

# **Background for Advisory Committee Meeting to Discuss Oral Tazarotene for the Treatment of Moderate to Severe Psoriasis**

## **I. Introduction to Psoriasis**

Psoriasis is a polygenic disease and various triggering factors, e.g. trauma, infections, or medications, may elicit a psoriatic phenotype in predisposed individuals. There is some evidence that various cytokines and immunologic function may be involved in the pathogenesis of the disease. It is a chronic, relapsing disease with variable clinical features. Psoriasis occurs in all races and all age groups. There are many therapeutic modalities that are currently available for psoriasis. None of them is perfect and none of them induces a permanent remission.

### Genetics and Pathogenesis

There is some evidence that the immune system is involved in the pathogenesis of psoriasis. The strongest evidence is the association of psoriasis with the major histocompatibility complex (MHC) situated on the short arm of chromosome 6 and its association with several histocompatibility antigens (HLA): HLA-B13, HLA-B17, HLA-B37, and HLA-Bw16. The strongest risk of developing psoriasis is associated with HLA-Cw6.

Some observations have suggested that psoriasis may be driven in part by a T-lymphocyte-mediated mechanism and that psoriasis is actually a systemic disease with skin manifestations being only one component. This is reflected in other clinical manifestations of the disease: Koebner phenomenon, elevated uric acid levels, which may lead to gouty arthritis, mild anemia, increased ESR, increased  $\alpha_2$ -macroglobulin, immunoglobulin aberrations, including increased IgA levels and increased quantities of immune complexes, psoriatic arthropathy, the aggravation of psoriasis by systemic factors such as stress, medication and focal infections, and the life-threatening forms of psoriasis.

### Prevalence

Psoriasis occurs in 2% of the world's population. Depending on the source, the prevalence in the U.S. and Canada may be as high as 4.6% and 4.7%, respectively. The prevalence in ethnic groups other than Caucasians is much lower. The frequency in Africans, African Americans, and Asians is between 0.4% and 0.7%. Psoriasis occurs with equal frequency in males and females. Psoriasis may occur at any age, from infancy to the 10<sup>th</sup> decade of life. First signs of psoriasis occur in females at a mean age of 27 and in males at a mean age of 29. Two peaks of occurrence are generally accepted, one at 20-30 years of age and one at 50-60 years of age. However, approximately 75% of patients have an onset of disease prior to the age of 40. The prevalence of psoriasis in children is much lower, somewhere between 0.5% and 1.1% in children 16 years old and younger with an estimated mean age of onset in children between 8 and 12.5 years of age.

Two-thirds of patients with psoriasis have mild disease, while one-third of patients have moderate to severe disease. Early onset of disease (prior to age 15) has been associated with more severe disease in terms of body surface area (BSA) involvement and response to therapy. Patients with early onset of psoriasis are also more likely to have a family history of the disease.

Once the disease occurs, it persists throughout life, manifesting itself at unpredictable intervals. There may be spontaneous remissions which have been reported to occur, and remission times of 5 years or more have been reported in approximately 5% of patients.

### Clinical Variants of Psoriasis

The characteristic lesion of psoriasis is a sharply demarcated erythematous plaque with micaceous silvery white scale. The scaly red plaque is a clinical reflection of the histopathology which includes hyperkeratosis, parakeratosis, acanthosis of the epidermis, tortuous and dilated vessels and an inflammatory infiltrate composed mostly of lymphocytes. The severity of the disease is associated, in part, with the degree of plaque elevation, erythema, and scale present on lesional skin. The evaluation of the severity of the disease is complex, as patients may have localized severe disease or widespread mild disease. It depends in part on the intensity of the 3 cardinal signs of the individual lesions: erythema, plaque elevation, and scale.

The most common variant of psoriasis is chronic plaque psoriasis. This is characterized by psoriatic plaques that may be as large as 20 cm in diameter. Sites of predilection include symmetrical lesions on the elbows, knees, presacrum, scalp, as well as the hands and feet. However, the lesions may be widespread and cover up to 90% of the BSA. The genitalia are involved in up to 30% of patients. The face is usually spared in psoriasis, except for areas that are contiguous with the scalp. Most patients with psoriasis have varying degrees of nail changes. These may range from nail pitting, to "oil spots", to involvement of the entire nail bed with onychodystrophy, to loss of the nail plate. Patients often complain of the unsightliness of the lesions, low self-esteem, feelings of being socially outcast, pruritus, and pain, especially when the hands, feet, or intertriginous areas are involved. Patients with more generalized psoriasis complain of excessive scale and heat loss.

Guttate psoriasis is characterized by numerous 0.5 to 1.5 cm papules and plaques over the upper trunk and proximal extremities. This form of psoriasis is characteristic of early age of onset and is the most common form in children. Streptococcal throat infection often is a trigger factor. Spontaneous remissions are the rule in children but in adults it can become chronic.

There are two variants of psoriasis associated with high morbidity and that can be fatal, generalized pustular psoriasis and erythrodermic psoriasis. Generalized pustular psoriasis is an unusual manifestation of psoriasis which may be gradual or acute in onset. It is characterized by waves of pustules on erythematous skin. Short episodes of fever, 39° to 40°, are followed by a new wave of pustules. Patients also experience weight loss,

muscle weakness, hypocalcemia, leukocytosis, and increased ESR. Although the cause of this illness is obscure, there are known triggering factors which include infection, pregnancy, lithium, hypocalcemia secondary to hypoalbuminemia, irritant contact dermatitis, and withdrawal from glucocorticosteroids.

In erythrodermic psoriasis, the classic lesion is lost and the entire skin surface becomes markedly erythematous with desquamative scaling. Clues that the erythroderma is secondary to psoriasis are the presence of the classic nail changes and usually, but not always, facial sparing. This disease can be fatal, and triggering factors include systemic infection, withdrawal of high potency topical or oral steroids, phototoxicity, and irritant contact dermatitis (e.g. tar).

### State of the Armamentarium

The focus of this advisory committee meeting is the treatment of moderate to severe psoriasis, thus treatments for less severe forms of the disease will not be discussed. As a background, there does not exist any perfect treatment for psoriasis. Treatments to date do not induce a permanent remission and most often must be given in cyclical or continuous fashion in an effort to circumvent unwanted adverse events in a disease that has to be treated over an individual's lifetime.

### Topical Corticosteroids

Topical corticosteroids have been the mainstay of treatment of psoriasis since their introduction in 1952. They are often first-line treatment for mild to moderate psoriasis as well as in sites such as the flexures and genitalia. The developments of high potency and super potent topical steroids have opened the door for successful treatment of severe psoriasis, as well. The high potency topical steroids include the fluocinonide family (cream, ointment, gel) as well as betamethasone dipropionate cream. The super potent topical steroids include the clobetasol propionate family (cream, ointment, gel, foam, lotion) as well as diflorasone diacetate ointment and betamethasone dipropionate ointment.

The efficacy of these drug products is well established in the treatment of chronic plaque psoriasis. A recent study of clobetasol propionate lotion in the treatment of moderate to severe psoriasis demonstrated efficacy after 4 weeks of twice daily treatment in 36.6% of patients compared to 0% in placebo. Treatment success was achieved in patients who obtained a score of clear or almost clear on the Investigator's Global Assessment Scale.

Side effects associated with the use of topical corticosteroids include skin atrophy, burning and stinging, and suppression of the hypothalamic-pituitary-adrenal (HPA) axis. This may occur after two weeks of use with certain topical corticosteroids.

### Topical Vitamin D<sub>3</sub> Analogues

The prototype of this group of drug products is calcipotriene, approved in the United States. It comes in 3 formulations, cream, ointment, and scalp solution. The former two are approved for plaque psoriasis and the scalp solution is approved for moderately severe psoriasis of the scalp. In clinical trials, the proportion of patients with at least marked improvement after 8 weeks of twice daily therapy was 50% and 49.6% for the cream and ointment formulations, respectively. Thirty-one percent of patients after 8 weeks of twice daily treatment with scalp solution were clear or almost clear.

