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 sponsor states that the AUC at this dose was 1.2 times the AUC in human acne patients. 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. The sponsor states that the AUC at 0.25 mg/kg/day in minipigs was 3.6 times that seen in acne patients.

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.

Histopathology Inventory for NDA #21-184

Study	98-3377	98-3378		
Species	dog	dog		
Adrenals	X*	X*		
Aorta		X		
Bone Marrow smear		X		
Bone (femur)	X	X		
Brain	X*	X*		
Cecum	X	X		
Cervix		X		
Colon	X	X		
Duodenum	X	X		
Epididymis	C	X		
Esophagus	C	X		
Eye	X	X		
Fallopian tube				
Gall bladder	X	X		
Gross lesions	X	X		
Harderian gland				
Heart	X*	X*		
Ileum	X	X		
Injection site				
Jejunum	X	X		
Kidneys	X*	X*		
Lachrymal gland	C	X		
Larynx				
Liver	X*	X*		
Lungs	X	X		
Lymph nodes, cervical				
Lymph nodes mandibular				
Lymph nodes, mesenteric	C	X		
Lymph nodes, mediastinal	C	X		
Mammary Gland	C	X		
Nasal cavity				
Optic nerves	X	X		

Ovaries	X*	X*		
Pancreas	X	X		
Parathyroid		X		
Peripheral nerve				
Pharynx				
Pituitary	X*	X*		
Prostate	C	X		
Rectum	X	X		
Salivary gland	C	X		
Sciatic nerve		X		
Seminal vesicles				
Skeletal muscle				
Skin	X	X		
Spinal cord	C	X		
Spleen	X*	X*		
Sternum				
Stomach	X	X		
Testes	X*	X*		
Thymus	C*	X		
Thyroid		X		
Tongue	C			
Trachea	C	X		
Urinary bladder	X	X		
Uterus	C	X		
Vagina	C	X		
Zymbal gland				
Standard List				

* organ weight obtained
C – tissue collected and preserved, but not examined
X – tissue colected, preserved, and examined microscopically

GENETIC TOXICOLOGY:

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 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.

CARCINOGENICITY:

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.

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

1. Study title: Tazarotene: Oral (gavage) fertility and general reproduction toxicity study in male rats.

Study number: TX99103 (
Site and testing facility:
GLP compliance: yes
QA- Reports Yes (X) No ( ):
Lot and batch numbers: lot #KG01544, raw material #91406
Protocol reviewed by Division Yes ( ) No (X):

Methods:

- Species/strain: rats
- Doses employed: 0 (vehicle – medium chain triglycerides), 0.3, 1, and 3 mg/kg/day, in a volume of 5 mL/kg/day

Reviewer's comment: These doses were based on the findings of a 90-day study of oral tazarotene in rats. The sponsor states that that study used a different formulation that resulted in higher systemic exposures than did the formulation used in this study. The sponsor also states that the high dose was anticipated to result in systemic exposures similar to those found in humans treated with the regimen in current clinical protocols. The vehicle is not the same as that found in the capsule fill material for the clinical formulation. The relative bioavailability between these formulations is unknown.

- Route of Administration: oral (gavage)
- Study Design: Male rats were administered test article or vehicle once daily for 70 days before cohabitation (maximum 21 days) and continuing through the day before sacrifice, at the completion of the cohabitation period. Each male was assigned to cohabitation with one female rat. If mating did not occur within the first 14 days, as evidenced by spermatozoa on vaginal smear or a copulatory plug, then an alternate female was assigned for a maximum of 7 additional days. Due to problems with fractures in the high dose group, those animals were treated for 59 days, then placed with selected proestrus females for a cohabitation period prior to early termination of that group.

Males were observed for effects of test article daily before dosing and approximately 1 hour after dosing. Body weights were recorded daily during the dosing period and at sacrifice. Feed consumption was monitored weekly during dosing period.

A satellite group of eight males was included for each dose for toxicokinetics. On day 70 (day 59 for high dose animals) of the premating period, blood samples were collected pre-dose, 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose from the orbital sinus and centrifuged. Plasma was stored at –15° C until analysis. Concentrations of tazarotenic acid were determined by LC/MS/MS with a quantitation range of 1-200ng/mL.

- Number of animals/sex/dosing group: 25 males per group
- Parameters and endpoints evaluated: The following mating and fertility parameters were evaluated: number of days in cohabitation, rats that mated, fertility index, rats with confirmed mating dates, and rats pregnant/rats in cohabitation. Gross necropsy of thoracic, abdominal and pelvic viscera was performed, and reproductive organ weights (right testis, left testis, left epididymis [whole and cauda], right epididymis, seminal vesicles [with and without fluid], and prostate) were determined. Histopathological examination of the testes was performed for the vehicle and high dose groups. Sperm evaluations were performed on samples from the left cauda epididymis.

For animals that died or were moribund sacrificed, necropsy for cause of death and gross lesions was performed. The testes and epididymides were excised, weighed, and fixed for histopathology. (*Reviewer's comment: No sperm analysis was performed in any of these animals. This may have further skewed the study results, since they represent approximately 1/3 of the high dose group.*)

Females (untreated) were sacrificed on GD 20. Uteri were examined for the presence, number, and distribution of implantation sites, early and late resorptions, and live and dead fetuses. Fetuses were weighed and examined for external alterations.

- Statistical evaluations: Clinical observations and proportion data was tested for homogeneity of variance only. Continuous data was analyzed using Bartlett's test for homogeneity of variance, followed by ANOVA (parametric, in the case of homogeneous variances) or Kruskal-Wallis test (non-parametric, in the case of non-homogeneous variances) as appropriate. In the case of significant differences, Dunnett's test or Dunn's method, respectively, was used for multiple comparisons. Count data at Caesarean-section was evaluated using the nonparametric methods. (*Reviewer's comment: It is unclear whether or not this is appropriate; it seems that the data should be evaluated for homogeneity of variance and the appropriate method used.*) Sperm motility data were expressed as percentages and evaluated by parametric methods.

Results:

- Clinical signs: Excess salivation was noted in all three treated groups. Additional signs seen in the high dose group only included: limited use of, broken and/or swollen and purple limb, vocalization to touch, urine-stained abdominal fur, chromorhinorrhea, scant feces and/or red dried perioral substance.
- Mortality: In the 3 mg/kg group, six rats were moribund sacrificed (due to broken limbs) and one rat was found dead (with three broken limbs) between study days 55 and 61.
- Body weight: Body weight gains were reduced in the 1 and 3 mg/kg groups. Body weights were significantly reduced in the 3 mg/kg group on days 36, 43, 50, and 57

(*Reviewer's comment: It is notable that these significant reductions were seen at weekly intervals, but that body weights were determined daily.*)

Animals that were found dead or were moribund sacrificed in the high dose group lost weight prior to death or sacrifice. (*Reviewer's comment: It should be noted that all of these animals had one or more broken legs, which could limit access to food and result in inappetance.*)

Terminal body weights were significantly reduced at 3 mg/kg relative to control animals at a comparable age.

- Food consumption: Absolute feed consumption was reduced for study days 43-50 in the 3 mg/kg group, and relative feed consumption was increased for study days 15-22 in the 1 and 3 mg/kg groups. These findings were not considered test article related.
- Toxicokinetics:

Dose (mg/kg/day)	Cmax (ng/mL)		Tmax (hours)	AUC_{0-t} (ng*hr/mL)		AUC interval (hours)
	mean	SD		mean	SD	
0.3 (70 days)	7.25	2.12	8	89.9	10.6	0-24
1 (70 days)	8.89	5.26	8	164	21	0-24
3 (59 days)	28.1	9.5	8	325	29	0-24

The sponsor states in the report that the high dose was chosen to approximate human clinical exposure.

