Organ-to-Body, and Organ-to-Brain Weights: Male liver weights were significantly below control values in all treated groups; high-dose males had significantly decreased spleen and kidney weights when compared to control values. High-dose females had significantly decreased adrenal weights; liver weight in treated females was less than control values, although the difference was not statistically significant.

Histopathology: Several treatment related effects were noted in the liver of mid- and high-dose males, including centrilobular hepatocyte enlargement; single cell degeneration; and increased centrilobular or generalized (high-dose only) fat deposition. Females in the high dose had an increased incidence of periportal fat deposition. Other treatment-related effects in males included increased minimal focal hyperplasia of the basal cells of the non-glandular stomach epithelium (high-dose), increased stomach acanthosis (high-dose), and increased peri-osteal osteocalcic activity/fibrosis (mid-and high-dose). High-dose females also experienced an increased incidence of peri-osteal increased osteoclastic activity.

2-year rat dietary study; Study No. 1643- /18-920710,
7/94

Animal Strain: Crl:CD-1 (SD) BR rats

No. of Animals: 55/sex/ group; plus satellite groups of 10/sex/group (one high-dose female was mis-sexed; high-dose females had only 54 rats)

Route: Dietary

Duration: 104 weeks

Study Design & Dose Levels:

Group	Dose Level mg/kg/day	Dose Level (mg/m ² /day)
1	0	0
2	0.025	0.15
3	0.050	0.30
4	0.125	0.74

Conversion factor of 5.9 was used to convert mg/kg to mg/m²

Methods: Rats were exposed to Tazarotene as an admixture to the diet (based on regularly evaluated body weight data) for 104 weeks. Over the course of the study, rats were evaluated for clinical signs (days 1-30, followed by weekly evaluations), mortality, bodyweights (weekly), food consumption, ophthalmoscopy (weeks 26, 52, 78, and 104), hematology and clinical chemistry changes, pharmacokinetics (weeks 12, 36, 72, and 104), and histopathology changes.

Results:

Mortality: Survival and mortality data are summarized below; no statistical differences were noted (evaluated by the log rank method).

Group	Total Survival		Known Mortality		Relative Death Rate *	
	Male	Female	Male	Female	Male	Female
1	32	26	58	65	0.99	1.09
2	30	33	55	60	0.88	0.96
3	32	35	58	64	1.15	1.17
4	32	28	58	52	1.00	0.80

* Relative death rate = observed deaths/expected deaths; numbers less than 1 indicate that the death rate was less than expected

Body Weight Values: Body weight values were similar for all treated groups when compared to control values except for high-dose females. High-dose female values were significantly decreased at weeks 21, 22, and weeks 25-66 (differences were = 9-12 %). The amount of

weight gained in weeks 0-60 was also significantly decreased for high-dose females (301 g compared to 249 g); this difference was no longer noticeable by week 104 (due to deaths and moribund sacrifice in the high-dose group). As a percent of control, body weight gains in weeks 104 for males were 100, 105, and 99; and for females the gains were 116, 94, and 99% for groups 2, 3, and 4, respectively. Changes in the satellite group body weights were similar, and the high-dose female gains were also significantly below control values at weeks 0-60.

Food Consumption: Food consumption values were similar between the control and treated groups, except for high-dose females which were significantly below control values at weeks 0-60. Food conversion ratios (food consumption/bodyweight gain, weeks 1-26) were similar between groups. High-dose females were noted with a slightly increased, but not statistically significant, food conversion ratio.

Ophthalmic Observations: No treatment-related effects were noted.

Hematology (7 parameters): At 104 weeks, mid- and high-dose females were noted with significantly decreased mean corpuscular volume (slight) and platelet count (20%) values compared to mean control values. Mid- and high-dose males had significantly decreased lymphocyte values (29-23%) when compared to control values.

Clinical Chemistry (9 parameters): Total protein values were decreased in all treated animals; the differences were significantly lower for all treated males and in high-dose females (less than 10%). Cholesterol was also decreased in all treated animals; the difference was significant in mid- and high-dose males and all treated females (as high as 54%). Glucose values were slightly increased above control values in all treated animals; the difference was statistically significant in high-dose females (15%). Urea nitrogen levels were also significantly decreased urea nitrogen in all treated females (to 20%). Aspartate aminotransferase was decreased in all treated animals and was significantly decreased in mid- and high-dose males (to 30%).

Necropsy Observations: The findings at necropsy were generally typical for this age and strain of animal. Of possible note was a single mass noted in the heart of a high-dose male, and a mass in the abdominal cavity of a high-dose female. Liver masses were noted in 3, 3, 2, and 2 males; and 1, 0, 2, and 4 in females for groups 1-4, respectively.

Non-Neoplastic Morphology: Non-neoplastic findings appeared in a non-treatment related fashion across all groups. Findings in the liver (a possible target organ), such as vacuolation and fat in periportal and centrilobular hepatic cells occurred across all groups and did not appear to be related to treatment.

Neoplasms: Tumors found in organs of possible concern (based on incidence and results from the retinoids) are shown below.

Neoplasia	Males with Neoplasia				Females with Neoplasia			
	Group 1				Group 2			
	1	2	3	4	1	2	3	4
Liver-- total adenomas or carcinomas	3	4	2	0	0	0	0	3
Liver-- adenomas	2	2	1	0	0	0	0	3
Liver-- carcinomas	1	2	1	0	0	0	0	0
Thyroid-- follicular adenomas or carcinomas	6	7	6	3	1	0	0	3
Thyroid-- fol. adenomas	6	4	5	1	1	0	0	3
Thyroid-- fol. carcinomas	0	3	1	2	0	0	0	0

The sponsor analyzed the hepatocellular adenomas in female rats using the logrank methods of Mantel (1966) and Peto (1974). Analyses included a test for heterogeneity, a one-tailed test for trend and pairwise comparison (against control), and a test for non-linearity. The test for trend gave a p value of 0.007 for the high-dose female adenomas. Results are summarized below.

Group, Dose Level, (mg/kg/day)	Initial Group Size	Number of Animals with Tumors		Relative Ratio (O/E)	Pairwise comparison p-value
		Observed	Expected		
1, 0.000	55	0	0.81	0	
2, 0.025	55	0	0.90	0	0.50
3, 0.050	55	0	0.44	0	0.50
4, 0.125	54	3	0.85	3.54	0.13

Treatment Effect	χ^2	df	p-values
Heterogeneity	7.731	3	0.052
Trend	6.157	3	0.007
Non-linearity	0.827	2	0.76

Pharmacokinetics

Satellite animals (4-5/sex/group) were sampled at 3, 6, 9, 12, 18, and 24 months (8-10 AM) using GC and GC/MS spectrophotometry. The sponsor measured the main metabolite of the parent drug, AGN 190299. Values are summarized in the table below.

AGN 190299 data (AM blood concentrations)^d are summarized in the table below:

Dosage mg/kg/day	AGN 190299 Concentration (ng/ml) ^{b,c}				
	3 Months ^d	9 Months	12 Months	18 Months	24 Months ^f
	Male				
0	BLQ ^e	BLQ	BLQ	BLQ	BLQ
0.025	0.578 ±0.141	0.343 ±0.081	0.375 ±0.068	0.422 ±0.052	0.712 ±0.206
0.05	0.825 ±0.234	0.403 ±0.153	0.568 ±0.228	0.683 ±0.130	0.894 ±0.330
0.125	1.30 ±0.45	0.915 ±0.279	0.827 ±0.219	1.21 ±0.53	2.56 ±1.26
	Female				
0	BLQ	BLQ	BLQ	BLQ	BLQ
0.025	0.468 ±0.223	0.407 ±0.170	0.615 ±0.337	0.534 ±0.028	0.790 ±0.357
0.05	0.661 ±0.272	0.749 ±0.152	1.16 ±0.306	0.858 ±0.296	1.62 ±0.81
0.125	1.28 ±0.55	1.86 ±1.04	1.52 ±0.37	2.00 ±0.76	3.27 ±2.10

- ^a AGN 190168 concentrations were not analyzed due to the rapid metabolism of AGN 190168 in the rat (1). Data are expressed as mean ± SD, n = 4-5/sex/dose.
- ^b Statistically significantly different between the sexes (p < 0.05, based on overall data).
- ^c No data were obtained for 6-month time point due to the failure of sample analysis.
- ^d Estimated data.
- ^e Below the limit of quantitation (< 0.05 ng/ml).
- ^f Statistically significantly different from all previous time points (p < 0.05).