Side effects are cutaneous and include burning, stinging, itching, skin irritation, and tingling of the skin.

### Topical Retinoids

Topical tazarotene gel is approved in two strengths, 0.05% and 0.1%, for the treatment of stable plaque psoriasis of up to 20% BSA involvement. In clinical trials, patients with at least moderate psoriasis were treated for 12 weeks once daily. The percentage of patient with at least a 75% improvement from baseline was 28% and 18% for the 0.05% concentration in two placebo controlled studies and 38% and 25% for the 0.1% formulation in two placebo controlled studies. The vehicle effect was 12% and 10%.

The most frequent adverse reactions were limited to the skin. These included pruritus, burning/stinging, erythema, worsening of psoriasis, irritation, and skin pain.

It should be noted that topical tazarotene has other indications. Tazarotene gel, 0.1%, is also approved for the treatment of facial acne vulgaris of mild to moderate severity, and tazarotene cream, 0.1%, is approved as an adjunctive agent for use in the mitigation of facial fine wrinkling, facial mottled hyper- and hypopigmentation, and benign facial lentiginosities in patients who use comprehensive skincare and sunlight avoidance programs.

Tazarotene gel and cream are pregnancy category X drug products and as such are contraindicated in women who are or may become pregnant. A negative pregnancy test should be obtained 2 weeks prior to initiation of therapy, and therapy should be initiated during a normal menses. Women of childbearing potential should use adequate birth control.

### Photo(chemo)therapy

Phototherapy is usually reserved for moderate to severe psoriasis. Phototherapy involves treatment with UVB alone. Broadband UVB phototherapy has been an effective approach to treatment of moderate to severe psoriasis. In recent years, a shift to narrow band UVB (311-313 nm) has become more optimal.

Treatment with UVB is time consuming, requiring 2-3 visits/week for treatment for several months and the possibility of experiencing an acute sunburn reaction.

Photochemotherapy consists of ingestion of or topical treatment with a psoralen followed by UVA. Photochemotherapy with a psoralen followed by UVA has been very successful in the treatment of severe, recalcitrant, disabling psoriasis, not responsive to other therapies. Patients must be protected from further ultraviolet light for 24 hours after exposure to the psoralen + UVA. In the case of oral ingestion, wrap around UV-blocking eyeglasses are worn for 24 hours post treatment. In most patients clearing of the disease is achieved after 19-25 treatments, approximately 100 - 245 J/ cm<sup>2</sup> of UVA.

Treatment with PUVA is time consuming, requiring visits 2-3 times per week for treatment. Side effects of oral psoralen can include nausea, dizziness, and headache. A major early side effect of PUVA is pruritus. Long term side effects include skin damage and an increased risk for skin cancer, particularly squamous cell carcinoma. For squamous carcinoma, the risk increases after 2000 J/cm<sup>2</sup> of UVA.

Contraindications to the use of psoralen include patients under 12 years of age, patients possessing a history of light sensitive disease states, patients with, or with a history of, melanoma, patients with invasive squamous cell carcinoma, and patients with aphakia because of increased risk of retinal damage due to the absence of lenses.

### Systemic Therapies - Oral

#### Methotrexate (Aminopterin)

Methotrexate (MTX) is a folic acid antagonist approved for the treatment of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy. Maximum improvement from MTX can be expected after 8-12 weeks of therapy. There are no recent placebo controlled trials in patients with psoriasis. However, in one series by A. Nyfors in the Danish Medical Bulletin, >75% improvement was observed in 90% of 248 patients. Of 141 patients with nail psoriasis, complete resolution was observed in 63 patients (44.7%).

Contraindications to the use of methotrexate include nursing mothers, patients with alcoholism, alcoholic liver disease, or other chronic liver disease, patients with overt or laboratory evidence of immunodeficiency syndromes, and patients who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia.

Methotrexate is a pregnancy category X drug product, as it is a human teratogen which can cause cranial defects and absence of digits. It is contraindicated in pregnant women with psoriasis. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment. Pregnancy

should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients.

The most serious side effects of methotrexate in psoriasis patients include acute or chronic hepatotoxicity, hepatic cirrhosis, leukopenia, thrombocytopenia, anemia, including aplastic anemia, and rarely interstitial pneumonitis. Erythrodermic psoriasis has occurred upon withdrawal of methotrexate. Other side effects include stomatitis, nausea/vomiting, alopecia, photosensitivity, and "burning of skin lesions."

Multiple prescreening tests must be performed before the use of MTX in the treatment of psoriasis including a liver biopsy in patients with risk factors for hepatic disease. All patients that receive a cumulative dose of MTX of 1.5 grams, which may occur after 2 years of continuous use, must have a liver biopsy.

### Neoral (Cyclosporine)

Neoral is a potent immunosuppressive agent approved for adult, nonimmunocompromised patients with severe, recalcitrant plaque psoriasis who have failed at least one systemic therapy. Although approved for a more severe form of psoriasis, many patients in an active controlled trial comparing Neoral to Sandimmune (cyclosporine) had moderate to severe disease. The percentage of patients that obtained a clear or almost clear on Neoral and Sandimmune was 58.8% and 50.0%, respectively, after 16 weeks of twice daily therapy.

Contraindications to the use of Neoral in psoriasis patients include concomitant PUVA or UVB therapy, methotrexate or other immunosuppressive agents, coal tar or radiation therapy. It is also contraindicated in psoriasis patients with abnormal renal function, uncontrolled hypertension, or malignancies. Cyclosporine should also not be given to psoriasis patients who are breast-feeding.

The most serious risk with cyclosporine therapy is the possibility of irreversible renal damage. The other serious risk is the development of new onset hypertension or worsening of existing hypertension. Other principal side effects associated with cyclosporine use include headache, hypertriglyceridemia, hirsutism/hypertrichosis, paresthesia or hyperesthesia, influenza-like symptoms, nausea/vomiting, diarrhea, lethargy, and arthralgia.

Multiple prescreening tests must be performed and monitored throughout the use of cyclosporine in patients with psoriasis to prevent end-organ damage.

### Soriatane (acitretin)

Soriatane is an oral retinoid approved for the treatment of severe psoriasis in adults.

Soriatane is contraindicated in patients with severely impaired liver or kidney function and in patients with chronic abnormally elevated blood lipid values. The combined use of methotrexate and Soriatane is also contraindicated.

Soriatane is a human teratogen and therefore is a pregnancy category X drug product. It is contraindicated in pregnant females or in those who intend to become pregnant during therapy or at any time for at least 3 years following discontinuation of therapy. Ethanol is also contraindicated when on therapy and for 2 months following therapy with Soriatane in female patients.

Side effects associated with Soriatane are those that are associated with retinoid therapy. Those include primarily cheilitis, alopecia, skin peeling, dry skin, pruritus, rhinitis, xerophthalmia, arthralgia, hypertriglyceridemia (66%), decreased HDL (40%), hypercholesterolemia (33%), elevated liver function tests (33%), elevated alkaline phosphatase (10-25%), hyperglycemia (10-25%), and elevated CPK (10-25%). Hepatitis and jaundice occurred in less than 1% of patients in clinical trials on Soriatane.

Multiple prescreening and continued monitoring with possible dose adjustment is necessary throughout therapy with Soriatane to prevent end-organ damage.

### Parenteral Therapy

There are 3 biologics that have recently been approved for the treatment of moderate to severe chronic plaque psoriasis in adults, Amevive (alefacept), Raptiva (efalizimab), and Enbrel (etanercept). Amevive will be discussed as a prototype for this class of drug products.

### Amevive (alefacept)

Amevive is an immunosuppressive dimeric fusion protein that consists of the extracellular CD2-binding portion of the human leukocyte function antigen-3 (LFA-3) linked to the Fc portion of human IgG1. It is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.

In clinical trials, patients received either 7.5 mg IV of Amevive or 15 mg IM of Amevive once weekly for 12 weeks. The percentage of patients who achieved a disease state of clear or almost clear was 11% and 14%, respectively.

The major side effect of amevice is a dose-dependent reduction in circulating CD4+ and CD8+ T lymphocytes. CD4+ T lymphocytes must be monitored before and throughout therapy with Amevive.