- Fertility in Males
  - In-life observations: There were no biologically important differences in mating and fertility parameters. There was a significant reduction in the number days in cohabitation in the 3 mg/kg group that was the result of selection of females that were in proestrus. (*Reviewer's comment: This selection invalidates many of the fertility parameters for this dosage group. Different values might have been obtained, had females been assigned at random, as with the other dosage groups.*)
  - Terminal and Necroscopic evaluations: Fore- or hind-limb fractures were observed at 3 mg/kg; all seven high dose animals that were found dead or moribund sacrificed had broken limbs. (*Reviewer's comment: This is a known adverse effect of systemic retinoids. The sponsor states that it was a result of "exaggerated pharmacologic activity," however calling the effect pharmacologic rather than toxic does not mitigate the adversity of the effect. It is also important to note that the high dose was chosen to approximate systemic exposure seen in the clinical setting.*) Associated findings of red and/or gelatinous areas seem consistent with bone trauma. Also at the high dose there was a statistically significant increased finding of visibly small seminal vesicles.

    Observations of red substance on the left cauda epididymis and red lymph nodes and prostate in one rat, and one rat with purple testes, and small epididymides in one rat were not considered test article-related, but systemic retinoids have been shown to have effects on clotting times and to produce testicular toxicity. It is possible that these lesions could be related to such effects.

    There was a dose-dependent reduction in absolute and relative weights of seminal vesicles with fluid in all treated groups. The absolute and relative weights of left cauda epididymis, seminal vesicles without fluid and prostate, and

the absolute weights of left and right epididymis were significantly reduced in the 3 mg/kg group.

Sperm evaluation revealed a significantly reduced sperm count and density in the 3 mg/kg group. There was also a reduced amount of seminal vesicle fluid in that group. (*Reviewer's comment: A pregnancy rate of 76 % was achieved in females mated to high dose males, compared to 92-100% in the other groups. It is unclear whether or not this reflects a drug effect, or is a result of moribund sacrifice of some males during the cohabitation period. There appeared to be a slight increase in the percent resorbed fetuses per litter in females mated to high dose males; it is unclear whether or not this may represent a drug effect.*)

There were no drug-related microscopic changes in testes on histopathologic examination. No other tissues were evaluated.

Reviewer's comment: High dose animals were assigned to cohabitation early and sacrificed after mating; the shorter duration of treatment relative to other dose groups may have minimized testicular and other effects of the drug.

Key study findings:

Because of early assignment to cohabitation of the high dose group and selection of proestrus females for those males, many of the reproductive evaluations were only valid for the low and mid-dose groups. Other effects, such as those on sperm count and testicular histopathology, may have been minimized due to early discontinuation of treatment.

Excessive salivation was seen at all doses. Broken limbs and mortality were prominent at the high dose (3 mg/kg) and resulted in early termination of that group. The sponsor states that the high dose was chosen to result in systemic drug exposure that would be comparable to clinical exposure in human patients.

Reduced body weight gains were evident at 1 and 3 mg/kg. There were no effects on fertility parameters at doses up to 1 mg/kg. At 3 mg/kg, small seminal vesicles were found on necropsy. There was a dose-dependent reduction in absolute and relative weights of seminal vesicles with fluid in all treated groups. The absolute and relative weights of left cauda epididymis, seminal vesicles without fluid and prostate, and the absolute weights of left and right epididymis were significantly reduced in the 3 mg/kg group. Sperm evaluation revealed a significantly reduced sperm count and density in the 3 mg/kg group.

The NOEL for effects on fertility appeared to be 1 mg/kg, but the terminal findings of decreased seminal vesicle weight in this and the 0.3 mg/kg group may indicate that these doses could have effects on the male reproductive system in the rat if dosing were continued for a longer period of time.

2. Study title: Tazarotene: oral (gavage) fertility and general reproduction toxicity study in female rats.

Study No: TX99104 (protocol)

Site and testing facility:

GLP compliance: yes

QA- Reports Yes (X) No ( ):

Lot and batch numbers: lot #KG01544, raw material #91406

Protocol reviewed by Division Yes ( ) No (X):

Methods:

- Species/strain:) rats

- Doses employed: 0 (vehicle – medium chain triglycerides), 0.3, 1, and 2 mg/kg/day, in a volume of 5 mL/kg/day. (*Reviewer's comment: The high dose was reduced from the 3 mg/kg used in the male rat Segment I study, presumably due to excessive toxicity. The report also states that administration of 3 mg/kg/day to pregnant rats on GD 6-17 in a range-finding study produced excessive maternal weight loss and some fetal toxicity. However, 3 mg/kg was chosen as the high dose in the male study because it was expected to result in systemic exposure to tazarotenic acid that would be comparable to that seen in patients in clinical trials.*

The vehicle is not the same as that found in the capsule fill material for the clinical formulation. The relative bioavailability between these formulations is unknown.)

- Route of Administration: oral (gavage)

- Study Design: Female rats were administered test article or vehicle once daily for 15 days prior to cohabitation (maximum of 21 days) and through day 7 of presumed gestation. Rats were observed for clinical signs daily before dosing and approximately one hour after dosing. Body weights were recorded daily during the dosing period and on the day of sacrifice. Feed consumption was recorded weekly to cohabitation and on GD 0, 7, 8, 14, and 20. Estrous cycling was evaluated by vaginal cytology for 14 days prior to dosing, for 14 days during dosing, and then during cohabitation until spermatozoa were observed on vaginal smear and/or a copulatory plug was observed.

A satellite group of eight females was included for each group for toxicokinetic evaluation. On day 15 of the pre-mating period, blood samples were collected from each group of rats at 0 (pre-dose), 0.5, 1, 2, 4, 8, 12, and 24 hours after dosing form the orbital sinus. Samples were centrifuged, and plasma was stored at -15°C until analysis. Concentrations of tazarotenic acid were determined by) with a quantitation range of , ng/mL.

- Number of animals/sex/dosing group: 25/group, plus 8 satellite animals per group bled on study day 15 for toxicokinetics.

- Parameters and endpoints evaluated: The following mating and fertility parameters were evaluated: number of days in cohabitation, rats that mated, fertility index, rats with confirmed mating dates, and rats pregnant/rats in cohabitation.

Rats other than those for toxicokinetics were sacrificed on GD 20 and subjected to Caesarean-section and gross necropsy. Ovaries and all gross lesions were retained. The number of corpora lutea on ovaries was recorded. Uteri were examined for the presence, number, and distribution of implantation sites, early and late resorptions, and live and dead fetuses.

Fetuses were weighed and examined for sex and gross external alterations. Live fetuses were sacrificed by intraperitoneal injection . All fetuses, including those with gross lesions were retained for possible future examination.

- Statistical evaluations: Clinical observations and proportion data was tested for homogeneity of variance only. Continuous data was analyzed using Bartlett's test for homogeneity of variance, followed by ANOVA (parametric, in the case of homogeneous variances) or Kruskal-Wallis test (non-parametric, in the case of non-homogeneous variances), as appropriate. In the case of significant differences, Dunnett's test or Dunn's method, respectively, was used for multiple comparisons. Count data at Caesarean-section was evaluated using the nonparametric methods. (*Reviewer's comment: It is*

unclear whether or not this is appropriate; it seems that the data should be evaluated for homogeneity of variance and the appropriate method used.)

Results:

- Clinical signs: Excessive salivation was observed in all tazarotene-treated groups. Of the observations that the sponsor did not attribute to test article, ataxia was noted in one animal on one occasion in each of the 1 and 2 mg/kg groups.
- Mortality: none
- Body weight: During the pre-cohabitation period, body weight gains were reduced at all tazarotene doses. Body weights were significantly reduced on study day 15 in the 1 and 2 mg/kg groups.