Summary

Tazarotene was submitted as an original IND in 1990; the NDA falls under _____ and has a user fee due date of 6/96. Tazarotene is the first retinoid intended to treat plaque psoriasis submitted to the agency as an NDA; Tazarotene is also under review for the indication of acne vulgaris. Expected clinical dosage of the 0.1% Tazarotene gel is 0.1 mg (assuming 20% of body surface). The active form of Tazarotene is the primary metabolite, which is formed through ester hydrolysis to the free acid.

The sponsor performed a large variety of PK/ADME preclinical studies. Tazarotene and its metabolites are highly bound to plasma proteins (mean unbound drug was less than 1%). Because of rapid hydrolyzation of the parent compound, most of the analytical studies quantified AGN 190299. In miniswine, percutaneous absorption was approximately 7% in the viable epidermis. In a rat topical study, 21-day topical administration of 0.1% radiolabeled gel resulted in a general distribution throughout the body with highest levels in the skin, liver, and intestinal tract (possibly due to ingestion). Following IV dosing in rats, radioactivity was first noted in the liver, plasma, small intestine, spleen, large intestine, cecum, liver, and ovaries. By 48 hours, radioactivity was still noted in the spleen, liver, adrenals, and ovaries. No sex differences in disposition were noted. Autoradiography of rats following topical dosing also revealed radioactivity in the skin, gastrointestinal tract, buccal mucosa, and liver. An autoradiography study in pregnant rats (oral dose on day 18) gave similar results; radioactivity was absorbed and distributed throughout maternal tissues, and fetal tissues had much lower ranges than maternal tissues: 7.1 - 14.2 ng-eq/g compared to 53.5 - 287.1 ng-eq/g. Similar studies were carried out in pregnant rabbits, and fetal tissue levels were also much lower than maternal tissue levels (1.2 ng-eq/g compared to 57.3-78.8 ng-eq/g). Single topical application of radiolabeled AGN 190168 (0.19 mg/kg) applied to nursing rats indicated secretion in the milk to 48 hours. (In all topical studies, the possibility of ingestion by the animals exists, and may skew results. The findings of radiolabeled material in the buccal mucosa and intestines in several studies of Tazarotene are suggestive of ingestion.)

In PK studies performed over time in mice, C_{max} increased in a general linear trend with dose; after 13 weeks of dosing, C_{max} ranged from _____ ng/ml following dosing of 0.050-0.50 mg/kg. In an IV mouse study, C_{max} values were 43 ng/ml (males) to 55 ng/ml (females) following 0.03 mg/kg dosing. Rats dosed topically (0.125-0.250) for 28 days were reported with C_{max} values of 3.4-6.4 ng/ml; AUC was as high as 71 ng·hr/ml; and T_{max} was 10-11 hours. Male miniswine values ranged _____ ng/ml (C_{max}, 0.05-0.25 mg/kg/twice per day).

The sponsor performed several single dose studies to define the expected toxicities associated with Tazarotene. No compound-related effects were noted in any of the single-dose IV studies, including a single-dose IV injection study in rats 2 mg/kg 0.02% AGN 190168), a single-dose infusion IV studies in rabbits (0.015 and 0.075 mg/kg 0.05% Tazarotene or 0.012 and 0.060 mg/kg 0.01% AGN 190168), a single-dose IV infusion study in dogs (0.012 and 0.060

0.060 mg/kg 0.01% AGN 190168), a single-dose IV infusion study in dogs (0.012 and 0.060 mg/kg in males and 0.015 and 0.075 mg/kg in females 0.01% AGN 190168) and in a single-dose IV study in cynomolgus monkeys (IV bolus 0.75 mg/kg AGN 190168; 3 ml/kg of a 0.025% solution).

In a minimum lethal oral dose study, rats given a single oral dose of 20 ml/kg 10% AGN 190168; clinical observations included lethargy, piloerection, soiled perianal region, slight paraphimosis, blood around the nose, hair loss, and bloody tears and all animals survived until day 14. In a 4-week oral range-finding toxicity study in Cynomolgus monkeys, monkeys dosed with 1.0, 2.5, 5, or 20 mg/kg AGN by oral intubation experienced of mortality, morbidity, and severe toxicity were noted at all dose levels but the lowest (1.0 mg/kg). Renal damage was indicated in creatinine, BUN, phosphorous, and calcium values by week 2 in the 5 and 20 mg/kg groups. Lesions noted in the kidney included tubular nephrosis, suppurative inflammation, and tubular mineralization.

Topical dermal studies first included single dose studies to define the initial effects on the skin. In a single-dose skin toxicity study, rats treated with a single dose of 0.01 to 0.1% AGN 190168 (0.1 ml) on the back were exhibited no treatment-related differences. In single-dose dermal studies, New Zealand white rabbits (6/sex) given a single topical dose of 0.05 or 0.1% AGN 190168 (0.1 ml) on the intact clipped occluded backs of the rabbits were noted with erythema, flaking/scaling, edema, and scabbing. In two additional studies, rabbits treated with a single topical dose (0.01, 0.025, or 0.05% AGN 190168; 0.1 ml) on shaved and abraded backs were observed with slight to mild erythema, and a few incidences of edema, flaking and scaling at the higher doses.

In a one-month abraded skin toxicity study, rats were treated with vehicle, 0.1, 0.05, or 0.1% AGN 190168 two times per day for 30 days on shaved, abraded animal backs. By the fourth week of treatment, all drug-treated animals were noted with erythema, fissures, scabs, flaking/scaling, and abrasion (very slight to mild).

Treated animals were noted with moderated epidermal pustule, hyperkeratosis, erosion, ulceration, acanthosis, severe subacute dermatitis, suppurative folliculitis, and superficial dermal fibrosis. Lesions increased in incidence and severity with dose level, although the mid- and high-dose groups were noted with very similar skin findings. However, in animals allowed to recover, no dose or treatment related effects were noted except for a single animal in each dose group. In a 4-week dermal study, mice dosed dermally (3 cm² area) every day with vehicle, 0.50, or 1.0 mg/kg of 0.1% AGN 190168 were noted with changes in the liver (males, centrilobular hepatocyte enlargement) and stomach (females, epithelial hyperplasia and hyperkeratosis). High dose males and females were noted with changes in the skin that included erythema, minimal erosion, epithelial acanthosis and hypertrophy. Blood samples were 0, 47.1, and 71.5 ng/ml for groups 1-3, respectively.

A one-month skin toxicity study with a recovery period in rats served as a bridging study

between formulation changes. Sprague-Dawley rats were dosed twice daily (3 cm² area) with 0.05 (0.125 mg/kg/day) or 0.10% (0.25 mg/kg/day) AGN 190168 and then allowed a two-week recovery period. The 0.05% preparations 8225X and 8607X were compared; and the 0.10% preparations 7997X and 8606X were compared. The "old" formulations, 8225X and 7997X contain approximately 0.5% less water and triethanolamine (trolamine), rather than tromethamine. The "new" formulations, 8606X and 8607X, contain tromethamine and are made-up of the same ingredients as the final clinical formulation. Skin findings consisted primarily of minor skin irritation, and microscopic changes (hyperkeratosis, epidermal, dermatitis, perifolliculitis) diminished in severity after the recovery period. There appeared to be no difference in severity of irritation between the two formulations, although increased dose of the active ingredient resulted in increased irritation in both formulations and females appeared to be somewhat more effected. Animals were examined for pharmacokinetic parameters following 4 weeks of treatment (2 hours post dosing). Blood levels of AGN 190299 (the major metabolite) ranged from ng/ml. No differences in blood levels were noted between formulations.

In a 10-day comedogenicity study, AGN 190168 (0.05 or 0.1%) was applied to the inner surface of rabbit ear pinneas (0.05 ml) for 10 days to test for comedogenicity. Both concentrations caused slight enlargement of the hair follicles when examined by whole mount technique. The follicles showed small globoid masses of horny material and treated animals also were noted with well-defined erythema, slight flaking/scaling, scabs, and abrasions. Histologically, AGN-treated animals were noted with the inflammatory cell periglandular infiltration, atrophy, and displacement of the sebaceous glands; inflammatory cell infiltration, hyperkeratosis and edema of the external root sheath of the hair follicle; and epidermal hyperkeratosis, edema, hemorrhage, and inflammatory cell infiltration in the dermis and epidermis. (The sponsor stated that they believed the changes were indicative of skin irritation.) In a dermal sensitization study, AGN 190168 (0.01, 0.05, or 0.1%) administered to guinea pigs followed by challenge caused no sensitizations. In an acute single-dose ocular study in rabbits, AGN 190168 (0.05% and 0.1%, 0.1 ml) caused moderate to severe ocular discomfort, tearing, and hyperemia was noted in all groups, including the vehicle control, immediately after dosing. After approximately one-hour post dosing, no ocular reactions were noted.