It may also increase the risk of malignancies, infection, and reactivate latent, chronic infections, as reflected in the clinical trials. The most serious adverse reactions were lymphopenia, malignancies, serious infections requiring hospitalization, and

hypersensitivity reactions. Malignancies accounted for 1.3% of amevive treated patients compared to 0.5% in the placebo group. The majority of malignancies were cutaneous malignancies, squamous cell and basal cell. There were, however, 3 cases of lymphoma diagnosed.

Since alefacept was approved only recently, the safety experience is substantially less than for methotrexate and other drug products that have been used for many years.



## **II. Summary of NDA 21-701**

Tazarotene capsule is an oral retinoid, a probable human teratogen, submitted under NDA 21-701 with a proposed indication of “the treatment of moderate to very severe psoriasis”. The drug is intended to be taken at a dose of 4.5 mg once a day, with or without food. The Sponsor proposes to market two dosage strengths, a 4.5 mg capsule and a 1.5 mg capsule, with the claim that there may be a compliance problem with the 4.5 mg capsule. It is proposed that the safety and efficacy of tazarotene capsules beyond 52 weeks of treatment has not been established. Tazarotene is currently marketed as a gel formulation under the trade name Tazorac<sup>®</sup> in two strengths, 0.05% and 0.1%, for the treatment of stable plaque psoriasis. Tazorac gel, 0.1% is also approved for the treatment of facial acne vulgaris of mild to moderate severity.

The terminal elimination half-lives of tazarotene and its metabolite are much shorter than that of the other systemic retinoids, isotretinoin (Accutane) and acitretin (Soriatane). The effective half-life range is from 6.68 to 11.8 hours for tazarotene. It is 17-50 hours (mean 25) for 4-oxo-isotretinoin, the major metabolite of isotretinoin, and 8-157 hours (mean 63) for cis-acitretin, the major metabolite of acitretin (see Appendix).

Semen analysis revealed that tazarotenic acid could be found in the semen in a 1:1 ratio with that of the plasma. In a few cases, the semen to plasma tazarotenic acid concentration ratio was 2.8:1 (see Appendix).

In toxicology animal studies, tazarotene appears to be a more potent teratogen when compared to other retinoids.

### Non-Clinical

General toxicology: Oral administration of tazarotene in rats (3 to 6 months), dogs (4 to 9 months), and monkeys (1 month to 1 year) produced effects that were characteristic of retinoid toxicity. Maximum systemic exposure (AUC) to tazarotenic acid in these studies was generally similar or greater than (dogs), or less than (rats and monkeys) systemic exposure in humans at the recommended daily oral dose (4.5 mg). Primary target organs/systems included bone, liver (including serum lipids), kidney, heart, thymus, testis, and skin.

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

Carcinogenicity: A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter-term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure ( $AUC_{de}$ ) in the rat less than

0.1 times that seen in humans given a single dose of 4.5 mg tazarotene (AUC = 478 ng·hr/mL).

A long term topical application study of up to 0.1% tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1.0 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no carcinogenic effects when compared to vehicle control animals; untreated control animals were not completely evaluated. Systemic exposure at the highest dose was below (0.7 times) the systemic exposure in humans given a single oral dose of 4.5 mg tazarotene.

Reproductive toxicology: No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1 mg/kg/day of tazarotene. That dose produced systemic exposure that was 0.3 times that observed in humans given the maximum recommended oral dose of 4.5 mg tazarotene. However, there was a significantly reduced sperm count and density in male rats treated orally with 3 mg/kg/day tazarotene, in which the systemic exposure was approximately 0.7 times the systemic exposure in humans given a single oral dose of 4.5 mg tazarotene.

No effect on parameters of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through day 7 of gestation with oral doses of tazarotene up to 2 mg/kg/day. However, there was a significant decrease in the number of estrus stages and an increase in developmental effects at this dose. This dose produced systemic exposure that was 0.6 times the systemic exposure in humans given a single oral dose of 4.5 mg tazarotene.

Teratogenic effects, including cleft palate and skull anomalies, developmental and behavior delays, and post-implantation loss were seen when parent rats were dosed orally with 0.25 mg/kg/day of tazarotene during gestation day 6 through 17. This dose produced systemic exposure that was 0.2 times the systemic exposure in humans given a single oral dose of 4.5 mg of tazarotene. Teratogenic effects, including pinnae anomalies, cleft palate, spina bifida, heart anomalies, skull anomalies, hyoid anomalies, and tympanic ring anomalies and post-implantation loss were seen when parent rabbits were dosed orally with 0.20 mg/kg/day of tazarotene during gestation day 6 through 18. This dose produced systemic exposure that was 4.7 times the systemic exposure in humans given a single oral dose of 4.5 mg of tazarotene. Tazarotene 0.05% gel administered topically during gestation day 6 through 17 at 0.25 mg/kg/day in rats resulted in reduced fetal body weights and reduced skeletal ossification. Rabbits dosed topically with 0.25 mg/kg/day of tazarotene gel during gestation day 6 through 18 were noted with single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies.

Stillbirths, decreased F1 survival and body weights, retinoid malformations, developmental delays and decreased reproductive capabilities of F1 females (reduced number of corpora lutea, implantations, and live litter size) were observed following an oral dose of 1 mg/kg/day of tazarotene in female F0 parental rats from gestation day 7 through lactation day 20. This dose produced systemic exposure that was 0.4 times the systemic exposure in humans given a single oral dose of 4.5 mg of tazarotene. The maternal and reproductive/developmental NOAEL for oral tazarotene in rats was 0.1 mg/kg/day.

Conclusion: Tazarotene was a teratogen in rats and rabbits. The maximum recommended human dose is 0.075 mg/kg/day for tazarotene, 0.83 mg/kg/day for Soriatane, and 2.0 mg/kg/day for Accutane. Based on the following information, tazarotene is more potent than the other retinoids based on a mg/kg/day basis in rats and rabbits, and tazarotene is a probable human teratogen.

Lowest Teratogenic Dose (mg/kg/day)

Species	Tazarotene	Acitretin) <sup>a</sup> (Soriatane)	Etretinate <sub>b,c</sub>	Tretinoin) <sup>b</sup>	Isotretinoin) <sup>b</sup> (Accutane)
Human			0.2	N.D.	0.4
Primates			5	7.5	5
Hamsters			2.8	1.25	25
Rabbits	0.2	0.6	2	2 - 10	10
Rats	0.25 – 1	15	2 – 8	0.4 - 2	150
Mice		3	4	4	100

<sup>a</sup> Pharmac. Ther. 40:29-43, 1989

<sup>b</sup> Toxicology 57:117-161, 1989

<sup>c</sup> J. Am. Acad. Dermatol. 6:652-659, 1982

### Clinical Safety

There have been a total of 987 patients treated with tazarotene and 383 patients treated with placebo. Of the patients treated with tazarotene 831 subjects were treated with 4.5 mg once daily. The 831 patient safety data base is derived from the two pivotal phase 2 trials, and 2 open-label trials. The pivotal phase 3 trials consisted of 12 weeks of treatment with 12-week post-follow-up. Study 052P, an open label phase 3 trial, enrolled patients in the placebo arm of the pivotal trials and those in the tazarotene arm with no response to treatment. These patients received 12 weeks of tazarotene followed by a 12-week post-treatment follow-up. Study 050P, an open label phase 3 trial, consisted of patients treated once daily with 4.5 mg of tazarotene over the course of 52 weeks, with a 12-week post-treatment follow-up.

In these studies, the majority of patients who did not complete the treatment period discontinued for treatment related reasons. Treatment related reasons (lack of efficacy and adverse events) accounted for 54% (93/173) discontinuations during the treatment period among patients treated with tazarotene 4.5 mg.