During gestation, body weight gains were reduced in all tazarotene treated groups. Body weight gains in the 2 mg/kg group showed a brief recovery (significantly increased over controls) in the first week post-dosing, but again declined in the second week, although the differences from control were considerably less pronounced than during the dosing period. In the 0.3 and 1 mg/kg groups, body weight gains were significantly increased through the post-dosing period. Body weights were significantly lower than controls in all treated groups on each day of the gestation period.

- Food consumption: In the pre-cohabitation period, absolute and relative feed consumption was decreased relative to controls in all tazarotene-treated groups. During gestation, those values were reduced in the 2 mg/kg group. During the post-dosing period, absolute feed consumption was decreased, but relative feed consumption was increased in the 2 mg/kg group, relative to controls.
- Toxicokinetics:

Dose (mg/kg/day)	Cmax (ng/mL)		Tmax (hours)	AUC_{0-t} (ng*hr/mL)		AUC interval (hours)
	mean	SD		mean	SD	
0.3	9.93	0.88	8	83.7	5.1	0-12
1	12.9	5.7	4	173	15	0-24
2	23.7	12.8	4	296	32	0-24

- Fertility and Early Embryonic Development in Females
  - In-life observations:

    The average number of estrous stages per 14 days was significantly reduced in the 2 mg/kg group. Mating performance and fertility (number days in cohabitation, fertility and pregnancy indices) appeared to be unaffected by treatment.
  - Terminal and Necroscopic evaluations:

    At Caesarean section, 25 (100%), 24 (96%), 23 (92%) and 22 (88%) litters were evaluated on GD 20 in the control, 0.3, 1, and 2 mg/kg groups, respectively. (*Reviewer's comment: Although the fertility index was not statistically affected, there appears to be a dose-dependent decrease in pregnancies/rats that mated.*) The average number of implantation sites, litter size, and number of live fetuses were significantly reduced in the 2 mg/kg group. One litter in that group consisted of only one early resorption. Fetal body weights were also reduced in that group.

Placentae were reported to appear normal. No effect was seen on the average number of corpora lutea, early and late resorptions, percent resorbed conceptuses, and percent male fetuses. (*Reviewer's comment: This would seem to indicate a possible increase in pre-implantation loss at the high dose.*)

Fetal gross alterations were evaluated. One litter in the 2 mg/kg group had five fetuses with exencephaly; two of these also had open eyes, and an additional fetus had a meningocele. The report states that this incidence is within the range of historical controls (The historical incidence was four litters with exencephaly out of 929 in 56 studies, with a range per study of 0-1 litters. *Reviewer's comment: This database appears to include control and treated litters.*), but the report acknowledges that the effect is related to treatment. An additional fetus in another litter in the 2 mg/kg group was reported to have medially rotated hindlimbs and whole body edema, but was not considered to be related to treatment.

Key study findings:

Excessive salivation, decreased body weight gains and body weights were seen in female rats at all tazarotene doses. The average number of estrous stages per 14 days was significantly reduced in the 2 mg/kg group. Mating performance and fertility was unaffected at all doses.

There appeared to be a dose related decrease in % pregnancies in treated groups, but that value was not significantly different from control in any group. The average number of implantation sites, litter size, and number of live fetuses were significantly reduced in the 2 mg/kg group. One litter in that group consisted of only one early resorption. Fetal body weights were also reduced in that group. One litter in the 2 mg/kg group had fetuses with exencephaly, open eyes, and/or meningocele. All of these findings may be retinoid-related, and the sponsor acknowledges in the report that these findings were related to treatment.

3. Study title: A comparative oral range-finding developmental toxicity study in rats on tazarotene, tretinoin, and adapalene.
Study number: 98-4144 (Sponsor study no. 20030040 1318)
Site and testing facility:
GLP compliance: yes
QA- Reports Yes (X) No ( ):
Lot and batch numbers: Tazarotene lot #KG01501, raw material no. 91414
Tretinoin lot #98-0279, identification #96/20-5
Adapalene lot #98-OC-FP-71
Protocol reviewed by Division Yes ( ) No (X):

Methods:

- Species/strain: Crl:CD® (SD) BR albino rats, and International Genetic Standard, Crl:CD® (SD) IGS BR albino rats
(*Reviewer's comment: These strains are referred to below as CD and IGS rats, respectively.*)
- Doses employed: Tazarotene – 0.05, 0.1, 0.25, 0.5, 1.0, and 3.0 mg/kg/day to IGS rats and 0.25, 0.5, 1.0, and 3.0 mg/kg/day to CD rats.

Tretinoin – 0.5, 1.0, 3.0, 5.0, and 20.0 mg/kg/day to IGS rats and 5.0 and 20.0 mg/kg/day to CD rats.

(Reviewer's comment: The report states under "Protocol Deviations" that one animal in Group VII received a dose of 1 mg/kg/day tretinoin instead of 0.75 mg/kg/day on GD 15-17. Group VII was the 1 mg/kg dose group, and there was no 0.75 mg/kg group, so it is unclear why this statement was made.)

Adapalene – 1.0, 5.0, 7.5, and 10 mg/kg/day to IGS rats only.

- Route of Administration: oral by gavage, in a volume of 5 mL/kg/day
- Study Design: Presumed pregnant female rats were designated for either the range-finding developmental toxicity study, placental transfer evaluation, or for toxicokinetics. They were dosed once daily from gestation day (GD) 6 through GD 17 with either vehicle control (medium chain triglyceride) or one of the three test articles for the range-finding developmental toxicity study and through GD18 or 19 for the placental transfer and toxicokinetics evaluations.
- Number of animals/sex/dosing group: Five to six dams were assigned to each dose for the range-finding study; 3-4 dams were sampled per time point for the toxicokinetics study (these animals either comprised a separate group or were sampled from animals intended for the placental transfer study), and 8 dams/dose (IGS only) were dosed for the placental transfer study.
- Parameters and endpoints evaluated: Dams were observed twice daily for mortality and clinical signs. Cageside observations were made at 0.5 –2 hours after dosing. Body weights were recorded on GD 0, 4, 6, 9, 12, 15, 18, and 20. Feed consumption was recorded for range-finding animals only on days 4-6, 6-9, 9-12, 12-15, 15-18, and 18-20. Physical examinations were performed daily through GD 20, prior to dosing on days the animals were dosed. Dams assigned to the developmental range-finding toxicity study were euthanized on GD 20 and necropsied. The number of corpora lutea and implantation sites were determined. The numbers of live and dead fetuses and early and late resorptions were recorded. The same was performed for the animals assigned to the toxicokinetic component of the study on GD 19 and for animals designated for the placental transfer study.

  All live and dead fetuses were removed, weighed, sexed (observing the ano-genital distance), and evaluated for external alterations. Crown-rump length was measured for dead fetuses. Late resorptions were also evaluated for external malformations and measured for crown-rump length.

  Plasma samples were obtained on GD 17 at 0 (pre-dose), 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose for toxicokinetics. Blood samples were taken from the orbital sinus, centrifuged, and frozen at -20°C until analysis. Amniotic fluid and fetal plasma samples were taken from designated animals at all doses 24 hours after dosing on GD 18, but data from the analysis of these samples were not provided. *(Reviewer's comment: During normal development, the placenta acts as a depot for endogenous retinoids. Placentas in this study were not analyzed.)*
- Statistical evaluations: Statistical determinations were limited to means and standard deviations, due to small sample sizes.

Results:

- Clinical signs: For tazarotene, no maternal toxicity was reported for doses of 0.05 to 0.5 mg/kg/day. At 3 mg/kg, there were isolated incidences of labored breathing, lethargy, and decreased activity.

  For tretinoin and adapalene, no maternal toxicity was reported at any dose.