A phototoxicity assay in guinea pigs was performed at dose levels of 0.1, 0.05, and 0.01% (0.15 ml) with skin exposed to UVA (320-400 nm, 10 Joules/cm²) for approximately 1 hour. No erythema or edema was noted in the AGN-treated groups after 0-96 hours of exposure. In a photoallergy study in guinea pigs, animals were induced with 0.1% test article 5 times over 15 days. After dose administration, guinea pigs were exposed to 30 J/cm² UVA radiation (102-140 seconds exposures, 310-400 nm). Animals were challenged 15 days after the last dosage; the elicitation phase applications duplicated the original exposure site and dose. Skin treated with AGN gels appeared irritated (as measured by erythema), but did not have a contact sensitization reaction on irradiated or non-irradiated skin.

Subchronic studies were performed across all dosing regimens. Two 3-month oral studies were performed, which included one rat and one monkey study; both revealed similar toxicity profiles. In the rat study, animals were dosed daily by gavage with 0.05, 0.25, or 2.00 mg/kg. In the high-dose, most animals died or were sacrificed moribund. The animals were noted with concentrated urine, blood around their ear, nose, and mouth, weakness, and difficult breathing. Significant body weight decreases were noted in all animals treated with drug, including the recovery animals. Clinical pathology changes were noted in liver and kidney-related parameters, as well as changes in electrolytes demonstrating an overall loss of homeostasis. Histopathology changes included bone (narrowing of the zone of proliferating cartilage, widening of the zone of maturing cartilage, multifocal chondrolysis), lung, thymus (involution, hemorrhage), heart (edema, epicarditis, chronic inflammation, and hemorrhage), and liver (hepatocellular hypertrophy, vacuolar change, extramedullary hematopoiesis). The changes were generally dose-dependent, and were not present in the lowest dose groups. In the monkey study, animals were dosed by nasal gastric intubation daily (0.05, 0.25, or 1.00, or 1.6 mg/kg AGN 190168) with a 4-week recovery phase. Results in the high-dose animals included deaths, prostration, hypothermia, inappetence, hypoactivity, decreased muscle tone and ocular discharge. The mid- and high-dose groups were noted with reduced body weights. Clinical pathology changes were noted in platelet, APTT, BUN, glucose, albumin, A/G ratios, creatinine and phosphorous. In the histopathological exam, high-dose males that died prior to the scheduled sacrifice were noted with mineralization in the heart and/or kidneys and two of the males, splenic lymphoid atrophy was noted. Thymic atrophy was noted in 5/8 high-dose males. One high-dose male exhibited myocardial serous atrophy and pneumonia. Although the pathologist did not consider it related to drug treatment, one moribund high-dose female was noted with a benign vascular tumor (hemangioma) in the liver. Two high-dose recovery males and one control male were noted with aspermagenesis.

Two three-month topical dermal studies were performed; one mouse and one miniswine study. AGN 190168 (0.005, 0.01, 0.025, and 0.05%) was applied daily or on alternate days to the clipped backs of CD-1 mice. All but the lowest dose group experienced erythema, dryness, and edema. Bodyweight gains were decreased for treated mice, especially at the higher doses. Changes were noted in eosinophils, total protein, cholesterol, and triglycerides. Microscopic evaluation of the skin revealed epidermal erosion, acanthosis with hyperkeratosis, and epithelial hypertrophy. Incidence and severity increased with dose. PK blood levels ranged from _____ ng/ml with daily dosing. In the alternate day dosing groups, the range was _____ ng/ml. In the miniswine study, pigs were dosed with 0.05, 0.125, 0.250, or 0.5 (0.025-0.5 %) AGN 190268. Numerous incidences of scabbiness and blackened skin were noted in the treated groups. Dermal irritation could not be evaluated after week 4 because black scab had formed over the sites. At the end of study, Group 5 male neutrophil count and Group 4 female eosinophil count were significantly lower than control values. At the end of the study, blood urea nitrogen in group 5, albumin in groups 3 and 5, and albumin-to-globulin ratio (A/G) in group 3 in males were significantly less than control values. In females, group 4 A/G, and group 5 globulin and A/G were significantly less than control values. The skin from the treated areas of all treated groups had acanthosis with

thickening stratum germinativum, inflammatory neutrophilic and cellular infiltration, cellular surface debris, and serum exudate and focal erosions in the epidermis. Groups 3, 4, and 5 animals also had focal ulcerations, focal fibrosis, and focal erosions in the epidermis (Groups 4 and 5 only). Observations increased in severity with dose level. Findings in all other organ systems were considered spontaneous and not treatment related. C_{max} values from blood PK samples varied from _____ ng·h/ml. The values quantified the metabolite AGN 190299. None of the parent compound, AGN 190168, was found in the high-dose-samples.

Two 6-month oral studies were performed, one rat and one monkey study. In the rat dietary study, animals were dosed with 0.025, 0.05, or 0.25 mg/kg/day AGN 190168. All treated animals had changes in neutrophil values, protein, glucose, calcium, cholesterol, and platelet counts. Mean thyroid values (up to 17%) and lung values (up to 18%) were increased in all treated. Treatment related changes included an increased incidence of centrilobular fat deposition in high-dose males and increased periportal fat deposition in high-dose females. The liver changes were not noted in the recovery animals. High-dose males had an increased incidence of myocardial fibrosis (papillary muscle). In the recovery group, however, the finding was noted in both control and high-dose males, and does not appear to be treatment related. Mean blood levels were 0.05 - 1.8 ng/ml. In the monkey study, animals were dosed by nasal gastric intubation with 0.05, 0.125, and 0.5 mg/kg/day. Two high-dose monkeys were euthanized prior to the 6-month sacrifice. The clinical observations (supported by histopathology at necropsy) gave the best indication of the toxicity associated with this compound. The most remarkable, treatment-related clinical signs noted were hunched posture, limited use of hind limbs with muscular atrophy and contraction of the tendons, hypoactivity, sores around the mouth and lips, slight to moderate tremors, slight to severe kyphosis in the high-dose animals, with 3 animals showing limited rotational ability of the head. These conditions developed gradually during the course of the study. When the dose was lowered, there was no obvious improvement noted. Likewise, there was no noticeable improvement in the high-dose animals during the approximately 2-month recover period. Body weight values were decreased in high-dose animals. Changes were noted in cholesterol, albumin, and potassium. Treatment-related changes were noted in the mid-and/or high-dose group included the femur, rib, vertebrae, sternum, and the hip. Several low-dose females had epiphyseal growth plate changes in the femur, although their relationship to treatment is unclear.

In a 6-Month Dermal Toxicity Study, rats were treated with 0.01%, 0.05%, and 0.1% AGN 19068 on their shaved backs. Two control males and one high-dose male were found dead, and one mid-dose male was euthanized in a moribund condition. Erythema, ranging from very slight in placebo animals to severe in high-dose animals, was noted over the course of the study. Animals also experienced edema, hardening, abrasion, flaking/scaling, and scabs in a dose- and time-dependant manner. Mid and high dose groups were noted with decreased body weights. Values that appeared treatment-related and were significantly different from control values included, in males: decreases in mean cell volume and monocytes; and increases in white blood cell count and neutrophils. In females, significant decreases were noted in

hematocrit, mean cell volume, and monocytes; and increases in neutrophils, lymphocytes, and red blood cell count. A large number of treatment-related clinical chemistry effects were noted, although most effects were reversed following the 23-day recovery period, changes were noted in albumin, albumin:globulin, alkaline phosphatase, cholesterol, triglycerides, and calcium. In general, abnormalities, especially at the skin treatment sites, became worse between the 3 and 6 month exposure periods and moderated after the recovery period. At 6 months, both epidermal and dermal histological changes were noted in all AGN-treated animals. Epidermal changes included ulceration, pustule formation, hyperkeratosis, parakeratosis, and acanthosis. Dermal changes include inflammation and fibrosis. The frequency and intensity of these findings increased with dose level. Systemic changes thought to be treatment related at the six-month sacrifice included the femoral bone, adrenal glands, and liver. Following the 23-day recovery period, histological evaluation revealed that the skin treatment sites had undergone "considerable resolution," although abnormalities were noted in all treatment groups. The pathologist stated that "Continued resolution would be expected with the further passage of time." Similarly, the adrenal abnormalities and hepatic/periportal lipidosis were still somewhat abnormal, although the degree had lessened and the pathologist expected eventual resolution. No residual bone lesions were noted in the end-of-recovery period sacrifice.