In the placebo-controlled studies, 3.4% (12/348) patients on tazarotene discontinued because of adverse events compared to 2.5% (9/358) in the placebo group. There were more adverse events that occurred in the tazarotene group vs. the placebo group, 90.2% and 74.6%, respectively (p<0.001). Tazarotene treated subjects had significantly more headache (18.7% vs. 12.0%), back pain (6.6% vs. 2.8%), foot pain (2.9% vs. 0.8%), cheilitis (65.5% vs. 16.8%), arthralgia (17.5% vs. 7.3%), myalgia (14.7% vs. 8.4%), joint disorder (4.0% vs. 1.1%), nasal dryness (3.7% vs. 1.1%), dry skin (23.6% vs. 14.8%), rash (2.9% vs. 0.6%), and dermatitis (1.4% vs. 0%) than did subjects

treated with placebo. In the post-treatment period, many of these adverse events improved. Only cheilitis remained a statistically significant event.

Overall decreases in bone mineral density (BMD) were seen in up to 17% of patients in the controlled studies. In study 048, at week 24 there were 4 patients treated with tazarotene and one with placebo who had decreases in BMD of >5%. All were men in the age range of 40-69 years. In addition, there was one patient who had a decrease of 50%. This is significant because men lose bone density at a rate of only 0.5 - 0.75% per year and women lose bone density at a rate of 1.5-2% per year. Thus, a loss of even 1-3% over 36 weeks implies a greater than normal bone loss over a year. Over a period of 5-10 years of treatment, this could be significant.

Laboratory evaluations to assess for risk for end-organ damage revealed significant elevations in plasma triglycerides as compared to placebo by the reviewer and hyperglycemia as compared to placebo by the Applicant. Other laboratory evaluations were not significant when compared to placebo. There were 4 cases of hypothyroidism, 3 in the short term trials and 1 in the long term trial. All patients were taking oral tazarotene. At the present time, there have not been any signals detected in the short term studies for psychiatric events. Full evaluation of ophthalmology and audiology data is still pending.

Discontinuation rate was slightly higher for those patients previously treated with tazarotene vs. those not (6.5% vs. 3.2%). It was found that patients treated with a 2<sup>nd</sup> course of tazarotene had significantly more back pain (17.4% vs. 7.7%), arthralgias (33.7% vs. 14.1%), and alopecia (5.4% vs. 0.9%) than patients who received only one course of tazarotene. There was also a significant increase in hyperostosis scores in the previously treated group than in the placebo group at weeks 12 and 24. The Sponsor found modest increases in triglyceride and alkaline phosphatase levels in both groups. However, the increases in alkaline phosphatase were higher in the group that received a second course and remained elevated in the post-treatment period.

The long term safety study was conducted for 64 weeks, 52 weeks of treatment and a 12 week post-treatment follow-up. Patients were instructed to take oral tazarotene, a 4.5 mg capsule once daily for 52 weeks. If the patient's OLA score was reduced to 0 (clear) at any visit, the patient was instructed to stop medication and subsequent visits would evaluate the need to resume medication. During the 52-week treatment period, the mean duration of exposure to tazarotene was 271.8 days (range 6 to 388 days, median, 359 days). Treatment exposure was at least 24 weeks for 76.8% (202/263) of patients, was at least 48 weeks for 58.2% (153/263), and was at least 52 weeks for 38.4% (101/263) of patients. Treatment exposure for 50 and 51 weeks was 55.1% (145/263) and 53.6% (141/263), respectively.

During the 52-week treatment period, 1 or more adverse events were reported for 98.9% (260/263) of patients. Adverse events that occurred in more than 5% of patients were cheilitis (64.3%), arthralgia (36.1%), myalgia (28.9%), infection (primarily upper respiratory tract; 28.5%), dry skin (22.8%), back pain (22.1%), headache (20.9%), asthenia (11.4%), and pruritus (11.4%), foot pain (9.9%), alopecia (7.6%), leg pain (7.2%), arthritis (6.8%), paresthesia (6.5%), flu syndrome (6.5%), nausea (6.1%), joint disorder (6.1%), insomnia (6.1%), rhinitis (5.7%), and bronchitis (5.7%). Most of the adverse events were reported as mild in severity.

In the long-term study, 14.4% (38/263) patients discontinued because of adverse events. The adverse events that led to discontinuation of treatment for more than 1 patient were arthralgia (10), myalgia (7), arthritis (4), back pain (4), alopecia (4), dermatitis (3), joint disorder (3), abnormal liver function tests (3), cheilitis (2), asthenia (2), depression (2), and emotional lability (2).

Laboratory adverse events were evaluated by including those patients who had normal values at screening but subsequently had elevated values on at least 2 monthly visits and those patients who had abnormal values at baseline and subsequently became worse at some point during the 52-week treatment period.

Abnormal laboratory tests included hypertriglyceridemia (41.1%), abnormal liver function tests (22.9%), elevated CPK (16.3%), elevated alkaline phosphatase (13.7%), elevated TSH (5.3%), elevated SGOT (6.5%), elevated SGPT (9.1%), abnormalities in hemic and lymphatic system (5.7%).

Compared to the placebo controlled trials, only the elevation in alkaline phosphatase is higher, 3.4% in the placebo controlled trials vs. 13.7% in the long term safety study. This elevation in alkaline phosphatase is may be related to an effect on bone synthesis. Alkaline phosphatase levels remained elevated at the end of the post-treatment period for 69.4% (25/36) of patients who had increases during treatment. Based on the review of the current data, there is a trend toward a dose- and follow-up time-related effect on osteosynthesis reactions to the drug, manifest in exacerbation of musculoskeletal symptoms, increased bone turnover, decreased bone mineral density and some mild increases in ligament calcifications.

There were 6 moderate fractures without known cause reported in the trials. Whether this is correlated to a decrease in bone mineral density (BMD) is still being evaluated. The mean BMD decreased over time for the entire set of patients tested in the trials, with some having decreases close to 30%. Over 10% had significant decreases greater than 5%. In the long term study, over 52 weeks of treatment, 5.3% (12/226) patients had significant changes in calcification and/or osteophyte formation scores of the cervical spine. Twenty-six percent of patients had worsening changes in hyperostosis and ligament calcification with each vertebrae of the cervical spine being involved. There was also a statistically significant increase in ankle ligament osteophyte formation at weeks 52 and 64.

Musculoskeletal complaints also accounted for the majority of adverse events that continued into the 12 week post-treatment period. Arthralgia continued for 19.7% of patients, back pain for 17.8%, myalgia for 15.8%, and arthritis for 6.6%. Other adverse events that continued for more than 3% of patients included cheilitis (38.2%), dry skin (17.1%), asthenia (7.9%), pruritus (6.6%), alopecia (4.6%), insomnia (3.9%), joint disorder (3.9%), bronchitis (3.3%), oral dryness (3.3%), and hemic and lymphatic (3.3%).

There have been 4 pregnancies that have occurred in trials with oral tazarotene, one in a psoriasis trial (study 050P) and 3 in acne trials. The pregnancy that occurred in the psoriasis trial was a result of nonconsensual sex. The pregnancy was electively terminated. In the acne trials, there was one elective termination, one spontaneous abortion 18 days after discontinuing tazarotene (fetal exposure of ~17 days), and one term delivery, 38 weeks gestation. The term baby was exposed to tazarotene 15 days

after presumed date of conception. At 16.5 months, the child had no evidence of complications.

Off-label use of oral tazarotene is a concern. There is already widespread recognition among physicians who treat acne that there is a topically delivered form of tazarotene approved for acne. Additional enthusiasm for off-label use in acne may follow the Roster exhibits at the Annual Meeting of the American Academy of Dermatology in February 2004. The following posters were presented:

- P65 Photographic Documentation of the Efficacy of Oral Tazarotene in Nodulocystic Acne
- P67 Safety of Oral Tazarotene in Nodulocystic Acne
- P69 Effects of Oral Tazarotene on Health-Related Quality of Life in Patients with Severe Nodulocystic Acne: Results from a Phase II Dose-Ranging Study
- P78 Oral Tazarotene Reduces Comedones

Further, in the April 2004 issue of Dermatology Times was an article by Cheryl Guttman, "Phase II Study Shows Oral Tazarotene Treatment Yields QOL Benefits For Suffering of Severe Acne," citing a statistically significant superiority of 3.0 mg and 6.0 mg per day over placebo.