- Mortality: One 20 mg tretinoin/kg female had signs of abortion on GD 19 and was euthanized.
- Body weight: In tazarotene-treated animals, mean body weight gains appeared lower at 1 and 3 mg/kg/day in IGS females. In tretinoin-treated animals, decreased mean body weight gain was reported in IGS females at 20 mg/kg (*Reviewer's comment: This may be accounted for, at least in part, by fetal loss and lower fetal body weights.*).
- Food consumption: Food consumption was decreased in IGS females treated with 3 mg/kg/day tazarotene.
- Toxicokinetics: All three test articles were absorbed by this route. Tazarotene and tretinoin were metabolized to their respective active metabolites. Systemic exposure to tazarotenic acid was not dose-dependent in this study, but was comparable between IGS and CD rats (*Reviewer's comment: In previous oral studies of tazarotene in rats, exposure was dose-dependent. It is also notable that exposures were approximately 2-6 times higher, with earlier Tmax values than seen in this study. The inconsistencies may be related to the vehicle used in the present study and resulting lowered bioavailability.*).

Toxicokinetic parameters for tazarotenic acid:

	AUC_{0-t} (ng*hr/mL)			Cmax (ng/mL)			Tmax (hours)		
Rodent strain:	IGS	CD	CD*	IGS	CD	CD*	IGS	CD	CD*
Tazarotene dose (mg/kg)									
0.05	24.9 ± 4.9	---	60.1	3.96 ± 2.81	---	20.4 ± 6.63	4	---	1
0.1	47.7 ±7.1	---	---	7.14 ± 3.93	---	---	4	---	---
0.25	52.3 ± 5.4	88.4 ± 9.8	115	7.51 ± 2.75	10.8 ± 2.2	50.7 ± 12.3	4	2	0.5
0.5	120 ± 18	---	---	13.8 ± 9.8	---	---	4	---	---
1	80.3 ± 7.1	73.9 ± 4.3	510	9.76 ± 0.58	9.53 ± 1.40	193 ± 62	4	1	0.5
3 (2.5*)	301 ± 44	202 ± 22	1200	34.7 ± 23.0	29.2 ± 7.6	637 ± 134	4	4	1

*data from study no. 1643-SLS-3202.11

Systemic exposure to tretinoin and its metabolites was more dose-dependent and comparable between IGS and CD rats. Adapalene exposure was dose-dependent up to a plateau at doses of 7.5-10 mg/kg/day.

Toxicokinetic parameters for tretinoin (parent compound only) and adapalene:

	AUC_{0-t} (ng*hr/mL)	Cmax (ng/mL)	Tmax (hours)
Tretinoin dose (mg/kg)*:			
0.5	6.21 ± 0.47 (IGS)	11.7 ± 2.3 (IGS)	1 (IGS)
1	24.2 ± 5.8 (IGS)	16.2 ± 14.7 (IGS)	1 (IGS)

3	91.6 ± 13.5 (IGS)	54.3 ± 28.9 (IGS)	1 (IGS)
5	124 ± 22 (IGS) 182.39 ± 39 (CD)	39.3 ± 18.0 (IGS) 88.6 ± 64.8 (CD)	1 (IGS) 1 (CD)
20	318 ± 65 (IGS) 538 ± 173 (CD)	39.9 ± 15.3 (IGS) 137 ± 58 (CD)	1 (IGS) 1 (CD)
Adapalene dose (mg/kg)*:			
1	315 ± 13	45.5 ± 5.3	4
5	550 ± 35	64.2 ± 6.3	4
7.5	639 ± 57	80.2 ± 27.4	4
10	643 ± 31	82.5 ± 10.7	4

*Tretinoin was administered to IGS and CD rat strains; adapalene was administered to IGS rats only.

- Embryo-fetal Development
  - In-life observations: There was no effect of any of the test articles on pregnancy rate.
  - Terminal and Necroscopic evaluations:
    - Dams: There were no treatment-related macroscopic findings at necropsy in any of the test article groups.
    - Offspring:

In tazarotene-treated litters, effects included decreased mean number of live fetuses, increased early and late resorptions and increased post-implantation loss at 3 mg/kg/day in IGS females. Decreased mean fetal body weights were seen at 3 mg/kg in both IGS and CD litters. Retinoid-related malformations were seen in all CD and IGS 3 mg/kg litters, including exencephaly, micropththalmia, anotphthalmia, domed head, cleft palate, open eyelids, reduced or absent facial papillae, spina bifida, and malformed tails. One fetus in the 1 mg/kg group (CD) had a filamentous tail.

All of the above findings also were reported for tretinoin-treated litters at 20 mg/kg/day in IGS females. Total implantation loss was seen in 2 of 5 rats at this dose. The same retinoid-related malformations noted in tazarotene-treated litters were seen in both IGS and CD litters of dams treated with 20 mg/kg tretinoin.

No adverse effects were noted in the offspring of adapalene-treated female rats.

Key study findings:

Retinoid-related developmental malformations were seen in litters of both IGS and CD rat strains treated with 3 mg/kg/day tazarotene. One fetus at 1 mg/kg/day had a malformation that could be retinoid-related. Decreased mean fetal body weights were seen at 3 mg/kg in both IGS and CD litters. Decreased mean number of live fetuses, increased early and late resorptions and increased post-implantation loss were seen at 3 mg/kg/day tazartotene in IGS females. In previous studies at a dose of 1 mg/kg/day, females had decreased numbers of corpora lutea, implantation sites and viable fetuses, decreased fetal weights, increased early resorptions and post-implantation loss, and retinoid-related malformations. Similar effects in either strain treated with 1 mg/kg tazarotene or in CD females at 3 mg/kg were not seen in the current study. Although the apparent NOEL for developmental toxicity and teratogenicity was 0.5 mg/kg tazarotene, in previous studies in rats, an oral dose of 0.25 mg/kg was associated with some increase in malformations relative to control and developmental delays. There appears to be a

bioavailability problem with this formulation as evidenced by inconsistent toxicokinetic data and comparison to previous developmental toxicity studies in rats of oral tazarotene.

Tretinoin treatment resulted in effects similar to those in tazarotene-treated litters. The apparent NOEL for embryo-fetal toxicity and teratogenicity was 5 mg/kg/day.

For adapalene, the apparent NOEL for maternal, embryo-fetal, and developmental toxicity was 10 mg/kg/day, the highest dose tested.

Tazarotene and tretinoin were chosen for use in the definitive study. Tazarotene appears to be a more potent developmental toxicant than either tretinoin or adapalene.

4. Study title: A comparative oral developmental toxicity and toxicokinetic/placental transfer study in the rat on tazarotene and tretinoin.
Study No: (Sponsor study no. TX99039)
Site and testing facility:
GLP compliance: yes
QA- Reports Yes (X) No ( ):
Lot and batch numbers: Tazarotene lot #KG01544, raw material no. 91406
Tretinoin lot #118H0518
Protocol reviewed by Division Yes ( ) No (X):
Methods:

- Species/strain: Crl: CD® (SD) IGS BR albino rats
- Doses employed: tazarotene –0.1, 0.5, 2.0 mg/kg day
tretinoin – 1.0, 5.0 and 10.0 mg/kg/day
vehicle – medium chain triglycerides, all at 0.5 mL/kg/day
- Route of Administration: oral by gavage
- Study Design: Pregnant females were dosed orally once daily from GD 6 through 17 with either vehicle or one of the two test articles. They were observed twice daily for mortality and clinical signs. Post-dose observations were made 0.5-2 hours after dosing during the dosing period. Detailed physical examinations were performed daily. Maternal body weights were recorded on GD 0, 4, 6, 9, 12, 16, 18, and 20 for all animals. Feed consumption was monitored in the main study animals only and was reported for the intervals of GD 4-6, 6-9, 9-12, 12-16, 18-20, 16-20, 6-18, and 6-20.