In a 12-month dermal toxicity study in miniswine, animals were treated with 0.025, 0.05, 0.1% (0.05, 0.125, 0.25 g/kg) AGN 19068 twice/day to the clipped intact backs. On day 22, however, a hard black colored scab had formed over the treatment sites and they could not be evaluated for the remainder of the study (occasional erythema was noted when sites could be graded). No treatment-related changes were noted in hematology values. After 13, 19, 26, 39, or 52 weeks of treatment, increases in total protein and globulin in treated animal, and decreased were noted in albumin values. At recovery, however, these values were similar to control animals. Treated skin was noted with microscopic signs of irritation, including acanthosis, dermal inflammatory cellular infiltration, cellular surface debris, neutrophilic cellular infiltration, focal erosion, focal ulceration, and focal dermal fibrosis. No treatment-related systemic changes were noted. In the recovery animals, similar skin changes were noted, as well as signs of healing including slight hyperkeratosis. PK evaluations in treated animals ranged from ng/ml for the low and high-dose animals.

The sponsor performed oral and topical reproduction studies and PK/ADME in pregnant rats and rabbits. An autoradiography study in pregnant rats gave similar results and revealed no placental transport. A placental transfer study following an oral dose on gestation day 18 in pregnant rats revealed radioactivity absorbed and distributed throughout maternal tissues. Fetal tissues had much lower ranges than maternal tissues: ng-eq/g compared to ng/eq/g. Similar studies were carried out in pregnant rabbits, and fetal tissue levels were also much lower than maternal tissue levels (1.2 ng-eq/g compared to 57.3-78.8 ng-eq/g). A single topical application of radiolabeled AGN 190168 (0.19 mg/kg) applied to nursing rats resulted in secretion in milk from 8 to 48 hours. These data indicate that a single topical application would result in drug being passed in the milk of lactating rats.

As expected for any retinoid, the oral formulations were teratogenic in all tested species. In the oral range-finding teratology study in rats, rats orally dosed with 0.05, 0.25, 1.0, or 2.5 mg/kg/day on gestation days 6-17 experienced fetal and maternal toxicity. Changes in high-dose females included decreased body weight gains (high dose), increased leucocyte values, AST, ALT, ALK, phosphorus, and cholesterol; and decreases in platelet and glucose values. At cesarean section, high-dose and to a lesser extent, mid-dose (1.0 mg/kg), females had decreased corpora lutea, implantation sites, viable fetuses, and fetal weights; and an increase in early resorptions and post-implantation loss. In the satellite groups (12/group), blood samples for toxicokinetics were collected on gestation day 17 at 0.5 to 24 hours. C_{max} ranged from 20-637 ng/ml; t_{max} was 0.5-1 hr, AUC (0-24 hr) ranged from 60 to 1200 ng*hr/ml, and t 1/2 ranged from 4-7 hours.

In the developmental toxicity study in rats, rats were dosed orally with AGN 190168 (0.0, 0.05, 0.25, or 1.0 mg/kg) during organogenesis. Maternal toxicity included mid- and high-dose unscheduled deaths and, decreased body weights and food consumption. High dose-findings included fetal toxicity and malformations. High-dose female pups had significantly decreased fetal weights and a significantly large number of malformations, including expected retinoid malformations of cleft palate and skull anomalies; overall there were 2, 0, 8, and 309 malformations in groups 1-4, respectively. The fetal effects continued through lactation, and involved delayed behavioral development that included the mid-dose pups to a lesser extent. Weights lagged through maturation, and high-dose females had significantly lower gestation weight values, decreased implantation scars, litter sizes, and no. of pups alive on day 1 and on day 4 prior to culling. At necropsy, no treatment-related observations were noted in the F₂ pups.

Oral studies were also performed in rabbits. In a range-finding developmental toxicity study, rabbits were dosed orally with vehicle, 0.05, 0.25, 1.0, or 2.5 mg/kg day AGN 190168 during organogenesis (gestation days 6-18). At all treatment levels except for 0.05 mg/kg, a high number of abortions (40-60%) were noted. In cesarean section data, the three highest dose groups had decreased corpora lutea, implantation sites, viable fetuses (0 in the two highest-dose groups); and increased early resorptions and post-implantation loss. Fetal loss was so high that no malformations or variations were noted in any of the treated groups.

Toxicokinetics sampling on day 18 indicated that the AGN 190299 (main metabolite) C_{max} (μg/ml) was 0.0560 ± 0.0054 to 2.35 ± 0.78, and T_{max} (hr) was 5.55 to 1.00 for the low and high doses, respectively. In general, C_{max} increased proportionally to dose. In the full developmental toxicity study, rabbits were dosed orally with doses of 0.025, 0.050, and 0.200 mg/kg/day. No treatment related changes were noted in the low- and mid-dose groups. In the high-dose, there was an increased number of early resorptions and post-implantation loss. An increase in malformations was also noted in the high-dose group, including pinnae anomalies, cleft palate, spina bifida, heart anomalies, skull anomalies, hyoid anomalies, and tympanic ring anomalies.

Maternal and fetal effects were greatly reduced in the dermal reproduction studies of Tazarotene. In a dermal range-finding teratology study, collared rats were administered AGN 190168 at dosage levels of 50, 125, 250 and 500 $\mu\text{g}/\text{kg}/\text{day}$ on their shaved backs during gestation days 6-17. Body weights were slightly decreased in the treated animals and skin irritation (erythema, scabs, hair loss, eschar) was noted on all treated animals and severity increased with dose. No treatment-related differences were noted among the control and treated groups in the number of viable fetuses, early resorptions, sex ratios, and fetal weights. High-dose females had fewer corpora lutea, implantation sites, and viable fetuses. At the high-dose, one fetus had a filamentous tail and anal atresia and one fetus had head anomalies and brachydactyly. A second dermal range-finding study evaluated the effects of Retin-A. Collared rats were dosed with 0, 50, 125, 250, 500 $\mu\text{g}/\text{kg}/\text{day}$ Retin-A on days 6-17 of gestation. No clear treatment related differences were noted in body weight and pregnancy parameters. One incidence of cleft palate was noted in one high-dose fetus and one incidence of anophthalmia was noted in a low-dose fetus. In the full dermal teratology study with AGN 190168 and Retin-A, rats were dosed with vehicle, 125 $\mu\text{g}/\text{kg}/\text{day}$ AGN 190168, or 125 $\mu\text{g}/\text{kg}/\text{day}$ Retin-A gel. Compound was applied daily to collared females on gestation days 6-15. All groups were noted with scabs, hair loss and erythema; erythema was greatly increased in the two retinoid-treated groups compared to the vehicle control. Body weights and food consumption were comparable. Pregnancy was slightly decreased in the treated animals; fetal data were comparable, except for a 50% increase in pre-implantation loss in the Retin-A group compared to the control and AGN 190168 groups. Malformations were minimal and were comparable between groups.

In the dermal peri- and postnatal study, rats (25/group) were topically dosed with 25, 50, or 125 $\mu\text{g}/\text{kg}/\text{day}$ AGN 190168 on gestation day 16 through lactation day 20. F₀ females were allowed to deliver and rear the F₁ generation. F₁ pups were mated at 12 weeks, allowed to deliver and rear their offspring until lactation day 21. Minor effects were noted in the high-dose group: decreased number of pups retrieved on lactation day 6, increased number of presumed cannibalized pups, and an increased number of found dead pups. No other treatment related effects were noted, including behavioral differences, copulation and fertility indices, pregnancy rates, or effect in the F₂ pups.