#### Efficacy Short Term Studies (Placebo Control & Open Label)

##### Study 048P & 049P

Two phase 3 pivotal trials were conducted to demonstrate efficacy and safety of tazarotene oral capsules: 190168-048P and 19068-049P. These two trials were exactly alike in design. Subjects 21 years of age and older with a diagnosis of chronic plaque psoriasis with a severity score of at least 3 on the Overall Lesional Assessment Scale and a minimum body surface area involvement of at least 10% could be enrolled into the studies. The majority of patients in the studies were male, 75% and 70% for studies 048P and 049P, respectively. The studies were multicentered, randomized, double-blind, placebo controlled trials in which patients took either tazarotene 4.5 mg once a day or placebo for 12 weeks with a 12-week post-treatment follow-up. An important exclusion criterion to note was the exclusion of any male who was not willing to use a condom when having sexual intercourse with a female of childbearing potential.

The primary efficacy variable was the Overall Lesional Assessment (OLA), which has severity grades from 0-5. Secondary efficacy variables included plaque elevation, scaling, and erythema, with severity scales ranging from 0-4. Treatment success, as defined by the Division, is the proportion of subjects who achieve a score of 0 or 1 on the OLA at week 12.

**Table 1**  
**Treatment Success**

Trial	Treatment Success <sup>1</sup>		
	Tazarotene Capsules	Placebo	p-value
190168-048P	24/158 (15.2%)	2/163 (1.2%)	<0.001
190168-049P	34/182 (18.7%)	9/187 (4.8%)	<0.001

<sup>1</sup>Overall Lesional Assessment - success = score of 0 or 1 at week 12  
Source: Sponsor's NDA submission, module 5, Volume 45, page 99 and Volume 73, page 94

Although the majority of patients in the studies were male, a larger percentage of females achieved success. Approximately two-thirds of the patients who entered the tazarotene arms of the studies had moderate psoriasis and it was the patients with moderate disease that consistently achieved success over placebo across both studies. For severe disease, this was true in only one of the two studies.

Oral tazarotene did not provide efficacy in the treatment of nail psoriasis but a subgroup analysis did demonstrate efficacy in scalp psoriasis. (See Biostatistics analysis below for details).

#### Study 052P

Patients entered this study from the pivotal studies, tazarotene and placebo arm, if they did not have a response, had no change or an increase in severity per the OLA.

Although an open-label study, after 12 weeks of treatment for the group being treated for the first time, the percentage of patients with success was 38/196 (19.4%). This analysis lends support to the placebo-controlled trials in that the point estimate for success is the same.

#### Biostatistics

Two multinational placebo-controlled trials (denoted as studies 048 and 049) were conducted to support the efficacy claim of tazarotene 4.5 mg capsule. Study 048 was conducted in the U.S., Canada, Panama and Guatemala during September 2001 and October 2002. Study 049 was conducted in the U.S., Canada, Ecuador and Costa Rica during November 2001 and November 2002. Totals of 337 and 369 patients were enrolled from 28 and 29 sites in studies 048 and 049, respectively. Among the study sites, 8 and 7 sites in studies 048 and 049, respectively, were located in foreign countries. The patient enrollment at foreign sites accounted for about 40% of study enrollment. The enrolled patients were randomized in a 1:1 treatment allocation ratio to receive either tazarotene or placebo. The randomization resulted in 166 and 171 patients in tazarotene and placebo, respectively, for study 048; while 182 and 187 patients in the respective group for study 049.

The primary efficacy endpoint is the percentage of patients with Overall Lesional Assessment (OLA) score of 0 or 1 at week 12. No significant statistical issue that affects efficacy results in the pivotal trials is noted.

The following tables present efficacy results of studies 048 and 049:

- Table 1: distribution of OLA scores and number (%) of patients with OLA score of 0 or 1 at week 12.
- Table 2: number (%) of patients with OLA score of 0 or 1 at week 12 for U.S. sites vs. non-U.S. sites. As the trials are multinational, patients recruited from non-U.S. sites accounted for about 40% of study enrollment. One may ask if tazarotene is better than placebo for patient population in the U.S.
- Table 3: Subgroup results of the primary efficacy endpoint for study 048.
- Table 4: Subgroup results of the primary efficacy endpoint for study 049.

#### Summary of the results in Tables:

1. Efficacy results are generally robust. The overall efficacy findings are:
  - a. The superiority of tazarotene to placebo is established with respect to the Division's recommended primary efficacy endpoint for each of studies 048 and 049 (p-value < 0.001, Table 1). The overall success rates are 15.7% vs. 3.5% for tazarotene vs. placebo in study 048; and 18.7% vs. 4.8% in study 049.
  - b. For patient population in the U.S., the superiority of tazarotene to placebo is established for each of studies 048 and 049 (p-value < 0.001 and = 0.003, Table 2). The success rates are 16.2% vs. 2.0% for tazarotene vs. placebo in study 048; and 21.3% vs. 7.3% in study 049.

The findings in subgroups are:

- c. There is a gender effect in the efficacy results. Even though a higher rate of patients in the studies are males (about 75% and 70% in studies 048 and 049, respectively), the response rates of male patients are lower than those of female patients regardless of treatments for each study. Moreover, female subjects in placebo group for study 049 had an exceptionally high success rate (14.6%). Female subjects with success responses are examined in terms of compliance. No outstanding compliance issue that resulted in higher response rates for female patients is noted.
- d. More than 70% of subjects are Caucasian, the response rates for Caucasian are similar to those based on the whole intent-to-treat (ITT) population. For Hispanic subjects, tazarotene group is better than placebo in study 049 with a significant magnitude (20.5% vs. 2.2%), and numerically better than placebo in study 048 (21.9% vs. 14.8%). For other races, it is difficult to make statistical comparisons, as the sample sizes are small.
- e. Age was divided into three groups, < 45 years, 45 – 65 years, and > 65 years. Generally, efficacy results over age group do not show outstanding differences except a high response rate for geriatric patients in tazarotene group for study 049. Tazarotene is better than placebo for subjects in age groups of < 45 years



and 45 – 65 years for each study in a significant manner. The geriatric patients in tazarotene group showed a high response rate (41.2%) in study 049 as compared to other age groups. Following examining the subjects, geriatric patients were generally compliant regardless of achieving success and treatment groups. No significant compliance issues are noted.

- f. The response rate of the primary efficacy endpoint generally decreases as the baseline OLA severity score increases. Tazarotene is better than placebo for patients with moderate or severe disease status at baseline. There were 5 (1.5%) and 10 (2.7%) patients having OLA score of “*very severe*” at baseline in studies 048 and 049, respectively. Only one patient in placebo group (study 048) achieved success at week 12 (i.e., OLA score of 0 or 1). The efficacy claim of tazarotene capsules in the labeling for the treatment of “*very severe plaque psoriasis*” is ***not*** supported.

Another finding of note is that the data from pivotal trials showed some effectiveness of oral tazarotene in treating scalp psoriasis, but not nail psoriasis. It should be noted that 2 and 1 patients in placebo arm achieved fingernail and toenail psoriasis severity score of 0 at week 12, respectively. However, none of the patients in oral tazarotene group achieved severity score of 0. Furthermore, treatment success in tazarotene group is not permanent. A relatively high percentage of patients had a relapse on or prior to week 24.

**Table 1: Percentage of Patients with OLA Score of 0 or 1 at Week 12**

Distribution of OLA score at Week 12	Study 048		Study 049	
	Tazarotene (n = 166)	Placebo (n = 171)	Tazarotene (n = 182)	Placebo (n = 187)
0 – None	4 (2.4%)	2 (1.2%)	7 (3.8%)	2 (1.1%)
1 – Minimal	22 (13.3%)	4 (2.3%)	27 (14.8%)	7 (3.7%)
2 – Mild	61 (36.7%)	20 (11.7%)	65 (35.7%)	21 (11.2%)
3 – Moderate	64 (38.6%)	94 (55.0%)	61 (33.5%)	102 (54.5%)
4 – Severe	14 (8.4%)	49 (28.7%)	22 (12.1%)	51 (27.3%)
5 – Very Severe	1 (0.6%)	2 (1.2%)	0	4 (2.1%)
Percentage of patients with OLA score of 0 or 1	26/166 (15.7%)	6/171 (3.5%)	34/182 (18.7%)	9/187 (4.8%)
Comparison <sup>1</sup>	< 0.001		< 0.001	
<sup>1</sup> p-value in comparison is based on Cochran-Mantel-Haenszel test controlling for analysis center.				