On GD 6 and 17, blood was collected from the orbital sinus of satellite animals for toxicokinetics at 0 (pre-dose), 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose (four rats at each time point). Samples were centrifuged, plasma was removed and stored at –20°C until analysis. Analysis for tazarotene was by with a range of quantitation from ng/mL.

For the placental transfer component, samples were taken from one satellite rat/timepoint/dose at 0 (pre-dose), 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose. The rats were anesthetized, the uterus was exteriorized, and fetuses were removed one at a time for sampling of amniotic fluid (pooled for each dam) and fetal blood (pooled for each litter). Maternal blood samples were taken from the abdominal vena cava. Amniotic fluid, and maternal and fetal plasma samples were stored at –20°C until analysis. Analysis for tazarotene was by LC-MS/MS with a range of quantitation from ng/mL. (*Reviewer's comment: It is unclear how useful data from only one animal per group per time point might be.*)

Main study dams were euthanized on GD 20 and necropsied. One tretinoin-treated animal was terminated early and also necropsied. Gross lesions and significant findings were retained in Bouin's solution, as were corresponding tissues from control animals.

- Number of animals/sex/dosing group: 25 pregnant females/dose group plus 8/dose group for toxicokinetics/placental transfer.
- Parameters and endpoints evaluated: Ovaries were examined for corpora lutea, which were counted and recorded. Uteri were evaluated for implantations, and the data were recorded, including live and dead fetuses, and late and early resorptions.
All (live and dead) fetuses weighed sexed and evaluated for external alterations. Crown-rump distance was measured for dead fetuses. Live fetuses were euthanized. Half of the fetuses in each litter were examined for visceral alterations and sex was confirmed by inspection of the gonads. The other half of the fetuses were evaluated for skeletal alterations after staining with Alizarin Red S. Late resorptions were examined for external alterations only, and their crown-rump length was measured and recorded.

Satellite animals were subjected to gross necropsy on GD 18 or 19. Uterine implantation data were recorded before the carcasses were discarded. Cmax, Tmax, and AUC were calculated for maternal plasma samples obtained on GD 6 and 17 from satellite toxicokinetics animals.

- Statistical evaluations: Continuous data were analyzed by ANOVA followed by a Dunnett's test to identify differences between control and treatment groups. A Kruskal-Wallis test was performed to test equality of means. Incidence data were analyzed by a Fisher Exact Test with Bonferonni correction.

Results:

- Clinical signs: No clinical signs of maternal toxicity were reported in any tazarotene-treated group. One female in the 1.0 mg/kg tretinoin group displayed signs of labored breathing, pale appearance, and red oral exudate on GD 13 and was euthanized. In the 10 mg/kg tretinoin group, there was an increased incidence of black-brown stains on the snout.
- Mortality: One female in the 1.0 mg/kg tretinoin group was euthanized on GD 13. One female in the 10.0 mg/kg tretinoin group was found dead on GD18.
- Body weight: Decreases in body weight gain from GD 6-9 and 9-12 that were not statistically significant were reported in the 0.5 mg/kg tazarotene group. Body weights were significantly lower than controls in the 2 mg/kg tazarotene group during GD 6-20, which due to decreased body weight gain reported during GD 6-9 and 9-12. Weight gain differences were more pronounced over GD 6-9 and appeared to be recovering over GD 9-12. Body weight measurements indicate no body weight loss for any time period. The sponsor states that body weight gain was depressed for the entire dosing period (GD 6-17), however body weights were not measured on GD 17, and body weight gains tabulated for GD 12-16 and 16-18 were comparable to controls.

No effect on body weights were seen in the tretinoin-treated groups.

- Food consumption: Decreased feed consumption was reported in the 0.5 and 2 mg/kg tazarotene groups, corresponding to reported changes in body weight. The decreases were most notable over the first few days of dosing (GD 6-9) and appeared to be recovering thereafter. There was no effect on food consumption seen in tretinoin-treated groups.
- Toxicokinetics:

Both drugs were absorbed into the systemic circulation and were metabolized to active metabolites. Systemic exposure to tazarotenic acid was dose-dependent on GD 6 and 17 (*Reviewer's comment: Exposure was not dose-related in the previous range-finding study. As in the range-finding study, Tmax values are later than have been seen in previous oral studies of tazarotene.*). Systemic exposure to tretinoin was dose-dependent on GD 6. On GD 17, tretinoin and its metabolites were either present in a manner that was not dose-dependent or were not quantifiable. For both test articles, exposure on GD 17 was decreased relative to GD 6 (*Reviewer's comment: For tazarotene, this finding is not consistent with previous toxicology and nonclinical ADME studies where exposure values have been found to increase over time. For tretinoin, this finding has been seen in previous studies and is understandable, as tretinoin induces expression of the intracellular binding proteins, or CRABP's, and its own metabolism. A similar phenomenon has not been demonstrated for tazarotene.*)

Mean toxicokinetic data for maternal plasma:

Gestation day	Dose (mg/kg/day)	Cmax (ng/mL)	Tmax (hours)	AUC_{0-t} (ng*hr/mL)
		Tazarotenic acid		
6	0.1	6.99	8	60.0
	0.5	41.3	4	339
	2.0	74.8	4	713
17	0.1	2.81	4	20.6
	0.5	11.0	4	94.0
	2.0	30.2	4	207
		Tretinoin		
6	1.0	34.0	1	52.4
	5.0	204	0.5	458
	10.0	408	0.5	1080
17	1.0	19.2	1	44.2
	5.0	53.9	1	246
	10.0	46.0	4	239

In the placental transfer component, levels of tazarotenic acid, tretinoin and tretinoin metabolites were detected in fetal plasma on GD 18 in groups treated from GD 6 through GD 18. The sponsor states that these materials were not transferred at significant levels across the placenta (*Reviewer's comment: The sponsor concludes that there is insignificant transfer of these compounds across the placenta, even in the face of obvious retinoid teratogenesis. It is important to note that there were detectable levels at some timepoint for all doses of tretinoin and all but the lowest dose of tazarotene. No evaluation of placental retinoid content was made. [Mobilization of endogenous vitamin A and tretinoin from the liver to the placenta in early pregnancy in the rat has been described; the placenta may act as a reservoir for this important developmental signaling molecule.] The numbers of samples per timepoint per dose in this experiment are clearly insufficient to draw such a conclusion.*) Fetal plasma tazarotenic acid concentration was

approximately one-third that of maternal plasma at Tmax on GD 18 in the few animals that were sampled.

There is no mention in the toxicokinetics report of analysis of the collected amniotic fluid samples for tazarotenic acid concentrations.

- Embryo-fetal Development
  - In-life observations: There was no effect of test article on pregnancy rate.
  - Terminal and Necroscopic evaluations:
    - Dams: For tazarotene-treated groups, there were no treatment-related maternal post-mortem findings, although 2.0 mg/kg females did have a higher incidence of discolored livers on necropsy. There was a significant increase in post-implantation loss at 2 mg/kg tazarotene. The sponsor did not consider this finding to be meaningful, as there was no corresponding decrease in the number of live fetuses per litter and the mean post-implantation loss in the control group was near the minimum of the range of historical controls. The only dead fetus in the study was in the 2 mg/kg group. All tazarotene-treated groups had a higher number of early resorptions that, although not significantly different from control, appeared to be dose-related. The mean number of late resorptions per animal was also not significantly different from control in tazarotene-treated groups, but did appear to be treatment related (one at 0.1 mg/kg and six at 2 mg/kg).