In the dermal teratology study and 2-generation reproduction study, rats were topically dosed with AGN 190168 (0, 50, 125, or 250 $\mu\text{g}/\text{kg}$) or with Retin-A (50, 125, or 250 $\mu\text{g}/\text{kg}$). In the F₀ generation, irritation (erythema, desquamation) was noted in all retinoid-treated groups. No other treatment-related effects were noted in the F₀ generation. In the F₁ pups, lower body weights were noted in the mid- and high-dose (Retin-A pups were normal). In the F₂ generation, a significant increase in the number of dead pups on lactation day 0 was noted for both the AGN mid dose and the Retin-A high dose. (The values were within historical control values.) All other parameters were normal for the pups. A dermal fertility and reproduction study in rats indicated parental toxicity; rats were dosed with 0, 25, 50, and 125 ($\mu\text{g}/\text{kg}$). Males were dosed for 70 days prior to mating and until euthanasia. Females were dosed for 14 days prior to mating, throughout gestation and lactation, and until

ethanasia. Deaths, rales, and wobbly gait, and signs of skin irritation were noted in all F0 groups, especially in the treated groups. Copulatory and fertility indexes, precoital interval, and gestation length were comparable between the treated and control groups. By lactation day 6, the mid- and high-dose animals had significantly fewer pups when compared to control values. Mean live litter size on lactation days 1-4 for the F1 pups decreased with dose. Although no single gross necropsy observation could be related to treatment, the number of remarkable findings increased with dose: 1, 4, 4, and 8 pups for groups 1-4, respectively. During maturation, body weights and gains lagged slightly for high-dose males, although the difference was not statistically significant. No treatment related differences were noted in F1 animal copulation, fertility, precoital interval, gestation length, or in the F2 generation.

In a dermal range-finding teratology study in rabbits, animals were dosed dermally on their shaved backs with 0, 50, 125, 250, or 500 $\mu\text{g}/\text{kg}$ AGN 190168 on days 6-18 of gestation. Dose-related erythema and desquamation were observed in all groups. Pregnancy rate was reduced by AGN 190168 treatment; the rate dropped from 100% to 60-80% for the three highest doses. A reduction in the number of corpora lutea and implantation sites was noted in the two highest dose groups. No external malformations or variations were noted. In the full study, the dermal teratology study, rabbits were topically dosed with AGN 190168 (0, 50, 125, or 250 $\mu\text{g}/\text{kg}$) on gestation days 6-18. Erythema was noted across the AGN 190168-treated groups; eschar was noted with increasing incidence in the highest dosed groups, and a single animal in the high-dose groups was noted with fissuring. No treatment-related differences were noted in cesarean section parameters. Malformations of concern included single incidences of spina bifida, hydrocephaly, and heart anomaly in the high dose group. Five mutagenicity studies were performed: Ames/Salmonella, in vitro chromosome aberration analysis in human lymphocyte, E. coli liquid pre-incubation, and CHO/HPRT mammalian cell forward gene mutation, and an in vivo micronucleus test in mouse bone marrow erythropoietic cells assay. All assays were negative for mutations.

In the dose-selection photocarcinogenicity study, albino hairless mice treated with 0.1, 0.01, 0.001, or 0.0001% AGN 190168 in a single exposure plus UVR light (sunlight simulation), were examined after irradiation, animals were examined for inflammation, and graded for the protective factor (PF) of the test material. In a second study, mice were treated with repeated doses (5 days/week for 8 weeks) of the test materials (0 to 1.0 mg/ml) with UVR exposure to determine the most appropriate concentrations for a full blown photocarcinogenicity study. AGN at all treatment levels did not elicit UVR responses indicative of phototoxicity or photoprotection. Treatment with 0.1% (1.0 mg/ml) caused severe cutaneous inflammation; 0.1 mg/ml caused mild to moderate cutaneous inflammation, and 0.001- 0.0001% (0.01-0.001 mg/ml) caused mild cutaneous inflammation. Based on the above two studies, recommended dose levels were 0.1 and 0.01 mg/ml, which are equivalent to the concentrations of tretinoin that enhance photocarcinogenesis. In the full 12-month photocarcinogenicity study in hairless mice, mice were dosed with 0.001, 0.005, 0.01% AGN 190168 with UVR (solar simulation, 120 RBU) applied pre- and post-dose. Control

groups were given low UVR (120 RBU), high UVR (240 RBU), or vehicle with low UVR. [RBU=Robertson-Berger Units (400 RBU = one minimal erythema dose in previously untanned skin).] On skin, thickening, flaking, erythema, ulceration, and scab were noted in all groups. The severity of the findings, however, increased significantly with Tazarotene treatment or increase of the UV dose. No obvious sex differences were noted in tumor prevalence. Throughout the 48 weeks of tumor observation and evaluation, more tumors were noted earlier in the groups treated with Tazarotene and in the high-UV dose group. Tumors appeared slightly earlier in the mid-dose, high-dose, and high-UV dose groups than in the low dose group, but this difference was only slight. The first tumors were noted in week 10. In addition to the observations of the first perceptible tumors, group differences were noted in the appearance of progressively larger tumors (i.e. 1, 2, or 4 mm tumors). Using Peto analysis of time to tumor, significant differences were noted for the high-dose UVR, and all Tazarotene treated groups for virtually all tumor size appearance when compared to the low-dose UV or the vehicle control group. The median onset of tumors (to 1 mm) was longest (i.e. more time was required to induce tumors) in the low-dose UV and the vehicle control group: 35 and 37 weeks respectively. The median onset of tumors in the high-UV group was 25 weeks, and the median onset for the low-, mid-, and high-dose Tazarotene groups was 26, 23, and 24 weeks respectively. A similar pattern of median latent period was noted for larger tumors, and no sex differences were detected. The sponsor performed Peto analysis of the onset to tumor (table below). A clear and statistically significant increase in tumor onset was noted in all Tazarotene treated groups. The number of tumors in surviving animals increased as expected in the Tazarotene treated groups compared to the low-dose UV and vehicle control group. These data mirror the cumulative tumor prevalence noted above. In general, the first perceptible tumors appeared first in the Tazarotene and high-UV treated groups.

Dose levels for the oral rat carcinogenicity study were set utilizing a 13-week oral toxicity study in rats. Rats dosed orally through the diet with 0, 0.05, 0.10, and 0.50 mg/kg/day. Dose-limiting effects were noted primarily in clinical pathology values, particularly in liver enzymes, and histopathology. Several treatment related effects were noted in the liver of mid- and high-dose males, including centrilobular hepatocyte enlargement; single cell degeneration; and increased centrilobular or generalized (high-dose only) fat deposition. Females in the high dose had an increased incidence of periportal fat deposition. Other treatment-related effects in males included increased minimal focal hyperplasia of the basal cells of the non-glandular stomach epithelium (high-dose), increased stomach acanthosis (high-dose), and increased periosteal osteocalcic activity/fibrosis (mid- and high-dose). High-dose females also experienced an increased incidence of peri-osteal increased osteoclastic activity.

Based on study above, doses for the 2-year rat dietary study were set at 0, 0.025, 0.050, and 0.125 mg/kg/day. No statistical differences were noted for survival rates in this study. Body weight changes or gains were decreased in the high-dose groups. At 104 weeks, mid- and high-dose females were noted with significantly decreased mean corpuscular volume (slight) and platelet count (20%) values compared to mean control values. Mid- and high-dose males had significantly decreased lymphocyte values (29-23%) when compared to control

values. Total protein values were decreased in all treated animals; the differences were significantly lower for all treated males and in high-dose females (less than 10%). Cholesterol was also decreased in all treated animals; the difference was significant in mid- and high-dose males and all treated females (as high as 54%). Glucose values were slightly increased above control values in all treated animals; the difference was statistically significant in high-dose females (15%). Urea nitrogen levels were also significantly decreased urea nitrogen in all treated females (to 20%). Aspartate aminotransferase was decreased in all treated animals and was significantly decreased in mid- and high-dose males (to 30%). Of greatest concern was the number of liver adenomas noted in the females; 0, 0, 0, and 3, for groups 1-4, respectively. All tumors found in organs of possible concern (based on incidence and results from other retinoids) are shown below.

Neoplasm	Males				Females			
	Group No.				Group No.			
	1	2	3	4	1	2	3	4
Liver-- total adenomas or carcinomas	3	4	2	0	0	0	0	3
Liver-- adenomas	2	2	1	0	0	0	0	3
Liver-- carcinomas	1	2	1	0	0	0	0	0
Thyroid-- follicular adenomas or carcinomas	6	7	6	3	1	0	0	3
Thyroid-- fol. adenomas	6	4	5	1	1	0	0	3
Thyroid-- fol. carcinomas	0	3	1	2	0	0	0	0

The sponsor analyzed the hepatocellular adenomas in females rats using the logrank methods of Mantel (1966) and Peto (1974). Analyses included a test for heterogeneity, a one-tailed test for trend and pairwise comparison (against control), and a test for non-linearity. The test for trend was not significant for the liver adenomas in females ($p = 0.007$), and the pairwise comparison was also negative ($p = 0.13$). Satellite animals (4-5/sex/group) were sampled at 3, 6, 9, 12, 18, and 24 months (8-10 AM) using spectrophotometry. The

sponsor measured the main metabolite of the parent drug, AGN 190299.