**Table 2: Percentage of Patients with OLA Score of 0 or 1 at Week 12 for U.S. vs. Non-U.S. Sites (ITT) – Studies 048 and 049**

Study	Study Site	Tazarotene	Placebo	Comparison <sup>1</sup>
<b>048</b>	U.S.	16/99 (16.2%)	2/102 (2.0%)	< 0.001
	Non-U.S.	10/67 (14.9%)	4/69 (5.8%)	0.078
<b>049</b>	U.S.	23/108 (21.3%)	8/110 (7.3%)	0.003
	Non-U.S.	11/74 (14.9%)	1/77 (1.3%)	0.002
<sup>1</sup> p-value is based on Cochran-Mantel-Haenszel test controlling for analysis center.				

**Table 3: Subgroup Results of the Primary Efficacy Endpoint<sup>1</sup>  
(ITT) Study 048**

<b>Subgroup</b>	<b>Tazarotene (n = 166)</b>	<b>Placebo (n = 171)</b>	<b>Comparison<sup>2</sup></b>
<b>Total</b>	26/166 (15.7%)	6/171 (3.5%)	< 0.001
<b>Age</b>			
< 45 years	13/76 (17.1%)	3/84 (3.6%)	0.004
45 – 65	11/76 (14.5%)	3/73 (4.1%)	0.030
> 65 years	2/14 (14.3%)	0/14 (0.0%)	0.481
<b>Gender</b>			
Female	9/34 (26.5%)	3/48 (6.3%)	0.011
Male	17/132 (12.9%)	3/123 (2.4%)	0.002
<b>Race</b>			
Caucasian	16/126 (12.7%)	2/134 (1.5%)	< 0.001
Black	2/5 (40.0%)	0/5 (0.0%)	0.444
Asian	1/1 (100.0%)	0/2 (0.0%)	0.333
Hispanic	7/32 (21.9%)	4/27 (14.8%)	0.488
Others	0/2 (0.0%)	0/3 (0.0%)	NA
<b>Baseline OLA Score</b>			
Moderate	19/100 (19.0%)	3/105 (2.9%)	< 0.001
Severe	7/64 (10.9%)	2/63 (3.2%)	0.164
Very severe	0/2 (0.0%)	1/3 (33.3%)	1.000
<sup>1</sup> Primary efficacy endpoint is per the Division's definition, percentage of patients with OLA score of 0 or 1 at week 12. <sup>2</sup> p-values listed are for reference purpose, as the study was not designed to show significance over subgroups.			

**Table 4: Subgroup Results of the Primary Efficacy Endpoint<sup>1</sup>  
(ITT) Study 049**

<b>Subgroup</b>	<b>Tazarotene (n = 182)</b>	<b>Placebo (n = 187)</b>	<b>Comparison<sup>2</sup></b>
<b>Total</b>	34/182 (18.7%)	9/187 (4.8%)	< 0.001
<b>Age</b>			
< 45 years	11/71 (15.5%)	3/77 (3.9%)	0.016
45 – 65	16/94 (17.0%)	6/96 (6.3%)	0.020
> 65 years	7/17 (41.2%)	0/14 (0.0%)	0.009
<b>Gender</b>			
Female	15/63 (23.8%)	7/48 (14.6%)	0.227
Male	19/119 (16.0%)	2/139 (1.4%)	< 0.001
<b>Race</b>			
Caucasian	25/134 (18.7%)	7/131 (5.3%)	< 0.001
Black	1/4 (25.0%)	1/6 (16.7%)	1.000
Asian	0/3 (0.0%)	0/1 (0.0%)	NA
Hispanic	8/39 (20.5%)	1/46 (2.2%)	0.010
Others	0/2 (0.0%)	0/3 (0.0)	NA
<b>Baseline OLA Score</b>			
Moderate	24/121 (19.8%)	7/125 (5.6%)	< 0.001
Severe	10/57 (17.5%)	2/56 (3.6%)	0.016
Very severe	0/4 (0.0%)	0/6 (0.0%)	NA

<sup>1</sup>Primary efficacy endpoint is per the Division's definition, percentage of patients with OLA score of 0 or 1 at week 12.

<sup>2</sup>p-values listed are for reference purpose, as the study was not designed to show significance over subgroups.

### **III. Evolution of Risk Management for Systemic Retinoids**

This section describes the evolution of FDA thinking and actions concerning fetal exposure prevention risk management programs for systemic retinoids. This information is intended to provide the Advisory Committee (AC) with some historical and scientific context for potential risk management discussions concerning oral tazarotene.

The FDA has granted marketing approval for four systemic retinoids for cutaneous conditions: isotretinoin (Accutane, Amnesteem, Claravis, Sotret), etretinate (Tegison), acitretin (Soriatane) and bexarotene (Targretin). Etretinate (Tegison) has been voluntarily withdrawn from the market by the sponsor, but the other three remain in use. Additionally, other systemic retinoids are in development for a variety of conditions. Isotretinoin is indicated for the treatment of severe recalcitrant nodular acne, etretinate and acitretin for severe psoriasis, and bexarotene for refractory cutaneous T-cell lymphoma.

The first FDA approved systemic retinoid and the one that is most widely used by women of reproductive potential is isotretinoin. Evaluations conducted over the 20 years encompassing isotretinoin's three successive risk management efforts as described below, have provided FDA the best quality and greatest amount of evidence about the effectiveness of different interventions to reduce fetal exposure to systemic retinoids. As such, the history and development of the three successive fetal exposure prevention risk management programs (RMP) for isotretinoin are described first, as a prototype and benchmark of Agency thought. The risk management programs of the other three systemic retinoids are outlined secondarily.

Isotretinoin, the first systemic retinoid marketed in the US, was approved on May 7, 1982, for the treatment of severe recalcitrant nodular acne. Accutane was introduced with a Category X pregnancy designation based on the identification of fetal abnormalities in animal studies and the determination that the risk of use in pregnant women clearly exceeded any possible benefit. Risk management at the time of approval was limiting to labeling, which described the risk of teratogenicity in the Contraindications, Warnings and Precautions sections of the package insert.

The first case of human malformation associated with Accutane exposure was reported in June 1983, and additional cases were reported in the ensuing months. In response, multiple Dear Doctor and Dear Pharmacist letters were issued to inform health care providers of these malformations and to reinforce the information in the package insert, and pharmacists were provided with red warning stickers for application to prescriptions. The package insert was updated to emphasize the information about potential teratogenicity, first by highlighting that information in boldface type within the Contraindications, Warnings and Precautions sections (Aug 1983), and then by adding a boxed warning at the front of the package insert (Feb 1984).

Despite these actions, fetal exposures to isotretinoin continued to occur. In response, a pregnancy prevention risk management plan, which the Sponsor entitled the Accutane

Pregnancy Prevention Program (APPP), was presented to the AC, approved, and implemented in October 1988. For purposes of discussion and simplicity, we consider the APPP to be the second isotretinoin risk management plan for pregnancy prevention, with product labeling being the first effort. The APPP was designed to provide patients and prescribers information about the teratogenicity of Accutane and preventive strategies for maintenance of a non-pregnant state for one month before, during, and for one month following Accutane treatment. The components of the APPP included blister packaging with the “Avoid Pregnancy” icon and boxed warning printed directly on the package label, informed consent for female patients, educational materials, referral and reimbursement for contraceptive counseling, and modifications of the package insert. Modifications to the package insert recommended a negative pregnancy test within one week before starting Accutane, monthly pregnancy testing and contraceptive counseling, and use of two forms of effective contraception simultaneously for one month before, during, and one month following Accutane therapy. The Accutane Survey, a voluntary patient survey, and the Accutane Prescriber Tracking Survey, a telephonic survey of prescribers, were introduced to monitor program effectiveness.

In the first year following implementation of the Accutane PPP, the total number of reported exposed pregnancies increased significantly, likely due to the introduction of a new reporting instrument, the Accutane Survey, while the number of spontaneously reported exposed pregnancies was relatively unchanged. In the subsequent ten years, the number of reported exposed pregnancies remained relatively constant. However, over this time period, the number of patients who received isotretinoin prescriptions each year more than doubled. Because of the increasing size of the population exposed to isotretinoin, as well as the fact that the total public health burden of isotretinoin-exposed pregnancies was not decreasing, an AC was convened in September, 2000. At that time, FDA had already seen preliminary data on the performance of another risk management program to prevent fetal exposure (for thalidomide), that had been approved by FDA in 1998. The AC that met in 2000 recommended augmentation of the isotretinoin risk management plan to incorporate some of the features of the thalidomide fetal protection program, in particular the closed linkage of pregnancy testing to product dispensing.

On October 30, 2001, following extensive negotiations with the manufacturer, the FDA approved the System to Manage Accutane Related Teratogenicity (S.M.A.R.T.<sup>TM</sup>) Program, the Sponsor’s response to the requested changes in the Accutane risk management program. The S.M.A.R.T.<sup>TM</sup> program as described below did not incorporate all the features of the thalidomide pregnancy prevention risk management program. In its October 2001 approval letter of S.M.A.R.T.<sup>TM</sup>, FDA required a report and the public meeting on the forthcoming program’s overall effectiveness after one year and stated the possibility that changes might be required at that time including a mandatory patient registry (such as was in use for thalidomide). The S.M.A.R.T.<sup>TM</sup> program linked prescriber qualification of patients to dispensing of Accutane through use of yellow stickers placed on prescriptions, and uses voluntary patient and pharmacy surveys to assess compliance. Components of the S.M.A.R.T.<sup>TM</sup> program included patient informed consent forms, a prescriber checklist, Letter of Understanding for prescribers, yellow qualification stickers, Medication Guide dispensed with each

prescription, instruction guide for prescribers, instruction guide for pharmacists, FDA Letter to Pharmacy boards, Dear Accutane Prescriber Letter, Dear Pharmacist Letter, separate patient brochures for women and men, carton dispensing instructions, and updated package insert, patient package insert, container and carton labels. One-year performance benchmarks were set at achievement of an Accutane survey enrollment rate of 60%, and qualification sticker use approaching 100%.

On February 26, 2004, the AC was again convened to comment on the metrics from the one-year evaluation of the S.M.A.R.T.™ program. Although sticker use was high, exceeding 90%, it proved an unsatisfactory surrogate endpoint for compliance with the RMP since the number of exposed pregnancies was unchanged within the first year of S.M.A.R.T.'s implementation. Accutane survey enrollment failed to reach 60%. Most significantly, the AC advised implementation of a more rigorous pregnancy prevention RMP to include mandatory registration of all prescribers, pharmacies, and patients (male and female). The Agency is currently working with the Sponsors of the innovator and generic isotretinoin products to implement these recommendations. Contributing to FDA and sponsor thinking and risk management program development has been well-documented and complete exposure-based evidence collected to date about pregnancy exposures under the thalidomide pregnancy prevention risk management program (called S.T.E.P.S.) Under this program there has been only one pregnancy exposure, albeit in a small population of females of childbearing potential.

On September 30, 1986, a second systemic retinoid, Tegison (etretinate), was approved for marketing in the US, indicated for the treatment of severe recalcitrant psoriasis. Because of malformations seen in animal studies as well as human experience with isotretinoin, Tegison received a Category X pregnancy designation. The pregnancy prevention risk management program for Tegison was similar to that current for isotretinoin at that time: a boxed warning at the beginning of the package insert and additional warnings in the Contraindications, Warnings and Precautions sections of labeling. Tegison was withdrawn from the market by the Sponsor on December 20, 2002, and is no longer available in the US.

On October 28, 1996, Soriatane (acitretin) became the third systemic retinoid approved for marketing in the US. Soriatane is indicated in adults for the treatment of severe psoriasis. In women of childbearing potential, acitretin use “should be reserved for patients who are unresponsive to other therapies or in whom such treatments are contraindicated.” Soriatane received a Category X pregnancy designation based on fetal malformations in exposed animals and human teratogenicity with other retinoids. Although possessing an indication and a risk-benefit calculus distinct from Accutane, the Soriatane sponsor was required to implement a risk management program analogous to the best known practice at the time in 1996 (the current for isotretinoin APPP) because of the potential that Soriatane would be used in women of childbearing potential. The risk management program for Soriatane, entitled the Soriatane Pregnancy Prevention Program (SPPP) included the essential elements of the APPP, such as the boxed warning about teratogenicity, recommendations in women of childbearing potential for a negative pregnancy test within one week before starting treatment and regularly during treatment,

use of two forms of contraception during and for three years after completion of therapy, and signed informed consent. The SPPP differed from the Accutane PPP in that the SPPP did not include a patient or prescriber survey to assess program effectiveness, did not use blister packaging, and required pregnancy prevention for a longer duration following completion of therapy. A Medication Guide was added to the SPPP on April 18, 2003.

On December 29, 1999, Targretin (bexarotene), indicated for the treatment of the cutaneous manifestations of cutaneous T-cell lymphoma in patients refractory to at least one prior systemic therapy, became the fourth systemic retinoid approved in the US. Like the other systemic retinoids, Targretin received a Category X pregnancy designation based on fetal malformations in exposed animals and human teratogenicity with other retinoids. Fetal exposure prevention risk management for Targretin is composed of elements similar to those of the APPP and SPPP, including a boxed warning about teratogenicity, information in the Contraindications and Precautions sections of labeling, recommendations for a negative pregnancy test within one week of treatment initiation and monthly thereafter and for use of two forms of contraception for one month before, during and one month after therapy, and limitation of amount dispensed to 30 days supply. A Medication Guide was added on April 21, 2003.

In summary, fetal exposure prevention risk management of systemic retinoids has evolved and been informed through three programs (labeling, APPP, and S.M.A.R.T.<sup>TM</sup>) implemented for the first FDA-approved product in this category, isotretinoin. Subsequent product approvals for systemic retinoids have employed analogous risk management programs to the APPP that was in place for isotretinoin at the time they were approved. Now that the one year implementation and evaluation of the isotretinoin S.M.A.R.T.<sup>TM</sup> program has been completed, discussed publicly, and found to be insufficiently effective in fetal exposure prevention for isotretinoin, FDA anticipates further discussion and exploration of fetal exposure prevention risk management programs that are similarly effective to what has been documented for thalidomide.