      For tretinoin-treated groups, there were few post-mortem observations. The 1 mg/kg female that was euthanized on GD 13 had enlarged adrenal glands, a finding consistent with systemic retinoid exposure. The 10 mg/kg female that died on GD18 had a discolored thymus and red vaginal exudate. Post-implantation loss in the 10 mg/kg dose group was high, but not statistically significant. Early resorptions in all tretinoin-treated groups were higher than in controls, but were not statistically different. The mean number of late resorptions per animal appeared dose-related at 5 and 10 mg/kg (one and five, respectively).
    - Offspring: For tazarotene-treated groups, mean fetal body weights were statistically significantly decreased at all doses relative to controls. This finding was particularly dramatic in the 2 mg/kg group and paralleled maternal decreases in body weight gain. (*Reviewer's comment: This may imply that the decreases in maternal gain could be accounted for by lack of fetal weight gain or development, and could not be interpreted as maternal toxicity.*)

      Fetal alterations were observed with tazarotene treatment. There was a significantly increased litter incidence of external malformations at 2 mg/kg tazarotene, including exencephaly, protruding tongue, pinnae alteration, open eyelids micropthalmia/anophthalmia, microtia, facial papilla anomalies, cleft palate, meningocele, and abnormal mouth or jaw development. At 0.5 mg/kg, two litters were seen with transposition of the great vessels of the heart. (*Reviewer's comment: The sponsor did not consider this finding to be treatment related, but cardiac alterations are a typical consequence of retinoid teratogenicity.*) An undefined "brain anomaly" was listed in a 0.1 mg/kg litter. Skeletal alterations were

increased at 0.5 and 2.0 mg/kg. At 2 mg/kg, there was a significant increase in the litter incidences of thoracic and lumbar vertebral malformations. Additional skeletal findings included reduced skull ossification, increased 14th rudimentary rib and reduced ossification in 5th or 6th sternebrae in 0.5 and 2.0 mg/kg groups, and increased fully developed pairs of 14th ribs at 2.0 mg/kg (*Reviewer's comment: Supernumerary ribs are a finding consistent with historical data on the effects of retinoids on rat fetuses.*) Visceral alterations at 2.0 mg/kg consisted of a significant increase in undeveloped renal papillae. The sponsor attributed this finding to the observed decrease in fetal body weight and developmental delay. (*Reviewer's comment: This finding was also present at all tretinoin doses, relative to control, in the absence of reduced body weight or developmental delay. This would seem to imply that the alteration is a retinoid-related effect.*)

For tretinoin-treated groups, there were no significant effects on fetal body weight. In tretinoin-treated litters, there was an increased incidence of external malformations including exencephaly, protruding tongue, pinnae alteration, open eyelids, microphthalmia/anophthalmia, microtia, facial papilla anomalies, cleft palate or face, and meningocele at 10 mg/kg. Open eyelids, exopthalmia and/or microphthalmia/anophthalmia were also seen at 1 and 5 mg/kg. Abnormalities of mouth or jaw development were reported at 5 mg/kg. The incidence of undeveloped renal papillae was increased at all doses. Skeletal variations were statistically significantly increased at 5 and 10 mg/kg. These included reduced skull ossification (occurred in a dose-related manner at all doses), bipartite thoracic centrum, and unossified sternebrae. The incidence of rudimentary 14th rib was increased at 5 and 10 mg/kg and the incidence of full 14th rib at was increased at 10 mg/kg (*Reviewer's comment: This finding is consistent with other studies of retinoid teratogenicity in rats.*)

Key study findings:

In tazarotene-treated dams, post-implantation loss was increased at 2 mg/kg. There were apparent dose-related incidences of early and late resorptions in tazarotene-treated groups, but these were not significantly different from control. Mean fetal body weight was reduced relative to controls in all tazarotene-treated groups. Retinoid-related fetal alterations were seen at 0.5 and 2 mg/kg tazarotene. The NOAEL for embryo-fetal developmental effects was 0.1 mg/kg, however fetal body weights were affected at this dose.

No developmental NOAEL was established for tretinoin; retinoid-related effects were seen at all doses.

Tazarotenic acid, tretinoin, and tretinoin metabolites were found to cross the placenta and were detectable in fetal plasma, which was consistent with the developmental findings in this study. However, maternal toxicokinetic data were inconsistent with data from previous studies. This may be related to differences in vehicle and associated unreliability of intestinal absorption of the drug.

5. Study title: A comparative oral range-finding developmental toxicity study in rabbits on tazarotene, tretinoin, and adapalene.

Study No: (Sponsor study no. 20030040 1318)
Site and testing facility:
GRP compliance: yes
QA- Reports Yes (X) No ( ):
Lot and batch numbers: Tazarotene lot #KG01501, raw material no. 91414
Tretinoin lot #98-0279, identification #96/20-5
Adapalene lot #98-OC-FP-71
Protocol reviewed by Division Yes ( ) No (X):
Methods:

- Species/strain: New Zealand White (NZW) rabbits SPF
- Doses employed: tazarotene – 0.05, 0.1, 0.25, 0.5 mg/kg day
tretinoin – 0.5, 1.0, 3.0 and 5.0 mg/kg/day
adapalene – 1.0, 5.0, 7.5, and 10 mg/kg/day
vehicle – medium chain triglycerides, all at 0.5 mL/kg/day
- Route of Administration: oral by gavage
- Study Design: Pregnant female rabbits were dosed once daily on gestation days (GD) 6 through 18. Cageside observations were made twice daily. Post-dose observations were made 0.5-2 hours after dose administration. Physical examinations were performed daily. Maternal body weights were recorded on days 0, 4, 6, 9, 12, 15, 19, 24, ad 29 of gestation. Feed consumption was recorded daily and reported for the following intervals: days 4-6, 6-9, 9-12, 12-15, 15-19, 19-24, and 24-29. On GD 18, blood samples were obtained from the marginal ear vein of all females (unanesthetized) at 0, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose for toxicokinetics. Samples were centrifuged, and the plasma was stored frozen at –20°C until analysis. Analysis was by with a quantitation range of . ng/mL. Animals were euthanized on GD 29 and necropsied.
- Number of animals/sex/dosing group: 5 females/group
- Parameters and endpoints evaluated: Macroscopic necropsy was performed at study termination. The number of corpora lutea and implantation sites were determined. The numbers of live and dead fetuses and early and late resorptions were recorded. Fetuses were weighed and evaluated for external malformations, including examination of the palate. Live fetuses were euthanized and discarded. Late resorptions were examined for external malformations, and the crown-rump distance was recorded.
- Statistical evaluations: Means and standard deviations were calculated for body weights and changes, feed consumption, uterine implantation data and fetal weights.

Results:

- Clinical signs: There were no significant clinical observations and no maternal toxicity noted with any of the three test articles at any dose.
- Mortality: One female rabbit in the 0.05 mg/kg tazarotene group and one female in the 0.5 mg/kg tazarotene group were euthanized due to abortions on GD 22.
- Body weight: Body weight and body weight gains were not affected by test article treatment, relative to controls.
- Food consumption: Feed consumption was not affected by test article treatment, relative to controls.
- Toxicokinetics:

All three test articles were systemically absorbed. Tazarotene and tretinoin were metabolized to their respective active compounds. Systemic exposures to drugs and metabolites were dose-dependent. (*Reviewer's comment: Tazarotene exposures in the present study were higher than at comparable doses in a previous study using a different formulation. Presumably this is a vehicle effect. However, it is interesting to note that exposures are higher with this vehicle in the rabbit, but lower with this vehicle in the rat, as compared to previous oral developmental toxicity studies of tazarotene in a different vehicle.*)

Treatment	Dose (mg/kg/day)	AUC_{0-t} (ng*hr/mL)		Cmax (ng/mL)		Tmax (hour)	
		present study	previous study	present study	previous study	present study	previous study
tazarotene (tazarotenic acid)	0.05	1144		89.0	0.0560	6.4	5.55
	0.1	2312		205		6.8	
	0.25	5049	2840	435		5	
	0.5	13365		1115		6.4	
tretinoin	0.5	57	---	47.5	---	0.88	---
	1.0	136	---	82.9	---	0.80	---
	3.0	259	---	136	---	1.20	---
	5.0	612	---	288	---	0.90	---
adapalene	1	75.8	---	5.07	---	5.80	---
	5	152	---	9.67	---	7.60	---
	7.5	194	---	11.8	---	5.00	---
	10	436	---	29.6	---	4.10	---

- Embryo-fetal Development
  - In-life observations: Abortions occurred in one 0.05 g/kg tazarotene dam and in one 0.5 mg/kg tazarotene dam on GD 22.
  - Terminal and Necroscopic evaluations:
    - Dams: In the tazarotene-treated groups, discolored lungs were noted in one or two animals at each dose. One animal at 0.25 mg/kg had a small, pale placenta. At 0.5 mg/kg, one female had resorptions only, and three were not pregnant. A decreased pregnancy rate was noted at 0.5 mg/kg/day.