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Discussion

The sponsor performed a sufficient number of preclinical studies to evaluate Tazarotene. Although two formulations were utilized in the dermal studies, the sponsor performed a 3-month bridging study that revealed no difference in toxicity or irritation between the two formulations. Of greatest importance to the NDA are the findings in the chronic toxicity, reproduction, and carcinogenicity studies. The following table summarizes results with expected/estimated blood levels from long term toxicology studies. (Animal PK values were collected from short-exposure studies. Toxicity findings of greatest concern were generally in long-term studies. We can expect the day-to-day blood levels in the long toxicity studies to approximate the findings in the shorter PK studies.)

	PK Studies			Preclinical Toxicity Studies
	0.1% Solution	0.1% Cream	0.1% Gel	
Human 0.1% Solution	1.2	14.4	0.2	na
Rat - 7 days dermal	0.06		2.6	6 month dermal; reversible effects, skin irritation, liver, bone, and adrenals, reversible
Miniswine - 52 weeks dermal	0.50		1.2	52 weeks; 0.50 mg/kg/day; erythema, no systemic effects
Monkey - 5 days oral	2.0		305	6-month oral; 0.05-0.5 mg/kg mortality, liver, kidney, bone

The noted effects in the oral studies are typical of those associated with retinoid toxicity. These effects are in doses well above the expected systemic values seen in humans given topical tazarotene. Similarly, the serious fetal toxicity and malformations noted in the oral reproduction studies were at values above the expected human systemic exposure. In rabbits dosed topically (0.25 mg/kg) during gestation days 6-18, the Cmax reached 86 ng/ml, several hundred times that seen in humans following topical dosing.

In the 2-year oral rat carcinogenicity study, the finding of liver adenomas in females was not considered to be meaningful, and the CDER Executive Carcinogenicity Assessment Committee (CAC) recommended leaving the finding out of the label. This appears to be a very reasonable recommendation. The positive finding of greatest concern was in the photocarcinogenicity assay; all dose levels tested positive for photocarcinogenicity. This finding is reflected in the labeling recommendations found below. (The dermal mouse carcinogenicity study has been submitted as an amendment; we await electronic data for this submission. Additional labeling

suggestions will follow review by the Executive CAC committee.)

Conclusions

This NDA is approvable in terms of preclinical studies and data.

Recommendations

1. The sponsor has submitted two studies as amendments; a dermal carcinogenicity study and a oral primate toxicity study. The two studies will be reviewed as an amendment review following submission of the dermal carcinogenicity data in electronic format and statistical analysis.
2. The following labeling changes should be made. (The final label should also address the findings in the two amended studies; see the amendment review for the specific recommendations.)

Hilary V. Sheevers 4/11/96

Hilary V. Sheevers, Ph.D.

cc:

~~HFD-540~~

- HFD-540
- HFD-540/PHARM/Sheevers
- HFD-540/MQ/Ko
- HFD-540/CHEM/DeCamp
- HFD-540/PM/Cross
- HFD-540/TLTOX/Jacobs

Concurrence Only:

- HFD-540/DD/Wilkin *923 4/28/96*
- HFD-540/TLTOX/Jacobs *u.g. 4/11/96*

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OCT 31 1996

Review and Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products, HFD-540

NDA#: 20-600 (000); submission filed as a safety update to the original NDA
Date submitted: 10/30/95 (from desk copy)
Date CDER Received: 12/13/95 (from COMIS)

Sponsor: Allergan 1-800-347-4500
2525 Dupont Dr.
PO Box 19534
Irvine, CA 92713-9534

Name of Drug: Tazarotene (AGN 190168) 0.05%, 0.1% gel
Chemical Name: Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate

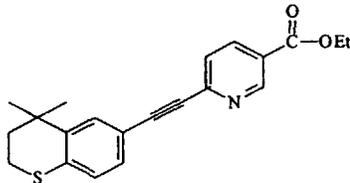
Pharmacological Category: Retinoid

Indication: Plaque psoriasis and acne vulgaris

Route of Administration: Topical dermal

Structure:

MW 351.5



Formulation:

Percent tazarotene:	0.1	.05	placebo
Ingredient:	<u>%w/w</u>	<u>%w/w</u>	<u>%w/w</u>
Tazarotene			
Benzyl alcohol			
Ascorbic acid			
Butylated hydroxyanisole			
Butylated hydroxytoluene			
Edetate disodium			
PEG 400			
Hexylene glycol			
Polysorbate 40			
Poloxamer 407			
Carbomer 934P			
Tromethamine			
Purified water			

Introduction

The sponsor submitted two studies, a mouse dermal carcinogenicity study and a chronic primate oral toxicity study, as a "safety update" to the NDA. The studies are reviewed below. Final labelling recommendations in regard to these two studies (which includes final CAC recommendations for the mouse dermal study) are presented in the final recommendations section.

One-year oral toxicity study in monkeys; Study no. 1643-985-125; 9/95.

Animal Strain: Cynomolgus monkeys, 2-4 years of age at the beginning of the study

No. of Animals: 6/sex/group

Route: oral by nasal intubation

Duration: 52 weeks

Study Design & Dose Levels:

Group	Dose (mg/kg/day)	Factor (ml/kg)	Concentration (mg/ml)
1	0	2	
2	0.0125	2	
3	0.025	2	
4*	0.25/0.125	2	

* Dose level for group 4 males was 0.25 mg/kg and 0.125 mg/kg for the females. Due to toxicity, the male dose level was reduced to 0.125 mg/kg on day 183

Methods: Animals were dosed once daily with test material, AGN 190168 (lot #'s 10543 and 10553, placebo solution lot #'s 10542 and 10549) by nasogastric intubation for at least 52 weeks. Two animals per sex per group were kept for an 8 week recovery period after cessation of dosing.

Results:

Clinical signs: There were no changes in animals dosed at 0.0125 or 0.025 mg/kg/day. High dose males exhibited hunched posture, inflexibility of the spine, hypoactivity, contracted tendons, limited use of joints of arms and legs, and occasional tremors/ataxia.

Mortality: Two high dose males were sacrificed for humane reasons, one at week 36 and one at week 48.

Body Weight Values: The males in the highest dose group did not exhibit body weight gain normally expected in animals of this age, as was seen in the control and other treatment groups.

Blood Pressure and Electrocardiograms (prior to dosing and weeks 13, 26, 39/40, 52, and 60): No changes were seen that could be attributed to drug treatment.

Ophthalmic Observations (prior to dosing and weeks 13, 26, 39, 53, and 60): One male in the 0.025 mg/kg treatment group had bilateral multifocal, equatorial cataracts, with no histopathological changes, noted at the week 53 examination. The ophthalmologist's report stated that this was unusual as a spontaneous event and may be associated with administration of the test compound. However, no such lesion occurred at the high dose. There was no report included for the week 60 observations in recovery animals.

Radiography (prior to dosing weeks 13, 21-24, 39, 52, and 60): Changes were seen in high dose animals only. In males, there was evidence of epiphyseal closure in most long bones and kyphosis. In females, epiphyseal closure was seen in the tibia and femur. Progressive degenerative articular changes were seen in males.

Hematology (prior to dosing weeks 4, 13, 26, 39, 52, and 60): No changes were seen that were of biological significance or that were suggestive of a drug-related effect. As an incidental finding, at week 52, segmented neutrophils were decreased significantly from control in all female treated groups, and also in group 3 females at week 39, but all values were still within the range of historical controls.

Clinical Chemistry (prior to dosing weeks 4, 13, 26, 39, 52, and 60): In high dose males and females, serum alkaline phosphatase activity was consistently lower than in control or lower dose animals. This decrease was only statistically significant in males at week 26. All values were within the reported range of historical controls.

Serum ALT activity was also consistently lower in high dose males than in control or other treated animals. This change was only statistically significant at week 26; this was also the only instance in which it was below the reported range of historical controls.

No effects were seen on serum calcium or phosphorus, or on urinalysis parameters.

Organ Weights: The absolute and relative spleen weights of all treated animals were greater than those of corresponding control animals, but the difference was not statistically significant.

Necropsy Observations: Articular lesions were noted in the proximal humerus and proximal and distal femur in high dose males. High dose males also exhibited growth plate closure. One high dose female had deformations, erosions and depressed areas in the articular surface

of the right proximal femur. One high dose male that was sacrificed prior to study completion had rigid kyphosis and deformation of the vertebral column.

Histopathology: Changes were seen in the skeletal tissues of the high dose animals only. In males, lesions were seen in the femur, tibia, humerus, and vertebrae. In 3 females, lesions were seen in the femur, tibia, and lumbar vertebrae. Lesions consisted of disorganization of the epiphyseal growth plate cartilage, articular cartilage disruption and fibrosis in the long bones, vertebral ankylosis and/or hyperostosis of the vertebral articular processes.

Pharmacokinetics: Test animals were sampled 2 hours after dosing on day 1, and at weeks 13 and 26. Samples were also taken on day 16 and at week 52 prior to dosing and at 1, 2, 4, 6, 8 and 24 hours after dosing. Serum levels of AGN 190168 (tazarotene) were below the limit of quantitation in animals in the low and mid-dose groups at all time points. At doses of 0.125 and 0.25 mg/kg/day, serum concentrations of the parent drug were less than ng/ml, when detectable.

Serum concentrations of AGN 190299, the free acid form and active metabolite of tazarotene, were detectable in all dose groups during treatment, but were undetectable at weeks 56 and 60 in recovery animals, indicating clearance of drug within 4 weeks of discontinuation of treatment. Mean C_{max} and AUC values are shown below.

		AGN 190168 dosage (mg/kg/day)				
		0 (vehicle)	0.0125	0.025	0.125	0.25
C_{2hr} (ng/ml)	BLQ		3.21 ± 0.88	5.29 ± 1.41	19.2 ± 4.4	37.3 ± 8.3
C_{max} (ng/ml)	BLQ		3.72 ± 1.68	5.29 ± 1.63	22.5 ± 7.6	54.1 ± 6.1
AUC _{24hr} (ng·hr/ml)	NA		24.6 ± 5.6	45.0 ± 9.0	128 ± 22	317 ± 54

In general, C_{2hr} was a good indicator of C_{max} . Increases in parameters were linear with respect to dose. No significant difference was seen between parameters calculated for males and females. Half-life of AGN 190299 was 4-7 hours.

Dermal Carcinogenicity Study in Mice; Study No. 1643- 25/951336, 9/95

Animal Strain: Crl:CD-1 (ICR) BR mice

No. of Animals: 55/sex/group; plus satellite groups of 10/sex/group

Route: topical dermal

Duration: 104 weeks planned; main study was terminated at 88 weeks and the satellite groups were terminated at 78 weeks due to high death rates.

Study Design & Dose Levels:

Group	Dose Level (mg/kg/day)	Dose Level (mg/m ² /day) ^a	Concentration (% w/w)	Dose Volume (ml/kg)
1	0	0	0	0
2	0	0	0	1.0
3	0.05	0.3	0.01	0.5
4	0.125	0.7	0.025	0.5
5	0.250	1.5	0.05	0.5
6	1.0/0.5 ^b	6.0/3.0 ^b	0.1	1.0/0.5

^a Conversion factor of *5.9 was used to convert mg/kg to mg/m².

^b Dosing was stopped for group 6 males during week 42 due to severe dermal ulceration. The males were allowed 10 weeks to recover, and drug at half the dosage volume was then re-introduced at week 53. Group 6 females received the full dose over the entire study.

Formulation:

Percent tazarotene:	0.1	.05	.025	.01	placebo
Ingredient:	<u>%w/w</u>	<u>%w/w</u>	<u>%w/w</u>	<u>%w/w</u>	<u>%w/w</u>
Tazarotene					
Benzyl alcohol					
Ascorbic acid					
Butylated hydroxyanisole					
Butylated hydroxytoluene					
Edetate disodium					
PEG 400					
Hexylene glycol					
Polysorbate 40					
Poloxamer 407					
Carbomer 934P					
Tromethamine					
Purified water					

Methods: Mice were treated with Tazarotene on their shaved backs (2 x 3 cm) for 88 weeks; satellite animals and all high-dose males were treated for a total of 78 weeks. Mice were evaluated for clinical signs (reported only in summary form), dermal irritation, dermal masses, mortality, bodyweights (weekly), food consumption, ophthalmoscopy (weeks 26, 52, and 78), hematology and clinical chemistry changes (15/sex/group at termination), toxicokinetics (weeks 16, 53, and 79), and histopathology changes.

Results:

Mortality: Survival and mortality are summarized below.

Group	<u>Total Deaths</u>		<u>Percent Mortality</u>		<u>Percent Survival</u>	
	Male	Female	Male	Female	Male	Female
1	17	29	31	53	69	47
2	7	21	13	38	87	62
3	18	24	33	44	67	56
4	22	23	40	42	60	58
5	32	28	58	51	42	49
6	42	38	76	69	24	31

Statistical analyses were performed by the sponsor using logrank methods (Mantel 1966, Peto 1974) for animals dying up to and including Week 88. Tests consisted of a 2-tailed test for trend and a 2-tailed pairwise comparison of each treated group against the pooled control groups.

Males

Dose (mg/kg/day)	Initial Group Size	Number of Deaths		Relative Death Rate (O/E)	Pairwise comparison (p value)	Test for trend (p value)
		Observed (O)	Expected (E)			
0	55	17	24	0.70		
0 (vehicle)	55	7	29	0.25		
0.050	55	18	25	0.72	0.18	0.088
0.125	55	22	24	0.92	0.02*	0.088
0.250	55	32	20	1.61	<0.001*	<0.001*
1.00 ^a	55	42	16	2.58	<0.001*	<0.001*

^a Treatment stopped weeks 41-52; dose reduced to 0.5 mg/kg/day week 53 to study end.

* Statistically different (pairwise comparison or test for trend) from pooled control values.

Females

Dose (mg/kg/day)	Initial Group Size	Number of Deaths		Relative Death Rate (O/E)	Pairwise comparison (p value)	Test for trend (p value)
		Observed (O)	Expected (E)			
0	55	29	28	1.05		
0 (vehicle)	55	21	29	0.73		
0.050	55	24	29	0.84	0.91	
0.125	55	23	29	0.79	0.71	
0.250	55	28	27	1.05	0.57	0.28
1.00	55	28	22	1.71	0.003*	<0.001*

* Statistically different (pairwise comparison or test for trend) from pooled control values.

Body Weight Values: High-dose male and female body weight values were below control values by 18% for males and 15% for females (week 88). All treated male body weight values were below the untreated control values, although the differences were generally less than 10%.

Food Consumption: High-dose male food consumption was above control values for most of the study (by 17% at week 88). All other food consumption values were comparable. Food conversion ratios (food consumption/bodyweight gain; measured over weeks 1-13) was increased for all treated animals (including vehicle control) in comparison to untreated controls, and especially for treated females (a ratio of 69 compared to values above 80 for all treated groups).

Ophthalmic Observations(weeks 26, 52, and 78): No treatment-related differences were noted.

Hematology (week 86): High-dose males had small, but statistically significant, decreased mean packed cell volume (7%), hemoglobin (8%), red blood cell counts (8%); as well as significantly increased platelet values (20%). Other values were comparable to mean control values.

Clinical Chemistry (week 89): High-dose males and females had statistically decreased high density lipoprotein (males, 40%; females, 22%), cholesterol (males, 42%; females, 15%) triglycerides (males, 29%; females, 20%, statistically significant for females only), and albumin (males, 17%; females, 15%). Statistically increased globulin values were noted in the high-dose animals (males, 12%; females, 10%). High density lipoproteins were also slightly decreased in the low- and mid-dose animals (generally less than 10%). Indications of changes in liver biochemistry were also slightly evident in the group 4 and 5 animals, although the differences generally were only sporadically significant and less than 10%. Differences were noted in creatinine and urea nitrogen in high-dose animals, although the changes were small. Other values were comparable to mean control values.

Organ Weights: Organ weight differences appeared sporadic and variable and do not appear to be related to treatment.

Necropsy Observations: The treated skin in males and females (terminal and unscheduled deaths) at necropsy generally appeared ulcerated, flaky, scabbed, thickened (high-dose group only), and dry; the incidence increased in number and severity with increasing dose. Enlarged axillary lymph nodes were noted in increasing numbers with increasing dose in both males and females (all deaths). For animals killed prior to scheduled death, masses (1-2) were noted in group 5 or 6 males on the head, axillary lymph nodes, hibernating gland, subcutaneously, spleen, and bone. In unscheduled-death females, masses (1-2) were noted in groups 5 or 6 in the axillary lymph node, adrenals, and the spinal cord. Terminal high-dose animals were noted with 1-2 masses in the spleen and the head. (In the histopathological examination, none of the masses appeared to be related to drug treatment.)

Non-Neoplastic Morphology: Non-neoplastic findings that increased or appeared with increasing dose are shown below. Dose-related increases were noted in the axillary and inguinal lymph nodes (plasmacytosis), the spleen (extramedullary hemopoiesis), and the skin. In untreated skin, an increase with dose was noted in the incidence of epithelial hyperplasia, scabs, ulcerations, and mast cells. In treated skin, increases were noted in ulceration, epithelial hyperplasia, prominent mast cells, and one incidence (high-dose male) of an epidermal cyst.

Neoplasms: No systemic tumors (adenoma or carcinoma) were noted in an obvious dose-related manner. Possible exceptions may include a malignant osteosarcoma noted in a group 5 male, and the same tumor type was noted in a group 4 female. In the group of malignant lymphoid tumors, single incidences of malignant lymphoma were noted both group 5 and group 6 males and females. Other malignant lymphoid tumors appeared sporadically or across several groups at a similar incidence rate. There were no skin tumors in males and no skin tumors at the treated site in females. No tumor differences between treated and control groups or trends in tumor incidence were statistically significant.

Pharmacokinetics: Satellite animals (1-4/sex/group) were sampled at 2, 4, 8, 12, and 12 hours following 79 weeks of topical dosing using spectrophotometry. The sponsor measured the main metabolite of the parent drug, AGN 190299. Values are summarized in the table below.

Dose (mg/kg/day)	C _{max} (ng/ml)	T _{max} (hr)	AUC ₁₂ (ng-hr/ml)
0.05	11.1	4.0	82.7
0.125	19.6	5.0	137
0.25	28.4	2.0	183
0.5 (males only)	36.4	2.0	136
1.0	67.6	2.0	344

Discussion

A one-year oral study was performed in primates. No adverse effects were seen in animals treated with up to 0.025 mg/kg/day, with the exception of bilateral cataracts in one male treated with 0.025 mg/kg/day that may or may not have been related to test article administration. At the high dose (0.125 mg/kg/day in females and 0.25/0.125 mg/kg/day in males), however, skeletal and articular lesions were prevalent, particularly in males. These consisted of kyphosis, articular degeneration and erosions, and epiphyseal closure. Lesions were more prevalent in incidence and severity in males.

Pharmacokinetic evaluation of the above primate study demonstrated rapid conversion of the parent drug to the free acid active metabolite. Serum concentrations and the AUCs of

the metabolite were linear with respect to dose. Half-life was 4-7 hours, and, as expected, the drug metabolite was cleared from the body within 4 weeks of discontinuation of treatment.

A dermal carcinogenicity study was performed in mice. The study was terminated at 88 weeks due to high death rates. Severe dermal ulceration was seen in high dose males (1 mg/kg/day) by week 42; the dose was halved for the duration of the study after a 10 week recovery period. The death rate was increased in male mice at doses of 0.125 mg/kg/day and higher relative to controls. This rate tested positive for trend at 0.25 and 1.0/0.5 mg/kg/day. The death rate in females was increased relative to controls at a dose of 1 mg/kg/day; this also tested positive for trend. Body weights were significantly less than those of control animals in high dose males and females. High dose males exhibited decreased red blood cell indices and an increase in platelet count. In high dose males and females, there were alterations in serum lipid and protein levels, and serum chemistries provided some evidence of hepatic and renal effects. There was a dose related enlargement of axillary lymph nodes, inguinal lymph nodes, and spleen in treated animals. In parameters examined in treated and untreated skin (epithelial hyperplasia, ulceration, mast cells), there were dose-related increases in males and females. Masses were present in some high dose animals, but none were attributed to drug treatment. No systemic tumors were present in an obvious dose-related manner. The possible exceptions were malignant osteosarcoma seen in a group 5 male and a group 4 female. There were no skin tumors in males and no skin tumors at the treated site in females. No tumor differences between treated and control groups or trends in tumor incidence were statistically significant.

Recommendations

The following label changes were recommended in the original NDA review:

Amy C. Nostrandt 10/9/96
Amy C. Nostrandt, D.V.M., Ph.D.

- cc:
- HFD-340
- HFD-540
- HFD-540/PHARM/Nostrandt
- HFD-540/MO/Ko
- HFD-540/CHEM/DeCamp
- HFD-540/PM/Cross
- HFD-540/TLTOX/Jacobs

Concurrence Only:
HFD-540/DD/Wilkin *92* 10/31/96
HFD-540/TLTOX/Jacobs *uj* 10/11/96

Rec'd 10/28/96 92

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DEC 19 1996

Review and Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products, HFD-540

Addendum to review

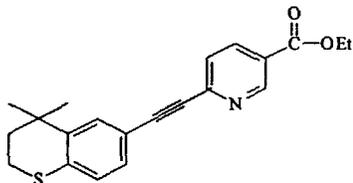
NDA#: 20-600 (000)

Sponsor: Allergan 1-800-347-4500
2525 Dupont Dr.
PO Box 19534
Irvine, CA 92713-9534

Name of Drug: Tazarotene (AGN 190168) 0.05%, 0.1% gel
Chemical Name: Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate

Pharmacological Category: Retinoid
Indication: Plaque psoriasis and acne vulgaris
Route of Administration: Topical dermal

Structure: MW 351.5



Formulation:

Percent tazarotene:	0.1	.05	placebo
<u>Ingredient:</u>	<u>%w/w</u>	<u>%w/w</u>	<u>%w/w</u>
Tazarotene			
Benzyl alcohol			
Ascorbic acid			
Butylated hydroxyanisole			
Butylated hydroxytoluene			
Edetate disodium			
PEG 400			
Hexylene glycol			
Polysorbate 40			
Poloxamer 407			
Carbomer 934P			
Tromethamine			
Purified water			

Amendment to labeling:

Amy C. Nostrandt 12/19/96

Amy C. Nostrandt, D.V.M., Ph.D.

cc:

HFD-340

HFD-540

HFD-540/PHARM/Nostrandt

HFD-540/MO/Ko

HFD-540/CHEM/DeCamp

HFD-540/PM/Cross

HFD-540/TLTOX/Jacobs

Concurrence Only:

HFD-540/DD/Wilkin *WJ* 12/19/96

HFD-540/TLTOX/Jacobs *UJ* 12/19/96

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Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products, HFD-540

NDA No.: 20,600 AZ

MAR 6 1997

Date Submitted: 1/17/97

Date CDER Received: 1/21/97

Date Review Completed: 3/4/97

Sponsor: Allergan 1-800-347-4500
2525 Dupont Dr.
PO Box 19534
Irvine, CA 92713-9534

Name of Drug: Tazarotene (AGN 190168) 0.05%, 0.1% gel
Chemical Name: Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate

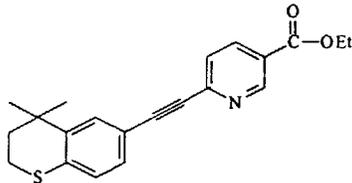
Pharmacological Category: Retinoid

Indication: Plaque psoriasis and acne vulgaris

Route of Administration: Topical dermal

Structure:

MW 351.5



Formulation:

Percent tazarotene:	0.1	.05	placebo
<u>Ingredient:</u>	<u>%w/w</u>	<u>%w/w</u>	<u>%w/w</u>
Tazarotene			
Benzyl alcohol			
Ascorbic acid			
Butylated hydroxyanisole			
Butylated hydroxytoluene			
Edetate disodium			
PEG 400			
Hexylene glycol			
Polysorbate 40			
Poloxamer 407			
Carbomer 934P			
Tromethamine			
Purified water			

Related INDs/NDAs: IND

INTRODUCTION

This amendment was made in response to the Approvable Action Letter sent to the sponsor 12/30/96. This submission, as it relates to pharmacology/toxicology, primarily addresses revision of the labeling and, in particular, presents arguments for changing the Pregnancy Category from X to C.

PREGNANCY CATEGORY

5 Pages (3-7)

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cc:

NDA 20,600

HFD-340

HFD-540

HFD-540/PHARM/Nostrandt

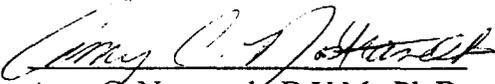
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HFD-540/MO/Ko

HFD-540/CHEM/Gilman

HFD-540/PMS/Cross

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 3/6/97
Amy C. Nostrandt, D.V.M., Ph.D.
Pharmacologist/Toxicologist

Concurrence Only:

HFD-540/DD/WILKIN  4/13/97

HFD-540/TLPHARM/JACOBS  3/6/97