#### **IV. Discussion Topics**

The Joint Advisory Committee will be asked to consider and discuss the following topics:

- the evidence for the effectiveness of oral tazarotene in moderate to severe plaque psoriasis
- the safety profile for oral tazarotene, including teratogenicity, presence of tazarotenic acid in the semen, bone and liver abnormalities, and hyperlipidemia, especially for repeated, intermittent, long-term use
- the risk-benefit calculus for oral tazarotene for the proposed population with moderate to severe psoriasis
- the appropriate teratogenic risk management plan to prevent fetal exposure
- the need for additional studies, and whether this information is needed before or can be obtained after marketing approval



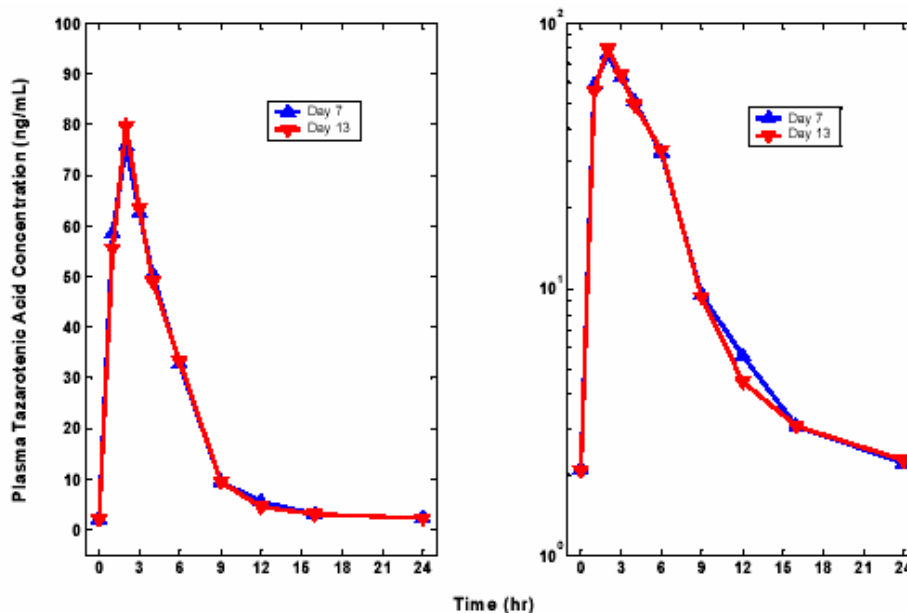
## Appendix

### Clinical Pharmacology and Biopharmaceutics Section

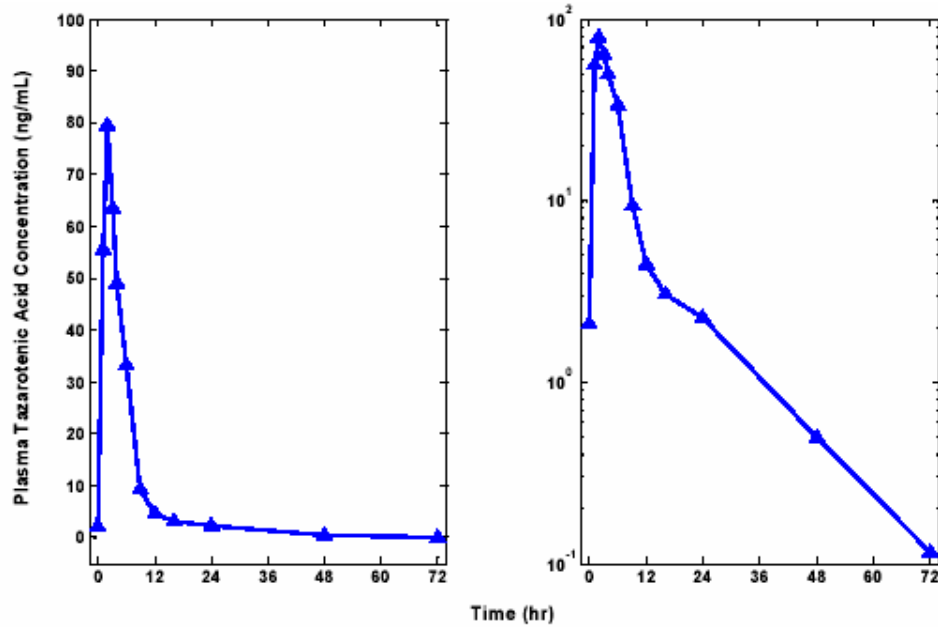
#### Background:

- Once in the body, tazarotene is hydrolyzed quickly and extensively to tazarotenic acid (TA), the primary active entity and the only species present in the systemic circulation.
- The absolute bioavailability of TA was estimated to be approximately 83% when systemic drug exposure from an intravenous study (15  $\mu\text{g}/\text{kg}$ ) was compared to those from an oral study at a similar dose (1.5 mg).
- TA exposure is proportional to oral dose from 3 mg to 6.3 mg.
- Following intravenous administration, tazarotene was measurable in the plasma and was eliminated from the body rapidly with a terminal half-life of 6.2 hours.
- Following intravenous administration, plasma TA concentration rose rapidly and declined bi-exponentially with a terminal half-life of 13.8 hours.
- When tazarotene was administered once-daily orally, plasma TA concentration dropped approximately 42 times from its peak level within 24 hours with a mean terminal half-life of 12.5 hours (range 7.1 to 41.1 hours) at proposed dose of 4.5 mg/day.

#### Mean TA Plasma Concentration-Time profiles on Study Days 7 and 13



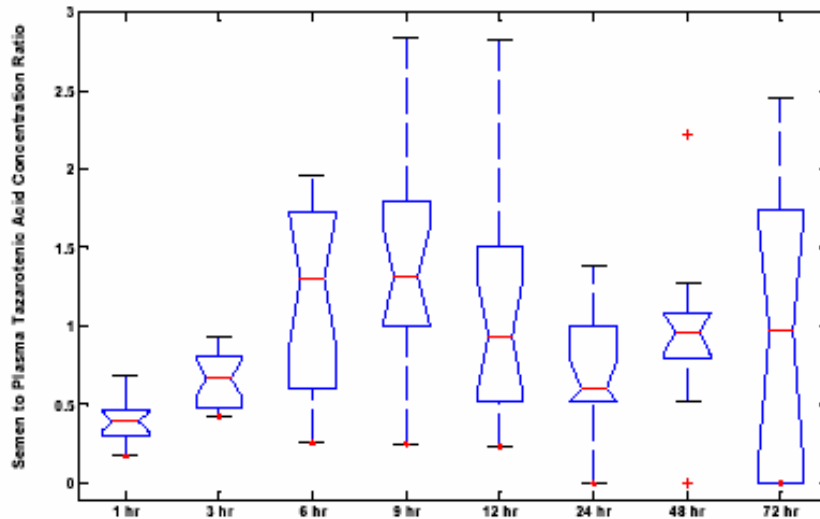
### Mean TA Plasma Concentration-Time profiles on Study Days 13 to 15



- Steady state is expected to reach by day 7 following oral administration.
- Accumulation ratio was approximately 1. (i.e. there was essentially no accumulation) following oral administration.
- TA is highly bound to plasma proteins, with an unbound fraction of less than 1%.
- Fecal elimination of TA is the predominant pathway, since 63.0% of an oral dose was eliminated in the feces, mostly as the *active* metabolite.
- In the urine, tazarotene was excreted, primarily as the *inactive* sulfoxide metabolite of TA.
- The following describes a comparison of systemic exposure of TA from various topical and oral formulations:

Formulation	Indication	BSA	Parameters	
			C <sub>max</sub> (ng/mL)	AUC <sub>0-24h</sub> (ng.h/mL)
0.1% Cream	Acne	15%	1.20±0.41	17.0±6.1
0.1% Gel	Acne	15%	4.84±6.05	44.6±38.9
0.1% Cream	Psoriasis	14±11%	2.31±2.78	31.2±35.2
0.1% Gel	Psoriasis	13±5%	12±7.6	105±55
4.5 mg Tablet	Psoriasis	NA	95.2±27.1	427±105

- Following Once-Daily oral dosing of tazarotene 4.5 mg capsules for two weeks in healthy male subjects, TA concentrations in > 79% semen samples were above the LLOQ (0.1 ng/mL).
- Semen to Plasma Tazarotenic Acid Concentration Ratio -Time Profiles from Samples Pooled together within and between Subjects over the Entire Study Period are presented using boxplot in the following figure:



- The highest individual semen to plasma TA concentration ratio was found to be 2.8.
- The highest individual TA concentration observed in semen was 83.1 ng/ml. (vs 161.0 ng/mL peak plasma level).
- Mean semen to plasma TA concentration ratio from samples pooled together over the entire study period is approximately 1 (one) indicating that there is no preferential uptake of TA.
- Assuming an ejaculate volume of 10 mL, the amount of drug transferred in semen would be 831 ng which is about 1/ 5,000th of a single 4.5 mg capsule.
- The no-effect limit for teratogenicity for tazarotene/TA is unknown.
- Fertilized egg may remain exposed to TA in the semen following continuous sexual encounters.
- Risk to a fetus, if any, while a male patient is taking the drug or after it is discontinued can not be ruled out.