      In tretinoin-treated groups, discolored lungs were seen in one animal at 3 mg/kg. Other incidental findings included a red discolored uterus and placenta in one animal at 0.5 mg/kg, a discolored small placenta in one animal at 3.0 mg/kg, and a mottled liver and pale, small kidneys in one animal at 5.0 mg/kg. A decreased pregnancy rate was noted at 5.0 mg/kg.

One rabbit treated with 10 mg/kg adapalene had a discolored ovary. There was no effect seen on pregnancy rate in adapalene-treated animals.

- Offspring: In tazarotene-treated groups, there was a dose and treatment-related increase in embryolethality. There were no viable fetuses at 0.5 mg/kg, and there was a decrease in the mean number of live fetuses in the four evaluable litters at 0.25 mg/kg, with corresponding significant increases in early resorptions and post-implantation loss. Treatment-related malformations were seen at 0.25 mg/kg tazarotene, including pinnae alteration, spina bifida, agenesis of the tail, exencephaly, micrognathia/agnathia, microstomia, cephalocele, calveria anomaly, and carpal/tarsal flexure.

In tretinoin-treated groups, embryolethality was seen at 3 and 5 mg/kg as decreased mean number of live fetuses and increased early resorptions. Treatment-related malformations at 3 and 5 mg/kg tretinoin included cleft palate, microglossia, and gastroschisis.

At the highest dose of adapalene (10 mg/kg), there was a decrease in the mean number of live fetuses, without a corresponding increase in post-implantation loss. The sponsor considered this finding to be incidental and not treatment-related. No other embryo-fetal effects were noted in adapalene-treated groups.

There was no significant effect on fetal body weight in any test article group when compared to controls.

Key study findings:

Embryo-fetal toxicity and retinoid-related teratogenicity were seen at ≥0.25 mg/kg day tazarotene and at 3 and 5.0 mg/kg/day tretinoin in the absence of maternal toxicity at any dose. No maternal or developmental toxicity was noted with adapalene. The apparent NOEL's for embryo-fetal toxicity were 0.1 mg/kg tazarotene, 1.0 mg/kg tretinoin, and 10 mg/kg adapalene. Tazarotene appeared to be a more potent embryo-fetal toxicant than tretinoin or adapalene. Toxicokinetic data in this study indicate that tazarotenic acid exposures are considerably higher at embryo-fetal toxic doses that those indicated in a previous oral study of developmental toxicity of tazarotene in rabbits. In fact, the AUC at the apparent NOEL (0.1 mg/kg/day) is slightly greater than that seen in a previous range-finding study at a teratogenic dose (0.2 mg/kg/day). Other studies in the rat employing this vehicle appear to indicate that bioavailability is decreased and inconsistent.

6. Study title: A comparative oral developmental toxicity study in the rabbit on tazarotene and tretinoin.

Study No: (Sponsor study no. TX99023)

Site and testing facility:

GLP compliance: yes

QA- Reports Yes (X) No ( ):

Lot and batch numbers: Tazarotene lot #KG01544, raw material no. 91406
Tretinoin lot #118H0518, and . lot no. 98-0279, identification #96/20-5 (no expiration date for the latter)

Protocol reviewed by Division Yes ( ) No (X):

Methods:

- Species/strain: Hra (NZW)SPF rabbits
- Doses employed: tazarotene – 0.05, 0.1, or 0.25 mg/kg/day
  tretinoin – 0.5, 1.0, or 3.0 mg/kg/day
  vehicle control – medium chain triglycerides
  vehicle
- Route of Administration: oral gavage; all doses were administered in a volume of 0.5 mL/kg
- Study Design: dosed once daily on gestation days (gd) 6-18 (organogenesis). euthanized on gd 29 by iv overdose of sodium pentobarbital. Macroscopic post-mortem examination on all does, including those aborting or delivering prematurely.
- Number of animals/sex/dosing group: 20 mated female rabbits/dosing
- Parameters and endpoints evaluated: observed at least twice daily for mortality and effects. post dose observation at 0.5-2 hours (not on tk animals on gd 6 and 18). Physical examinations were performed daily. bw was obtained on gd 0, 4, 6, 9, 12, 15, 19, 24, and 29. Feed consumption was recorded daily throughout gestation and reported for the intervals of gd 4-6, 6-9, 9-12, 12-15, 15-19, 19-24, 24-29, 6-19 and 19-29. At necropsy, cl, uterine implantation data recorded, live/dead fetuses, and early and late resorptions. fetuses removed evlauated for external malf, (dead fetuses – measured crown-rump distance) euthanized (ip inj of sodium pentobarbital) and weighed. all fetuses - examination for visceral alterations and sexed internally. all staining with Alizarin Red S and evaluated for skeletal alterations. Aborted fetuses were examined for external alterations only. Late resorptions were examined for external malformation and the crown-rump distance was recorded.

  Blood samples on gd 6 and 18 from marginal ear vein in five animals per group after fasting(the same five animals were used on both blood collection days. seven intervals – at 0, just prior to dosing, 3, 6, 8 , 10, 12, and 24 hours post-dose for taz treated animals and at 0, 1, 2, , 4, 6, 8 and 24 hours post-dose for tretinoin-treated animals. Samples were centrifuged, plasma was collected and stored frozen at –20°C until analysis. Assay for tazarotenic acid was by with range of quantitation from ng/mL.
- Statistical evaluations: For continuous data, ANOVA followed by Dunnett's test was performed to identify differences between control and treatment groups. A Kruskal-Wallis test was performed to test equality of means. there was no testing for homogeneity of variance. to determine whether parametric or nonparametric methods would be appropriate.

  For incidence data, a Fisher exact test with Bonferonni correction was performed to identify differences between control and treatment groups.

Results:

- Clinical signs: There were no treatment-related clinical signs in any treatment group.
- Mortality: There was no effect of either drug on survival. One animal in the vehicle control group was euthanized because of signs of abortion on gd 25. One animal in the 0.1 mg/kg tazarotene group was euthanized because of signs of abortion on gd 22 and four animals in the 0.25 mg/kg tazarotene group were euthanized for the same reason on gd 21-22.

- Body weight: There was no significant effect on body weight by either drug. Body weight gains in the 0.25 mg/kg tazarotene group were decreased in the last days of the dosing period (gd 15-19), but there was no corresponding decrease in feed consumption. (*Reviewer's comment: It seems likely that this could be accounted for by fetal effects.*)
- Food consumption: There was no effect of treatment on absolute or relative feed consumption in any group.
- Toxicokinetics: Both tazarotene and tretinoin were absorbed after oral administration and were metabolized to their respective active metabolites. Systemic exposures were dose-dependent on gd 6 and 18.

Mean toxicokinetic data for maternal plasma:

Gestation day	Dose (mg/kg/day)	Cmax (ng/mL)	Tmax (hours)	AUC_{0-t} (ng*hr/mL)
		Tazarotenic acid		
6	0.05	99.9	7.6	1310
	0.1	168	6.6	2130
	0.25	474	6.0	5820
18	0.05	110	5.8	1570
	0.1	199	6.6	2520
	0.25	418	5.2	5300
		Tretinoin		
6	0.5	128	1.0	255
	1.0	161	1.0	342
	3.0	193	1.6	510
18	0.5	67.4	1.2	169
	1.0	124	1.2	294
	3.0	143	1.2	449

- Embryo-fetal Development
  - In-life observations: There was an increased incidence of abortion in the 0.25 mg/kg tazarotene group. There was no apparent effect on pregnancy rate in any treatment group.
  - Terminal and Necroscopic evaluations:
    - Dams: There were no treatment-related macroscopic post-mortem findings.
    - Offspring: At 0.25 mg/kg/day tazarotene, there was a decreased number of live fetuses, corresponding with an increase in the mean number of pre- and post-implantation losses and in the mean number of early resorptions. There was no effect of tazarotene on fetal body weight. There was no effect in tretinoin-treated groups on uterine implantation data or fetal body weight.

      In tazarotene-treated litters, fetal alterations included microtia, cleft palate/lip/face, exophthalmia, open eyelids, facial papilla anomalies, heart

and/or great vessel anomalies (including ventricular septal defects), spina bifida, tail anomalies, and unossified hyoid body/arches at 0.25 mg/kg/day.

In tretinoin-treated litters, fetal alterations included microtia, cleft palate/lip, exophthalmia, open eyelids, facial papilla anomalies, hydrocephalus, and heart anomalies (including ventricular septal defects) at 3.0 mg/kg. There was also a significant increase in ventricular septal defects and skeletal malformations (fused sternebrae and additional sternebrae adjacent to the first sternebra) at 1.0 mg/kg. The latter was not considered by the sponsor to be treatment-related.

Additional alterations that were not considered by the sponsor to be treatment-related included one litter each with meningocele and microphthalmia at 0.05 mg/kg tazarotene, and a low litter incidence of heart and/or great vessel anomalies in the vehicle control group. Agenesis of the thymus was seen at 0.05 and 0.25 mg/kg tazarotene in 2 and 3 litters, respectively, and hypoplastic thymus was seen in one 0.25 mg/kg tazarotene litter.

Key study findings:

At a tazarotene dose of 0.25 mg/kg/day (AUC=5300 ng*hr/mL)during organogenesis, significant developmental toxicity was observed in the absence of maternal toxicity, consisting of increased abortions, decreased number of live fetuses, increased pre- and post-implantation loss, increased early resorptions, and retinoid-related fetal alterations. Retinoid-related fetal alterations were seen at 1.0 mg/kg/day tretinoin and above, also in the absence of maternal toxicity. For tazarotene, the maternal NOEL was 0.25 mg/kg/day and the developmental NOEL was 0.1 mg/kg/day (AUC=2130 ng*hr/mL). For tretinoin, the maternal and developmental toxicity NOEL's were 3.0 mg/kg and 0.5 mg/kg/day, respectively. Tazarotene, administered orally, appears to be a more potent developmental toxicant than tretinoin on a nominal dose basis.

7. Study title: A toxicokinetic and placental transfer study of tazarotene and tretinoin in pregnant rabbits via oral administration.

Study No: (Sponsor study no. PK-99-P013)

Site and testing facility:

GLP compliance: yes

QA- Reports Yes (X) No ( ):

Lot and batch numbers: Tazarotene lot #KG01544, raw material no. 91406
Tretinoin lot no. 98-0279, identification #96/20-5 (no expiration date)

Protocol reviewed by Division Yes ( ) No (X):

Methods:

- Species/strain: Hra(NZW)SPF rabbits
- Doses employed: tazarotene – 0.05, 0.1, and 0.25 mg/kg/day
  tretinoin – 0.5, 1.0, and 3.5 mg/kg/day
  all in medium chain triglyceride vehicle in a volume of 0.5 mL/kg
  (no vehicle control group)
- Route of Administration: oral gavage
- Study Design: Pregnant rabbits were dosed once daily on days 6-21 of gestation. Clinical observations were made at least twice daily, with a post-dose observation made

between 0.5-2 hours after dosing during the treatment period. A detailed physical examination was made daily from the day of receipt of the animals through the day of sacrifice (examination was performed prior to dosing during the treatment period). Body weight was recorded on gd 0, 4, 6, 9, 12, 15, 29 and 21.

On gd 21, 1 animal per time point at 0, 3, 6, 8, 10, 12, and 24 hours post dose for tazarotene and at 0, 1, 2, 4, 6, 8, and 24 hours post-dose for tretinoin was anesthetized with isoflurane gas via mask. The uterus was exteriorized, and one fetus was exteriorized and processed at a time until the litter was completely sampled. Amniotic fluid was collected and pooled for each litter. It was frozen at –20°C, but was not analyzed. Fetal blood was collected and pooled for each litter, centrifuged, and the plasma collected and frozen at –20°C until analysis. Analysis for tazarotenic acid, tretinoin, and isotretinoin was by)

- Number of animals/sex/dosing group: 7 pregnant does per dose group (one per time point per dose)
- Parameters and endpoints evaluated: Does were subjected to a macroscopic postmortem exam. The total number of live, dead and resorbed fetuses and total number of implantation sites were recorded.
- Statistical evaluations: none

Results:

- Clinical signs: There were no significant clinical observations in any group.
- Mortality: One rabbit at 0.1 mg/kg tazarotene was found dead on gd 14, and one rabbit at 0.5 mg/kg tretinoin was sacrificed on gd 12. Each was found on postmortem exam to have a perforated esophagus as a result of a gavage error.
- Body weight: Body weight and body weight gains were unaffected by either treatment.
- Food consumption: not evaluated
- Toxicokinetics: Both tazarotene and tretinoin were absorbed systemically after oral administration. Maternal plasma levels of tazarotenic acid, tretinoin and isotretinoin were measurable at all doses and were present in a dose-related manner.

Tazarotenic acid was detectable in fetal plasma at maternal doses of 0.1 and 0.25 mg/kg/day in a dose-related manner. Tretinoin was present in fetal plasma at 0.5 and 3.5 mg/kg/day.

- Embryo-fetal Development
  - In-life observations: none
  - Terminal and Necroscopic evaluations:
    - Dams: There were no treatment related postmortem findings.
    - Offspring: There was an observed increase in embryolethality at 0.25 mg/kg/day tazarotene and at 3.5 mg/kg/day tretinoin. Decreased mean numbers of live fetuses and corresponding increases in the mean numbers of post-implantation loss and early and late resorptions were seen in both groups.

Key study findings:

Measurable concentrations of tazarotenic acid were found in fetal plasma at maternal doses of 0.1 mg/kg/day tazarotene and above. Measurable concentrations of tretinoin were found in fetal plasma at maternal doses of 0.5 mg/kg/day and above.

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 in psoriasis[a]	Multiple of human exposure in acne[b]
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	30
			0.25	115	Developmental delays; external malformations	1.3	6.7
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	12

			0.5 mg/kg	94	Increased skeletal alterations, including supernumerary ribs; two litters with cardiac anomalies	1.1	5.5
			0.1	20.6	Decreased fetal body weight	0.2	1.2
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	6.3
			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	133
			0.05	779	NOAEL	8.8	45.8
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	312
			0.1	2130	NOAEL	24	125
1643-SLS-3202.9	Rabbit	Topical	0.25	1160	Single incidences (1/20 litters) each of hydrocephaly, heart anomaly, spina bifida	13	68

[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 mean $AUC_{0\text{-}24h}$ (17.0 ng*hr/mL) seen in acne patients treated over 15% bsa 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 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 acne 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 acne indication, as are the tazarotene gel formulations and this cream formulation, approved for psoriasis.

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.

ADDENDUM TO REVIEW:

(if necessary)

APPENDIX/ATTACHMENTS: