

PRODUCT MONOGRAPH

^{Pr}TAZORAC[®]

Tazarotene Cream 0.05% and 0.1% w/w

Anti-Psoriasis Agent
Anti-Acne Agent
Agent for the Treatment of Photodamaged Skin

Allergan Inc.
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L6G 0B5

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Tazarotene Cream 0.05% and 0.1% w/w

THERAPEUTIC CLASSIFICATION

Anti-Psoriasis Agent
Anti-Acne Agent
Agent for the Treatment of Photodamaged Skin

ACTIONS AND CLINICAL PHARMACOLOGY

Tazarotene is a retinoid prodrug which is converted to its active form, M1 (“tazarotenic acid”, or AGN 190299), by rapid deesterification in most biological systems. “Tazarotenic acid” binds to and regulates gene expression through all three members of the RAR family of retinoid nuclear receptors, RAR α , RAR β , and RAR γ , but shows selectivity for RAR β and RAR γ .

Psoriasis: The exact mechanisms of tazarotene action in psoriasis are not completely defined. Among its specific pharmacological activities, demonstrated in cellular and in *in vivo* studies, topical tazarotene blocks induction of epidermal ornithine decarboxylase (ODC) activity, which is associated with cell proliferation and hyperplasia, suppresses expression of MRP8, an inflammatory marker present in psoriatic epidermis at high levels, and inhibits cornified envelope formation and build-up, which is an element of psoriatic scale. Improvement in psoriatic patients appears to occur in association with restoration of normal cutaneous morphology and reduction of the inflammatory markers ICAM-1 and HLA-DR. There is also a diminution of markers of epidermal hyperplasia and abnormal differentiation such as keratinocyte transglutaminase, involucrin and keratin 16.

Tazarotene also induces the expression to TIG3 (tazarotene induced gene 3), a tumour suppressor, which may inhibit epidermal hyperproliferation in treated plaques. Tazarotene, therefore, has multiple effects on keratinocyte differentiation and proliferation, as well as on inflammatory processes which contribute to the pathogenesis of psoriasis. The clinical significance of these findings is unknown.

In two 12-week vehicle-controlled clinical studies, tazarotene 0.05% and 0.1% creams were significantly more effective than vehicle in reducing the severity of plaque psoriasis. Tazarotene creams demonstrated effectiveness as early as 1 week after starting treatment, and initial treatment success (global response to treatment of moderate, marked, almost cleared or completely cleared) was reached significantly earlier than with vehicle. Treatment success rates with the 0.1% cream were generally superior (numerically) to those with the 0.05% cream.

During these studies, the number of patients with none, minimal or mild overall disease was significantly greater with tazarotene 0.05% and 0.1% vs vehicle at most follow-up visits.

In one of these studies, patients were evaluated for 12 weeks following cessation of therapy, and it was found that subjects treated with the 0.05% and 0.1% tazarotene creams continued to show a therapeutic effect during the 12-week post-treatment period.

Improvements in plaque elevation, scaling, and erythema were generally significantly greater with tazarotene cream 0.1% and 0.05% than with vehicle. Tazarotene cream 0.1% was generally more effective than the 0.05% concentration in reducing the severity of the individual signs of disease. However, tazarotene 0.1% was associated with a somewhat greater degree of local irritation than the 0.05% cream.

Acne: The mechanism of tazarotene action in acne is not defined. Acne is a multifactorial disease. The four main factors involved in its development are excessive follicular keratinization, hyperactivity of the sebaceous gland, proliferation of *Propionibacterium acnes* (*P. acnes*) and other microbes found in sebum-rich skin, and perifollicular inflammation. Acne vulgaris is the most common form of acne and is characterized by a mixture of inflammatory lesions (papules, pustules, and nodules) and non-inflammatory lesions (open comedones and closed comedones).

The basis of tazarotene's therapeutic effect in acne vulgaris appears to be due to its anti-hyperproliferative, normalizing-of-differentiation and anti-inflammatory effects. Its primary mechanisms of action in humans are believed to be the normalizing of keratinization and a decrease in the coherence of follicular keratinocytes as evidenced by animal and in-vitro studies that show that tazarotene inhibits corneocyte accumulation in rhino mouse skin (in vivo) and cross-linked envelope formation in cultured human keratinocytes (in vitro). Both mechanisms contribute to a comedolytic effect against existing comedones and prevention of the development of new microcomedones. The anti-inflammatory effect is suggested by data from skin rafts, where it inhibits the expression of a presumed pro-inflammatory marker, migration inhibitory factor related protein type 8 (MRP8). Furthermore, tazarotene indirectly hinders the development of inflammatory acne by suppressing the microcomedo, the precursor acne lesion. In addition, by clearing obstructed follicles, tazarotene also allows aeration and release of accumulated sebum, making the follicles a less desirable environment for *P. acnes* and indirectly halting the progression of inflammatory acne.

In two 12-week vehicle-controlled clinical studies, tazarotene 0.1% cream was significantly more effective than vehicle in reducing the total number of lesions, the number of inflammatory lesions and the number of non-inflammatory lesions. Tazarotene cream 0.1% demonstrated effectiveness in reducing the total number of lesions as early as 4 weeks after starting treatment.

After 12 weeks, the number of patients whose overall acne assessment improved from baseline by one or more grades (clinical improvement rate) was significantly greater with tazarotene cream 0.1% than with vehicle.

Tazarotene cream 0.1% was also associated with a significantly higher treatment success rate, based upon numbers of patients with a moderate response to treatment or better, than vehicle cream.

Photodamage: The mechanism of tazarotene action in photodamage is unknown. Photodamaged or photoaged skin, resulting from over-exposure to the sun, is characterized by wrinkles, laxity, uneven pigmentation, brown spots, and a leathery appearance. In contrast, chronologically aged skin that has been protected from the sun is thin and has reduced elasticity, but is otherwise smooth and unblemished.

Improvement in the appearance of photodamaged patients appears to occur in association with increased epidermal thickness, decrease in percentage area of melanin, and compaction of the stratum corneum. A study of the histological safety of tazarotene cream 0.1% applied to photodamaged but otherwise normal skin for 24 weeks showed that tazarotene is not associated with the formation or worsening of keratinocytic atypia or melanocytic atypia. Tazarotene cream 0.1% was associated with significant improvements in the distribution/severity of melanocytic atypia when compared with vehicle. Furthermore, tazarotene cream 0.1% was shown to be associated with (i) significant increases in epidermal thickness and (ii) significantly greater proportions of patients who showed an increase from baseline in the number of granular cell layers. Tazarotene cream 0.1% was also associated with significantly greater proportions of patients who showed an increase from baseline in epidermal edema. The clinical significance of these changes is unknown.

In two 24-week vehicle-controlled clinical studies, tazarotene cream 0.1% was significantly more effective than vehicle in reducing the severity of fine wrinkling, mottled hyperpigmentation, elastosis, lentigines, pore size, and irregular depigmentation and in showing improvement in Overall Integrated Assessment (OIA) of Photodamage. (OIA is an assessment by the investigator of the overall severity of facial photodamage.)

The incidence rates of patients who improved by one grade or more from baseline were significantly higher for tazarotene cream 0.1% than vehicle as early as Week 2 for mottled hyperpigmentation and Week 8 for fine wrinkling. Improvement for lentigines was observed as early as Week 4, elastosis and pore size as early as Week 12, and irregular depigmentation as early as Week 16. Improvement in OIA was observed as early as Week 8. Tazarotene cream 0.1% was also associated with a significantly higher treatment success rate, (based upon the numbers of patients with a moderate response to treatment or better, than vehicle cream).

The distribution of patients' overall self-assessment of photodamage scores in the tazarotene-treated group demonstrated significantly greater improvement from baseline compared with the vehicle-treated group. (Patients' Overall Assessment was a measure in which at each follow-up visit patients evaluated their overall response to treatment compared to their condition at baseline). According to the Patients' Overall Assessment, in each study, more than 60% were either somewhat or much improved after Week 4, more than 70% were somewhat or much improved after Week 8, and more than 80% were somewhat or much improved after Weeks 12, 16, 20 and 24. In one study 93.1% were somewhat to much improved after Week 24.

Pharmacokinetics: Following application, the drug undergoes esterase hydrolysis to its primary active metabolite, “tazarotenic acid” (the only metabolite of tazarotene known to have retinoid activity), and oxidative metabolism to inactive sulfoxide and sulfone derivatives. Little parent compound can be detected in the plasma. “Tazarotenic acid” is highly bound to plasma proteins (>99%). The half-life of “tazarotenic acid” following topical application of tazarotene gel is similar in normal and psoriatic subjects, approximately 18 hours.

During clinical trials for the treatment of psoriasis with 0.05% and 0.1% tazarotene cream, plasma concentrations of tazarotene and “tazarotenic acid” were monitored. In 139 patients tested, quantifiable tazarotene was detected in only three patients, with the highest concentration at 0.09 ng/mL. The majority of plasma samples were quantitated at less than the limit of the assay for “tazarotenic acid” (< 0.1 ng/mL). Only six patients had plasma “tazarotenic acid” concentrations greater than 1 ng/mL, the highest of which was 2.4 ng/mL.

In a Phase 3 clinical trial, tazarotene 0.1% cream was applied once daily to each patient with facial acne vulgaris for 12 weeks. The mean \pm SD values of plasma tazarotenic acid at weeks 4 and 8 were 0.078 ± 0.073 ng/mL (N = 47) and 0.052 ± 0.037 ng/mL (N = 42), respectively. The highest observed individual plasma tazarotenic acid concentration was 0.41 ng/mL at week 4 from a female patient. The magnitude of plasma tazarotenic acid concentrations appears to be independent of gender, age, and body weight.

In a phase 3 study tazarotene cream 0.1% was applied once daily for 24 weeks under clinical conditions (double-blind period) to patients with photodamaged skin. The mean plasma tazarotenic acid concentrations following topical treatment with tazarotene cream 0.1% were 0.092 ± 0.073 ng/mL (week 2; N=55), 0.108 ± 0.081 ng/mL (week 12; N=54), and 0.108 ± 0.098 ng/mL (week 24; N=50). The single highest observed tazarotenic acid concentration throughout the 24-week study was 0.423 ng/mL (observed at week 24). Systemic availability of tazarotenic acid was minimal and remained steady following once daily application of tazarotene cream 0.1% to the faces of patients with photodamaged facial skin for up to 24 weeks. The plasma tazarotenic concentrations observed are much lower than the endogenous concentrations of retinoids which are naturally present in plasma: all-trans retinoic acid has been reported to be present at concentrations of 1.32 ± 0.46 ng/mL, 13-cis retinoic acid at 1.63 ± 0.85 ng/mL, and 13-cis-4-oxo retinoic acid at 3.68 ± 0.99 ng/mL.

Results from the well-controlled clinical pharmacokinetic and therapeutic drug monitoring studies using tazarotene cream in the treatment of plaque psoriasis, acne vulgaris, and photodamaged skin demonstrated limited systemic exposure after daily topical applications of tazarotene cream.

INDICATIONS AND CLINICAL USE

TAZORAC[®] Cream (tazarotene 0.05% and 0.1% w/w) are indicated for topical application in the treatment of plaque psoriasis.

TAZORAC[®] Cream 0.1% is indicated for the topical treatment of:

- 1) acne vulgaris
- 2) signs and symptoms (appearance and texture) of premature aging of the skin due to over exposure to the sun, including fine wrinkling, mottled hyperpigmentation, lentigines, elastosis, pore size, and irregular depigmentation-

CONTRAINDICATIONS

TAZORAC[®] is contraindicated in individuals who have shown hypersensitivity to retinoid compounds, or to any of the product excipients (see PHARMACEUTICAL INFORMATION). Topical retinoids should not be used in the presence of seborrheic dermatitis.

TAZORAC[®] is contraindicated in women who are pregnant or may become pregnant. TAZORAC[®] may cause fetal harm when administered to a pregnant woman. Tazarotene elicits teratogenic and developmental effects associated with retinoids after topical or systemic administration in rats and rabbits (see WARNINGS, Use in pregnancy).

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued and the patient should be apprised of the potential hazard to the fetus (see WARNINGS, Use in pregnancy).

WARNINGS

TAZORAC[®] Cream 0.1% in the treatment of photodamaged (sun-damaged) skin, should be used under medical supervision as part of a comprehensive skin protection programme, including use of sunscreen products and protective clothing.

Retinoids can cause severe irritation of eczematous skin and should therefore be used with the utmost caution in patients with this condition.

Excessive use of TAZORAC[®] should be avoided. Keep away from the eyes, nose, mouth, and other mucous membranes. When using TAZORAC[®] for the treatment of photodamaged skin, care should be used when treating wrinkles around the eyes (Crows' feet) and mouth. In the event of contact with the eye, flush with cold water. TAZORAC[®] should not be applied to severely inflamed skin or open lesions.

In some patients, temporary skin irritation may occur, especially during the early weeks of treatment. If excessive pruritus, burning, skin redness or peeling occur, the medication should either be discontinued until the integrity of the skin is restored, or the dosing should be adjusted to a level or interval the patient can tolerate. Application should be closely monitored by careful

observation of the clinical therapeutic response and skin tolerance. Efficacy at reduced frequency of application has not been established.

Use in Pregnancy:

Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when TAZORAC[®] is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test should be obtained within 2 weeks prior to TAZORAC[®] therapy, which should begin during a normal menstrual period. (See CONTRAINDICATIONS). Although there may be less systemic exposure in the treatment of acne of the face alone due to less surface area for application, tazarotene is a teratogenic substance, and it is not known what level of exposure is required for teratogenicity in humans (see CLINICAL PHARMACOLOGY).

There have been no adequate and well-controlled prospective studies on the use of tazarotene or other **topical** retinoids in pregnant women. There have been rare reports of birth defects among babies born to women exposed to topical retinoids during pregnancy, although a causal relationship has not been determined. A retrospective study of mothers exposed to topical tretinoin during the first trimester of pregnancy found no increase in the incidence of birth defects.

As with all retinoids **oral** tazarotene is teratogenic. (see **TOXICOLOGY/Reproduction Toxicity**)

Tazarotene 0.05% gel, administered topically during gestation days 6 through 17 in rats and days 6 through 18 in rabbits, has been shown to be non-teratogenic and non-fetotoxic at maximum tolerated doses of 0.25 mg/kg/day. However, at these doses, slightly reduced fetal body weights and reduced skeletal ossification occurred in rats. These changes may be considered variants of normal development and were usually corrected after weaning. Multiple topical dosing to pregnant rats at 0.2 mg/kg daily resulted in undetectable radioactivity in the fetus. These findings indicate very little drug exposure to the rat fetus via placental transfer after topical treatment with tazarotene.

PRECAUTIONS

General: For external use only.

TAZORAC[®] should be applied only to the affected areas. Avoid contact with eyes, eyelids, and mouth. If contact with eyes occurs, rinse thoroughly with water.

Because of heightened susceptibility to sunlight, excessive exposure to ultraviolet light, either natural source (sunlight) or artificial (ultraviolet lamps) should be minimized or avoided unless deemed medically necessary. Patients who have considerable sun exposure due to occupation and those inherently sensitive to the sun should exercise particular caution when using TAZORAC[®]. Sunscreen (minimum SPF of 15) and protective clothing should be used when using TAZORAC[®] and exposure to sunlight cannot be avoided.

Patients with sunburn should be advised not to use TAZORAC[®] until fully recovered.

Weather extremes such as wind or cold may be more irritating to patients using TAZORAC[®].

The treatment area should not be covered with dressings or bandages.

Application to normal skin should be avoided in the treatment of psoriasis. In acne the whole of the skin prone to acne should be treated. In the treatment of photodamaged skin, the entire face should be treated.

Drug Interactions: Concomitant dermatologic medications and cosmetics that have a strong drying effect or high amounts of alcohol, astringents, spices, lime peel, medicated soaps or shampoos, permanent wave solution, or other products that may irritate the skin should be avoided. It is also advisable to "rest" a patient's skin until the effects of such preparations subside before use of TAZORAC[®] begins.

TAZORAC[®] should be administered with caution if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term studies of tazarotene following topical application in mice and oral administration to rats showed no indications of increased carcinogenic risks related to treatment. Marked skin irritation, possibly contributing to enhancement of photocarcinogenesis, was observed in hairless mice following chronic topical dosing with intercurrent exposure to ultraviolet radiation at tazarotene concentrations of 0.001%, 0.005%, and 0.01% for up to 40 weeks. Relevance of these studies to use in humans has not been established, but patients should minimize exposure to sun or ultraviolet light.

Tazarotene was found to be non-mutagenic and non-clastogenic in a standard battery of *in vitro* and *in vivo* tests. (See TOXICOLOGY Section for more information.)

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of tazarotene gel.

Reproductive capabilities of F1 animals, including F2 survival and development, were not affected by topical administration of tazarotene gel to female F0 parental rats from gestation day 16 through lactation day 20 at the maximum tolerated dose of 0.125 mg/kg/day.

Use During Lactation: After single topical doses of ¹⁴C-tazarotene gel to the skin of lactating rats, secretion of radioactivity at very low levels was detected in milk, suggesting that there would be limited transfer of drug-related material to the offspring via milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when tazarotene is administered to a nursing woman.

Pediatric (< 12 years of age): The safety and efficacy of tazarotene have not been established in pediatric patients under the age of 12 years.

Geriatrics (> 65 years of age):

Of the total number of subjects in clinical studies of Tazarotene Cream in the treatment of psoriasis, 120 were over the age of 65 years. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Tazarotene Cream for the treatment of acne has not been clinically tested in persons 65 years of age or older.

In the photodamage studies, 44 male patients and 180 female patients out of the total population of 1131 patients were older than 65. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Psoriasis: The most frequent adverse reactions ($\geq 5\%$) reported as being treatment related during Phase 3 clinical trials with tazarotene cream in the treatment of psoriasis (n=860) included pruritus (20.7%), erythema (14.3%), burning (12.7%), and irritation (8.3%). Reported less frequently ($\geq 1\%$ - $< 5\%$) were desquamation (2.9%), skin pain (2.4%), contact irritant dermatitis (2.3%), worsening of psoriasis (2.3%), stinging (2.1%), rash (2.1%), dermatitis (2.0%), eczema (1.5%), dry skin (1.1%), hypertriglyceridemia (1.0%). The incidence and severity of these adverse reactions appeared to be dose-related.

Acne: The most frequent adverse reactions ($\geq 5\%$) reported as being treatment related during Phase 3 clinical trials with tazarotene cream 0.1% in the treatment of acne (n=424) included desquamation (29.2%), dry skin (26.9%), erythema (20.5%), and burning sensation (13.9%). Reported less frequently ($\geq 1\%$ - $< 5\%$) were pruritus (4.5%), irritation (4.0%), face pain (1.9%), and stinging (1.7%).

Photodamage: The most frequent treatment-related adverse reactions ($\geq 5\%$) reported during the clinical trials with TAZORAC[®] in the treatment of signs and symptoms of premature aging of the skin due to overexposure to the sun (n= 567) included desquamation (39.3%), erythema (33.2%), burning sensation (24.5%), dry skin (15.7%), skin irritation (9.3%), pruritus (8.8%), irritant contact dermatitis (7.2%). Reported less frequently ($>1\%$ - $< 5\%$) were stinging (3.2%), acne (2.3%), and rash (1.9%).

In human topical safety studies, tazarotene 0.1% and 0.05% creams were moderately irritating under the exaggerated conditions of the studies, but did not induce allergic contact sensitization, phototoxicity or photoallergy. (See TOXICOLOGY.)

Postmarketing Experience: No adverse drug reactions have been reported through post-market surveillance.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Excessive topical use of TAZORAC[®] may lead to marked redness, peeling, or discomfort (see WARNINGS). Inadvertent oral ingestion of tazarotene may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A including teratogenesis in women of childbearing age. If accidental oral ingestion occurs, the patient should be monitored, and appropriate supportive measures should be administered as necessary, including pregnancy testing in women of childbearing age.

In case of oral ingestion or drug overdose, contact your doctor, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

DOSAGE AND ADMINISTRATION

General: For dermatological (topical) use only.

Application may cause excessive irritation in the skin of certain sensitive individuals. In cases where it has been necessary to temporarily therapy, or the dosing has been reduced to a lower concentration (in patients with psoriasis) or to an interval the patient can tolerate, therapy can be resumed or the drug concentration or frequency of application can be increased as the patient becomes able to tolerate the treatment. Frequency of application should be closely monitored by careful observation of the clinical therapeutic response and skin tolerance. Efficacy has not been established for less than once-daily dosing frequencies.

For psoriasis: It is recommended that treatment starts with TAZORAC[®] Cream, 0.05%, with strength increased to 0.1% if tolerated and medically indicated. Apply a thin film (2 mg/cm²) of TAZORAC[®] once a day, in the evening, to cover only the psoriatic lesions. If a bath or shower is taken prior to application, the skin should be dry before applying the cream. If emollients are used, they should be applied at least an hour before application of TAZORAC[®]. Because unaffected skin may be more susceptible to irritation, application of TAZORAC[®] to these areas should be carefully avoided.

For acne: Cleanse the face gently. After the skin is dry, apply a thin layer (2 mg/cm²) of TAZORAC[®] Cream 0.1% once a day, in the evening, to the skin areas where acne lesions appear. Use enough to cover the entire affected area.

For photodamage: For photodamage (premature aging of the skin due to over exposure to the sun), apply a pea-sized amount once a day to lightly cover the entire face, including the eyelids if desired. Facial moisturizers may be used as frequently as desired. Moisturizers may be applied either before or after tazarotene cream, but whichever is applied first should be allowed to absorb into the skin before the next one is applied. If any makeup is present it should be removed before applying TAZORAC[®] to the face.

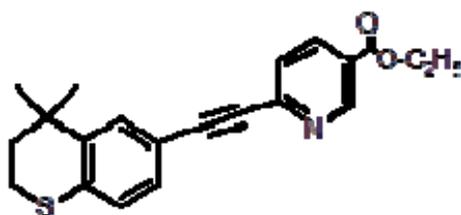
The duration of mitigating effects on facial fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentiginos following discontinuation of TAZORAC[®] Cream 0.1% has not been established.

PHARMACEUTICAL INFORMATION

Proper Name: tazarotene

Chemical Name: ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)-ethynyl] nicotinate

Structural Formula:



Molecular Formula: C₂₁H₂₁NO₂S

Molecular Weight: 351.46

CAS Number: 118292-40-3

Description:

Yellowish powder or crystals, insoluble in water, slightly soluble in ethanol, very soluble in benzyl alcohol.

Composition:

A white to slightly off-white emollient cream containing tazarotene 0.1% or 0.05% (w/w). Non-medicinal Ingredients: benzyl alcohol 1.0% (w/w) as a preservative, Carbomer 934P, Carbomer 1342, edetate disodium, medium chain triglycerides, mineral oil, purified water, sodium thiosulphate, sorbitan monooleate, and sodium hydroxide to adjust the pH.

Stability and Storage Recommendations:

TAZORAC[®] should be stored at room temperature (15° - 25°C).

AVAILABILITY OF DOSAGE FORMS

TAZORAC[®] is available in concentrations of tazarotene 0.1% w/w and 0.05% w/w. It is available in a collapsible aluminum tube of 30 grams. A 3.5 gram physician's sample size is also available.

PHARMACOLOGY

Preclinical

Metabolism and Pharmacokinetics

Absorption:

The systemic exposure of “tazarotenic acid” after multiple daily topical doses of 0.1% tazarotene cream was demonstrated in toxicologic studies:

Duration	C _{max} (ng/mL)	AUC (ng·hr/mL)	N
Rats			
3 months	11.4 ± 10.9	111 ± 15	4
Miniswine			
3 months	3.74 ± 2.11	61.5 ± 31.2	10

The systemic absorption of tazarotene in rat and monkey was 40% and 2%, respectively, after a single topical dose of tazarotene gel. After multiple topical doses of tazarotene gel to rats, the apparent half-life of the primary active metabolite, “tazarotenic acid”, was three days in the systemic circulation.

The elimination half-lives of tazarotene after intravenous dosing in the mouse, hamster, guinea pig, rabbit, and monkey were short but quantifiable, i.e., less than 20 minutes. The disposition of “tazarotenic acid” was rate-limiting with a half-life of 1.3 to 3 hours. The half-lives for tazarotene and “tazarotenic acid” in miniswine were 5.7 and 11 hours, respectively. Due to the rapid hydrolysis of tazarotene to its primary metabolite, “tazarotenic acid”, tazarotene was not detected in the rat following intravenous or oral administration, and “tazarotenic acid” was the only drug-derived species in the systemic circulation.

Distribution: After intravenous dosing of ¹⁴C-tazarotene in rats, tissue concentrations of radioactivity after 30 minutes were high and declined to very low levels by 48 hours in most tissues. The tissues with the highest concentration of radioactivity initially were the liver, spleen, and plasma. High radioactivity levels were observed in the gastrointestinal tract due to biliary excretion. The decline of radioactivity levels in adrenals, bone marrow, ovary, liver, and spleen was slower compared with that in plasma.

When a single dose of 0.1% cream was applied topically, ¹⁴C-tazarotene rapidly distributed into skin layers of miniswine and attained high concentrations in the skin after 24 hours, e.g., 10.5 µg-eq/g in the epidermis and 0.412 µg-eq/g in the dermis. The skin concentrations increased over a 7 day dosing regimen to 76.8 µg-eq/g (epidermis) and 0.732 µg-eq/g (dermis) after daily topical application of tazarotene cream for 7 days.

Tissue distribution of ¹⁴C-tazarotene gel in rats after topical administration resulted in significantly lower concentrations than after intravenous dosing in all tissues except skin. A small amount of ¹⁴C-tazarotene crossed the placenta of pregnant rats and rabbits. After topical administration of ¹⁴C-tazarotene to lactating rat dams, the total radioactivity concentration in

plasma and milk were comparable. These results indicate distribution of drug-derived species from maternal plasma into milk.

Over 99% of the circulating “tazarotenic acid” was bound to the plasma proteins resulting in a small volume of distribution of approximately 0.5L/kg in the mouse, rat, rabbit, and monkey. The volume of distribution of tazarotene was <2L/kg in the mouse, hamster, rabbit, and monkey, and about 8 L/kg in the miniswine.

In all maternal and fetal tissues examined (except the maternal liver), “tazarotenic acid” was the main drug-derived species. Rapid systemic metabolism limits the propensity for tissue distribution and body exposure to tazarotene.

Metabolism: The metabolic pathways of tazarotene were similar among animals and man and were well characterized including ester hydrolysis to form the free acid and oxidation to form sulfoxide and sulfone metabolites. Tazarotene was not excreted unchanged. In most species the major urinary metabolite was AGN 190844, the sulfoxide of the free acid “tazarotenic acid”, accounting for up to 90% of the urinary radioactivity. The metabolites excreted in the feces were “tazarotenic acid”, AGN 190844, AGN 190843 (the sulfone of “tazarotenic acid”) and a polar metabolite identified as an oxygenated derivative of “tazarotenic acid”.

When injected intraperitoneally in rats for eight days at doses leading to blood levels about 100 times greater than the anticipated exposure in man, tazarotene did not affect the liver weight, P-450 content, or activities of P-450 and UDP-glucuronyl transferase.

Excretion: The major route of drug excretion in rats was fecal, due to extensive biliary excretion. In monkeys, urinary and fecal routes of excretion for the drug were of equal importance.

Clinical

Pharmacodynamics

Psoriasis:

The pharmacological effects of tazarotene 0.05% gel were assessed on several epidermal differentiation and inflammation markers that have been shown to be abnormal in psoriatic lesions. Seven patients with psoriasis applied tazarotene 0.05% gel to bilateral plaques twice a day for two weeks followed by twice a day applications of the vehicle gel for an additional two weeks. Although the changes were not statistically significant, all five differentiation markers (TGase K, filaggrin, keratin 16, involucrin, EGF-R) normalized during the four week study period. Expression of the inflammatory markers ICAM-1 and HLA-DR was reduced in both the epidermis and dermis. With the exception of HLA-DR dermal cells, these decreases were statistically significant. In six of the subjects, the absence of ICAM-1+ epidermal cells was marked.

Metabolism and Pharmacokinetics

Absorption and half-life: Controlled pharmacokinetic studies with 0.1% ¹⁴C tazarotene gel indicated that less than 1% of the dose is absorbed when applied topically as a single dose (unoccluded) to psoriatic plaques, and approximately 5% of the dose is absorbed after application to normal skin under occlusion.

When tazarotene 0.05% and 0.1% gels were applied to normal skin over 20% of the body surface area for 10 hours, tazarotene was not detectable in the plasma, and the maximum plasma concentrations of “tazarotenic acid” (0.33 ± 0.17 and 0.47 ± 0.25 ng/mL, respectively) were attained approximately 15 hours post-dosing.

After a seven day topical dosing period with tazarotene 0.1% gel to normal skin over 20% of the body surface area (0.1 mg/kg/day), the maximum plasma concentration was 0.72 ± 0.58 ng/mL at nine hours, and the area under the plasma concentration time curve over a 24 hours time period was 10.1 ± 7.2 ng·hr/mL.

In a 14-day study in nine psoriatic patients, measured doses of tazarotene 0.1% cream were applied daily by medical staff to involved skin without occlusion (5% to 35% of total body surface area; mean \pm SD: $14 \pm 11\%$). The C_{\max} was 2.31 ± 2.78 ng/mL occurring 8 hours after the final dose, and the AUC_{0-24hr} was 31.2 ± 35.2 ng·hr/mL in the five patients who were administered clinical doses of 2 mg cream/cm². At an exaggerated dosing rate of 10 mg cream/cm², the C_{\max} was 3.07 ng/mL \pm 2.63 ng/mL (N=4) at 7 hours post dose, and the AUC_{0-24hr} was 46.4 ± 37.6 ng·hr/mL. Both the recommended clinical dose and an exaggerated dose, i.e., 2 and 10 mg cream/cm², respectively, produced comparable systemic exposure of “tazarotenic acid” in psoriatic subjects. Extrapolation of these results to represent dosing on 20% of total body surface area under an exaggerated dosing regimen (i.e., 10 mg cream/cm²) yielded estimates of C_{\max} of 6.04 ± 1.09 ng/mL and AUC_{0-24hr} of 98.4 ± 18.6 ng·hr/mL.

In a study to investigate the use of TAZORAC[®] in patients with acne vulgaris, tazarotene 0.1% cream was applied once daily to either the face (N = 8) or to 15% (exaggerated) of body surface area (N = 10) of female patients with moderate to severe acne vulgaris for approximately 30 days. The maximum average C_{\max} and AUC values of tazarotenic acid occurred on Day 15 and the single highest C_{\max} value was 1.91 ng/mL from the “exaggerated dosing” group. The mean \pm SD values of C_{\max} and AUC_{0-24} of tazarotenic acid on day 15 were 1.20 ± 0.41 ng/mL (N = 10) and 17.01 ± 6.15 ng·hr/mL (N = 10), respectively. In the “face-only” dosing group, the mean \pm SD values of C_{\max} and AUC_{0-24} were 0.10 ± 0.06 ng/mL (N = 8) and 1.54 ± 1.01 ng·hr/mL (N = 8), respectively, on Day 15.

Tazarotene cream 0.1% was topically applied under standard use (application to the face only, N = 8 [6 females and 2 males]) and exaggerated use (application to 15% body surface area with signs of photodamage, N = 16 [8 females and 8 males]) after a single dose and after repeated topical applications over four weeks in patients with photodamaged skin.

Results of this study demonstrated that tazarotenic acid plasma concentrations following application to the face only were very low. In the “face-only” dosing group, the maximum average C_{\max} and AUC values of tazarotenic acid occurred on Day 15 with mean \pm SD values of C_{\max} and $AUC_{0-24 hr}$ of tazarotenic acid being 0.236 ± 0.255 ng/mL (N = 8) and 2.44 ± 1.38 ng·hr/mL (N = 8), respectively. Gender had no influence on the systemic bioavailability of tazarotenic acid.

Plasma concentrations of tazarotenic acid after the application to 15% photodamaged body surface area were higher. In the exaggerated-dosing group, the maximum average C_{\max} and

AUC values of tazarotenic acid occurred on Day 22. The mean \pm SD value of AUC₀₋₂₄ of tazarotenic acid on day 22 was 23.8 ± 7.0 ng \times hr/mL (N = 16). The mean maximum concentration was 1.75 ± 0.53 ng/mL. This mean maximum concentration was within the range for some of the individual endogenous concentrations of all-trans retinoic acid and its metabolites, which have been reported to range from 1 to 4 ng/mL, with the total concentration as high as 6.63 ng/mL.

Following intravenous infusion of tazarotene 15 μ g/kg to healthy volunteers, intact drug was eliminated from the systemic circulation, with a terminal half-life of 6 hours. “Tazarotenic acid” concentrations rose rapidly to reach higher concentrations than tazarotene, then declined biexponentially, with a terminal half-life of 14 hours. After a single topical administration of tazarotene 0.1% gel to the same volunteers (2 mg gel/cm² over 20% of the body; removed 12 hours later), the systemic bioavailability of tazarotene was determined to be less than 1% of the applied dose. The terminal half-life of “tazarotenic acid” after topical administration of tazarotene gel was comparable to the terminal half-life of intravenous tazarotene.

During clinical trials for the treatment of psoriasis with 0.05% and 0.1% tazarotene cream, plasma concentrations of tazarotene and “tazarotenic acid” were monitored. In 139 patients tested, quantifiable tazarotene was detected in only three patients, with the highest concentration at 0.09 ng/mL. The majority of plasma samples were quantitated at less than the limit of the assay for “tazarotenic acid” (< 0.1 ng/mL). Only six patients had plasma “tazarotenic acid” concentrations greater than 1 ng/mL, the highest of which was 2.4 ng/mL.

In a Phase 3 clinical trial, tazarotene 0.1% cream was applied once daily to each patient with facial acne vulgaris for 12 weeks. The mean \pm SD values of plasma tazarotenic acid at weeks 4 and 8 were 0.078 ± 0.073 ng/mL (N = 47) and 0.052 ± 0.037 ng/mL (N = 42), respectively. The highest observed individual plasma tazarotenic acid concentration was 0.41 ng/mL at week 4 from a female patient. The magnitude of plasma tazarotenic acid concentrations appears to be independent of gender, age, and body weight.

Therapeutic drug monitoring was included in one of the two phase 3 studies to evaluate the systemic exposure following application of tazarotene cream 0.1% once daily for 24 weeks under clinical conditions (double-blind period) to patients with photodamaged skin. The mean plasma tazarotenic acid concentrations following topical treatment with tazarotene cream 0.1% were 0.092 ± 0.073 ng/mL (week 2; N=55), 0.108 ± 0.081 ng/mL (week 12; N=54), and 0.108 ± 0.098 ng/mL (week 24; N=50). The single highest observed tazarotenic acid concentration throughout the 24-week study was 0.423 ng/mL (observed at week 24). Systemic availability of tazarotenic acid was minimal and remained steady following once daily application of tazarotene cream 0.1% to the faces of patients with photodamaged facial skin for up to 24 weeks. The plasma tazarotenic concentrations observed are much lower than the endogenous concentrations of retinoids which are naturally present in plasma: all-trans retinoic acid has been reported to be present at concentrations of 1.32 ± 0.46 ng/mL, 13-cis retinoic acid at 1.63 ± 0.85 ng/mL, and 13-cis-4-oxo retinoic acid at 3.68 ± 0.99 ng/mL.

The apparent plasma half-life of “tazarotenic acid” after topical administration of tazarotene was approximately 18 hours, supporting a once-daily dosing regimen. “Tazarotenic acid” is the primary metabolite of tazarotene.

Distribution: Dosing normal skin topically under occlusion with tazarotene gel, 5% of the dose was recovered in the stratum corneum and 0.5% was recovered in the epidermis-dermis layers. In psoriatic patients, 1.4% of the topical doses applied without occlusion was recovered in the stratum corneum and 2.4% was recovered in the epidermis-dermis layers.

Tazarotene and “tazarotenic acid” are extensively bound (more than 99%) to human plasma, and albumin. The blood to plasma ratio of ¹⁴C-tazarotene was less than one, indicating a greater affinity toward plasma proteins than red blood cells.

Metabolism: When topically applied to freshly excised human skin *in vitro*, ¹⁴C-tazarotene gel was metabolized to “tazarotenic acid” in the skin.

After topical administration to healthy subjects, ¹⁴C-tazarotene gel underwent rapid esterase hydrolysis to “tazarotenic acid” and oxidative metabolism to inactive sulfoxide and sulfone derivatives. Secondary metabolites of “tazarotenic acid” (such as the sulfoxide, the sulfone, and an oxygenated derivative of “tazarotenic acid”) were detected in human urine and feces.

Rapid systemic metabolism limits the propensity for tissue distribution and body exposure to tazarotene.

Excretion: Tazarotene was not excreted unchanged. After topical dosing with ¹⁴C-tazarotene gel under occlusion to healthy volunteers, systemic absorption accounted for approximately 5% of the applied dose; 2.6% and 2.7% of the dose were excreted in urine and feces respectively over a 7 day period. Following a topical non-occluded dose to psoriatic patients, total systemic absorption was less than 0.8% of the applied dose; 0.3% of the dose was excreted in the urine and 0.4% was excreted in the feces. Greater than 75% of total drug excretion was completed within 72 hours after drug removal, with equal excretion of the radioactivity in urine and feces.

TOXICOLOGY

Animal Studies

Acute Toxicity

The acute toxicity of tazarotene was evaluated in rats, rabbits, dogs, and monkeys by topical, oral, or intravenous administration. Following topical administration to the skin, tazarotene produced mild irritation but no systemic toxicity. Single topical applications of up to 0.1 mg tazarotene in a gel formulation to the shaved intact skin of rats without occlusion and to intact and abraded skin of rabbits with occlusion revealed no signs of systemic toxicity and only mild erythema in the treated skin.

When systemically administered, large doses of tazarotene were well tolerated. A single oral dose of 2 g/kg to rats produced no lethality. Single doses of tazarotene administered intravenously to rats (2 mg/kg) and cynomolgus monkeys (0.75 mg/kg) produced no untoward effects. When given to rabbits intravenously through the ear vein, a dose level up to 0.075 mg/kg of tazarotene in a 95% ethanol vehicle produced local, vehicle related irritation, while a dose level up to 0.060 mg/kg in a 45% ethanol vehicle induced no adverse effects. Intravenous

infusion of tazarotene in 45% ethanol at dosages up to 0.075 mg/kg produced no local or systemic effects in dogs.

Repeated Dose (Subchronic/Chronic) Toxicity

Multiple Dose Topical Studies - Tazarotene Cream

a. Rat

Topical application of 0.025%, 0.05% or 0.1% tazarotene cream at 0.05, 0.125 or 0.25 mg/kg/day, respectively, for 3 months in rats induced reversible, dose-related skin irritation. Systemic effects typical of retinoid exposure included decreased mean body weight gain, red blood cells, hemoglobin, hematocrit, albumin and cholesterol, and increased liver enzymes at 0.125 or 0.25 mg/kg/day. Hepatocellular vacuolation was observed at 0.25 mg/kg/day. At doses of 0.05, 0.125, or 0.25 mg/kg/day, “tazarotenic acid” C_{max} concentrations were 1.22, 2.89 and 11.4 ng/mL, respectively, and AUC values were 20.2, 49.1 and 111 ng-hr/mL, respectively.

b. Miniswine

Topical application with 0.025%, 0.05% and 0.1% concentrations of tazarotene cream at 0.05, 0.125 and 0.25 mg/kg/day, respectively, for 3 months in miniswine induced reversible, dose-related skin irritation. No systemic effects were observed. At doses of 0.05, 0.125, or 0.25 mg/kg/day, “tazarotenic acid” C_{max} values were 0.386, 1.57 and 3.74 ng/mL, respectively, and AUC values were 7.12, 27.6 and 65.5 ng-hr/mL, respectively.

Multiple Dose Oral Studies

a. Rats

Oral administration of tazarotene in rats elicited systemic toxicity with blood drug levels indicating gastrointestinal absorption. Tazarotene admixed in the diet at 0.05, 0.1 or 0.5 mg/kg/day resulted in blood concentrations of “tazarotenic acid” from 0.4 to 1.6 ng/mL. The low dose of 0.05 mg/kg/day produced no significant adverse effects. Tazarotene administered in diet at dosages of 0.025, 0.050 or 0.250 for 26 weeks resulted in mean maximal blood “tazarotenic acid” levels of 0.5, 0.7, and 1.8 ng/mL, respectively. At the 0.025 mg/kg/day dose level, a slight reduction of serum albumin and cholesterol was found only in the males. Females were not affected. Overall, consistent signs of toxicity observed at higher doses included reduced serum albumin, calcium and cholesterol and elevated alkaline phosphates. At a higher toxic dose, a reduction of body weight gain, indications of hepatic functional impairment such as increased bilirubin and amino transferases, and bone effects were present, but were reversible after withdrawal of the treatment. Death associated with an excessive dose is believed to be due to internal haemorrhage and overburden of hepatic function. The rat appears to be the most sensitive species to tazarotene and 0.05 mg/kg/day is considered to be the no effect level.

b. Monkeys

Oral administration of tazarotene to cynomolgus monkeys induced various effects which were both dose and duration dependent. In studies up to 3 months of dosing, with dosages up to 1.60 mg/kg/day, renal failure with secondary mineralization of various soft tissues appeared to be the main effects. A daily dose level of 0.25 mg/kg/day for 3 months did not induce any significant adverse effects in male or female monkeys. Tazarotene solutions administered at dosage levels of 0.05, 0.125 and 0.25/0.50 mg/kg/day for 6 months (0.5 mg/kg/day dose reduced to 0.25 mg/kg/day at the beginning of the 11th week) resulted in mean blood “tazarotenic acid” levels of 10.3, 26.1, 37.0/49.8 ng/mL respectively at two hours post-dosing during the study. There were

no haematological or blood chemistry changes at any dose level. Histological examination of the femur revealed a disruption and/or premature closure of the growth plate in the 0.125 and 0.50/0.25 mg/kg/day dose groups. In the rib, a reduction of calcification in the area of costochondral junction was observed in the females at 0.125 mg/kg/day and in both sexes in the high dose group. In the vertebra and sternum, ankylosis and disruption of the growth plate were present in both male and females in the high dose group. Vertebral growth plate disruption was also present in the males of the 0.125 mg/kg/day dose group.

A 52-week oral study in monkeys was conducted at doses of 0.0125, 0.025, and 0.125 (reduced from 0.250 in males after 6 months of treatment) mg/kg/day. Results following 12 months of treatment showed no treatment-related effects nor radiological evidence of bone toxicity in the low and mid doses. There was clear evidence of bone effects in high dose males and to a lesser extent, females. These included effects on skeletal development, articular changes, kyphosis and closure of the epiphyses. Blood concentrations measured during the study indicated average C_{max} values for “tazarotenic acid” of 3.72, 5.29, 22.5, and 54.1 ng/mL, at doses of 0.0125, 0.025, 0.125, and 0.25 (male only) mg/kg/day.

Carcinogenicity/Photocarcinogenicity

No indications of increased tumorigenicity related to treatment were observed following topical applications of 0.01%, 0.025%, 0.05%, and 0.1% tazarotene gels to mice for approximately 21 months at respective dosages of 0.05, 0.125, 0.25, 1.00 (females), and 1.00/0.50 (males) mg/kg/day. Due to severe skin irritation, treatment of high dose 1.00 mg/kg/day male mice was discontinued on week 42, and resumed again at one half the dose, 0.50 mg/kg/day, on week 53. Mean C_{max} values assessed at weeks 16, 53, and 79 indicated “tazarotenic acid” levels ranging from 11.1 (0.05 mg/kg/day) to 67.6 ng/mL (1.0 mg/kg/day). There was no increase in tumorigenicity related to treatment with tazarotene noted in this study.

Dietary administration of tazarotene compound to rats for 2 years resulted in no indications of treatment-related tumorigenicity at dosage levels of 0.025, 0.050, and 0.125 mg/kg/day. Mean blood levels of “tazarotenic acid” at the end of the treatment period ranged from 0.746 ng/mL at the 0.025 mg/kg/day dose to 2.96 ng/mL at the 0.125 mg/kg/day dose. The high dose blood level provides more than a 3-fold level of safety when compared to the mean maximal “tazarotenic acid” concentrations observed following topical administration in healthy volunteers.

Tazarotene gel concentrations of 0%, 0.001%, 0.005%, and 0.01% were administered to hairless mice and ultraviolet radiation (UVR) exposures were conducted once daily, five days per week, for 40 weeks during a chronic photocarcinogenicity study. Due to marked cutaneous irritation attributed to the test article for some of the male and female mice in the 0.005% and 0.01% groups, test article administrations were discontinued during week 24 in these two groups. UVR exposure for all mice was continued. Enhancement of photocarcinogenesis was observed in all 0.001%, 0.005%, and 0.01% test article concentration groups. Cumulative Tumor Prevalences were accelerated, Median Latent Periods were reduced and significantly greater risks ($p < 0.001$) of tumor onset occurred. Similar enhancement of photocarcinogenesis has been demonstrated for related compounds, including the topical retinoid tretinoin, at concentrations of 0.001% and 0.01%. Although the significance of this study to man is not clear, patients should minimize exposure to sun and UV light.

Mutagenicity Studies

A standard battery of *in vitro* and *in vivo* mutagenicity assays were conducted with tazarotene. *In vitro* assays included the Ames assay in both *Salmonella typhimurium* and *Escherichia coli* strains, chromosome aberration in human lymphocyte cultures, and a CHO/HPRT mammalian cell forward gene mutation assay. An *in vivo* mouse micronucleus assay was also performed. Tazarotene did not show any mutagenic or clastogenic activity in these test systems.

Reproductive Toxicity

Topical administration of tazarotene gel to F0 male and female rats produced no evidence of systemic toxicity nor impaired fertility or reproductive capabilities at dosage levels of 0.025 and 0.050 mg/kg/day with 0.01% gel and 0.125 mg/kg/day with 0.05% gel. No impairments occurred in the growth, development, behaviour, fertility or reproductive capabilities of the F1 generation.

In rats, neither tazarotene gel nor tretinoin was teratogenic when topically applied at comparable doses of 0.05, 0.125, 0.250, and 0.500 mg/kg/day in range-finding studies and 0.05, 0.125, and 0.250 mg/kg/day in the main study. No adverse effects were observed on behavior or reproductive capability in the offspring. Topical application of tazarotene gel in rabbits at dosages of 0.050, 0.125 and 0.500 mg/kg/day in the range-finding study and 0.05, 0.125, and 0.250 mg/kg/day in the main study were found to be non-teratogenic, with no significant effects on maternal body weight, gross necropsy findings, or fetal development at the 0.050 mg/kg/day level.

In an oral teratology study in rats at dosages of 0.05, 0.25, and 1.0 mg/kg/day with 0.025% tazarotene, maternal and developmental effects were observed at dosage levels of 0.25 and 1.0 mg/kg/day, while 0.05 mg/kg/day was established as a no effect level. In a definitive rabbit study, tazarotene did not produce any evidence of maternal toxicity, embryotoxicity or fetal toxicity at dosage levels of 0.025 and 0.050 mg/kg/day. Teratogenicity was observed in rabbits at 0.200 mg/kg/day. The presence of adverse reproductive effects in both rats and rabbits was to be expected following high oral doses of tazarotene. Mean maternal blood drug levels in rats and rabbits at the no effect level of 0.050 mg/kg/day were 17.2 ng/mL and 60.4 ng/mL, respectively.

Topical administration of tazarotene gels at dosages of 0.025, 0.050, and 0.125 mg/kg/day in F0 female rats produced dose-dependent dermal irritation in the treated groups; however, no evidence of systemic toxicity was observed at any level tested. Developmental toxicity was observed in F1 males at the 0.050 and 0.125 mg/kg/day levels characterized by decreased lactation pup weights. No indications of impaired behavior, fertility or reproductive capabilities were observed in the F1 generation at any level tested. F2 growth and development appeared normal throughout lactation.

Other Toxicity Studies

Tazarotene cream was evaluated for delayed contact hypersensitivity, photoallergy, and phototoxicity following topical administration in guinea pigs. Ocular irritation potential and comedogenicity were evaluated by topical administration to rabbits.

In guinea pigs, tazarotene cream concentrations up to 0.1% were considered non-phototoxic and non-photoallergenic, but a very mild hypersensitivity response was observed with 0.05% and 0.1% tazarotene cream concentrations.

A single ocular instillation of 0.1 mL of tazarotene cream (0.1% containing 0.1% sodium thiosulphate) to rabbits, caused transient mild to severe ocular discomfort and reversible moderate hyperemia. These ocular reactions, which reversed within about 90 minutes, indicate that the test ingredients are irritating to the eye. Direct ocular contact should be avoided.

No comedogenicity was observed in rabbits following topical administration of up to 0.1% tazarotene cream.

Human Safety Studies

The 21-day cumulative irritation potential of tazarotene creams 0.1%, 0.05%, 0.025%, and 0.01% were compared with vehicle cream and sodium lauryl sulfate solution 0.5%. Forty healthy male and female subjects were enrolled, and 35 subjects completed the study. Study formulations were applied to semi-occlusive patches, and affixed with hypoallergenic tape to the same location on each subject's back for 21 consecutive days. The cumulative irritation scores were related to the concentration of tazarotene, with the irritation scores being significantly higher with increasing concentrations of tazarotene. The irritation potentials of the tazarotene cream formulations were consistent with those of other topical retinoids. Each of the tazarotene cream formulations, however, demonstrated an acceptable safety profile for topical application.

The contact sensitization potential of tazarotene creams 0.1%, 0.05%, 0.025%, and 0.01% were compared with vehicle cream. Two-hundred thirty healthy male and female subjects were enrolled, and 201 subjects completed the study. Each subject received each of the five formulations, applied to semi-occlusive patches and affixed with hypoallergenic tape to the same location on the back during the induction period. Nine patches were applied over a 3-week period, and after a 2-week rest period, challenge patches were applied to sites previously unexposed to the test material. Under the conditions of the repeated-insult patch test, the tazarotene creams did not induce contact sensitization. The results suggested that these creams have a low potential to cause allergic contact sensitization, and that they have acceptable safety profiles.

The phototoxic and photoallergic potentials of tazarotene creams 0.1%, 0.05%, 0.025%, and 0.01% were compared with vehicle cream. Thirty healthy male and female subjects were enrolled, and 28 subjects completed the study. Each subject received each of the five formulations, applied to semi-occlusive patches and affixed with hypoallergenic tape to duplicate sites on the back.

In the phototoxicity portion of the study, control sites for irritation potential (one set of treated sites that were not irradiated) and irradiation-induced responses (one site adjacent to the irradiated sites that was irradiated but not treated with test products) were included. Approximately 24 hours later, patches were removed and each test site was evaluated for irritation. Test sites designated for irradiation were then exposed to UVA (10 MED equivalents) and UVA/UVB (0.5X MED). Evaluations of test sites were made after approximately 5 minutes, 20 minutes, 3 hours, 24 and 48 hours after irradiation.

For the photoallergy assessment, the patches were removed approximately 24 hours later, and each test site was evaluated for irritation. Test sites designated for irradiation were then exposed

to 2 MEDs of UVA/UVB light. Evaluation of the test sites was made approximately 5 minutes and 24 hours after irradiation. This sequence continued until 6 test product applications and irradiations occurred over the 3-week “induction” period. After a two-week “rest” period, “challenge” patches were applied to test sites not previously exposed to test products. Approximately 24 hours later, patches were removed. The sites were then irradiated with UVA (10 MED equivalents) and evaluated approximately 5 minutes, 20 minutes, 24 and 48 hours after UV exposure.

The initial gradings of the irradiated sites generally noted faint to minimal erythema, which returned to normal (i.e., no sign of irritation) within 24 to 48 hours. In the opinion of the investigator, none of the test products caused phototoxic reactions. During the subsequent induction period, numerous faint and minimal irritation scores were noted at the irradiated sites with all test products. During the challenge phase, the majority of irradiated sites were graded as normal. In the opinion of the investigator, none of the test products caused photoallergic reactions. All tazarotene cream formulations demonstrated acceptable safety profiles and appear to have low potential for phototoxicity or photoallergy.

A second study was conducted to determine the photoallergic potential and safety of tazarotene creams 0.05% and 0.1% compared with vehicle cream in healthy subjects under semi-occlusive patch-test conditions. Thirty subjects were enrolled in the study, and 29 subjects completed the study. The study was conducted as described above, but during the challenge phase, the sites were irradiated with UVA (10 MED equivalents), followed immediately by UVB light (0.5 MED) and evaluated approximately 5 minutes, 20 minutes, 24, 48 and 72 hours after UV exposure.

During the induction period, numerous faint and minimal irritation scores were noted at the irradiated sites with both test products and the vehicle. During the challenge phase, the majority of irradiated sites were graded as normal. In the opinion of the investigator, the test products were irritating, but did not cause photoallergic reactions. All tazarotene cream formulations demonstrated acceptable safety profiles. There were no treatment-related adverse events.

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INFORMATION FOR THE CONSUMER

Pr TAZORAC[®] Cream

Tazarotene 0.05% and 0.1% w/w

This leaflet is part of the "Product Monograph" published when TAZORAC[®] was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TAZORAC[®]. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

TAZORAC[®] is a topical drug for the treatment of plaque psoriasis, acne and photodamage, to treat the signs and symptoms of premature aging due to overexposure to the sun such as the fine wrinkling, skin dryness, irregular or mottled pigmentation and liver spots on the skin.

What it does:

TAZORAC[®] is a preserved cream that contains tazarotene as the active ingredient which is a retinoid. The exact mechanism of action is not known. It is thought to act by helping skin cells to grow normally as well as having an anti-inflammatory effect in psoriasis and acne.

When it should not be used:

TAZORAC[®] must not be used by women who are or may become pregnant. If you become pregnant during TAZORAC[®] treatment, stop using TAZORAC[®] and contact your doctor immediately.

Do not use TAZORAC[®] if you have a skin condition called seborrheic dermatitis, a red, itchy, flaky, scaly inflammation of the skin.

Do not use TAZORAC[®] if you are allergic to tazarotene, retinoid compounds or any of the non-medicinal ingredients (see "What the important nonmedicinal ingredients are" section).

What the medicinal ingredient is:

Tazarotene

What the important nonmedicinal ingredients are:

Benzyl alcohol 1.0% (w/w) as a preservative, carbomer 934P, carbomer 1342, edetate disodium, medium chain triglycerides, mineral oil, purified water, sodium thiosulphate, sorbitan monooleate, and sodium hydroxide to adjust the pH

What dosage forms it comes in:

Cream, 0.05% and 0.1% w/w

WARNINGS AND PRECAUTIONS

Weather extremes, such as wind or cold, may be more irritating to patients using TAZORAC[®].

BEFORE you use TAZORAC[®] talk to your doctor or pharmacist:

- if you are pregnant or plan to become pregnant while using this drug
- if you are breast feeding or planning to breast feed
- if you are already using other skin products that make your skin dry (see INTERACTIONS WITH THIS MEDICATION)
- if you have recently undergone a skin procedure such as skin peeling, dermabrasion or other similar procedure, allow your skin to heal before starting TAZORAC[®]
- if you have a skin condition called eczema. TAZORAC[®] may cause severe irritation if applied to eczematous skin
- if you are sensitive to sunlight

Other warnings:

- Avoid contact with the eyes and mucous membranes, eyes, lips and nose. In case of accidental contact, rinse thoroughly with large amounts of water.
- TAZORAC[®] may cause skin irritation, burning or itching. Contact your doctor if these effects become troublesome

Pregnancy:

- This product may harm the fetus. There are rare reports of birth defects in babies born to women who have used topical retinoids during pregnancy, but retinoids have not been proven as a cause. Avoid pregnancy during TAZORAC[®] treatment.
- Use adequate birth control measures during treatment. Your doctor may request a pregnancy test in the 2 week period before TAZORAC[®] treatment. (see Warnings, Use in Pregnancy section of the Product Monograph)
- If you become pregnant while using TAZORAC[®], stop treatment immediately and contact your doctor.

Avoid excessive sun exposure, including sun lamps, as you may have a greater risk of sunburn during TAZORAC[®] treatment. Wear sunscreens SPF 15 or greater and protective clothing. If you get a sunburn, wait until full recovery before using TAZORAC[®].

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all the medications you are taking, including those without a prescription.

Medication that may interact with **TAZORAC**[®] include:

- medications that are applied to the skin and cosmetics that have a strong drying effect such as those containing alcohol, astringents, spices, lime peel, medicated soaps or shampoos, permanent wave solution, electrolysis, hair depilatories or waxes, or other products or processes that may dry or irritate the skin. Your doctor may tell you to stop using these products and allow your skin to heal before starting **TAZORAC**[®] treatment.
- medications that make you sensitive to the sun (e.g. thiazides (diuretics), antibiotics (tetracyclines, fluoroquinolones), phenothiazines, and sulfonamides)). Your doctor may advise that these medications should not be used during **TAZORAC**[®] treatment.

PROPER USE OF THIS MEDICATION

For external use only.

For all uses:

Wash your hands after applying the medication unless you are treating your hands for psoriasis. If the cream accidentally gets on areas you do not need to treat, wash it off to help prevent skin irritation.

Psoriasis:

Usual adult dose and dose for children above the age of 12:

If you bathe or shower, be sure the skin is dry before applying **TAZORAC**[®]. Apply a thin film of the cream to your psoriasis lesions once a day before going to bed.

If you use a cream or lotion to soften or moisten your skin, apply emollients first, at least 1 hour before **TAZORAC**[®]. Apply **TAZORAC**[®] only after ensuring that the first cream or lotion has absorbed into the skin.

Avoid application to normal skin. **TAZORAC**[®] is sometimes more irritating to normal skin.

You may notice an improvement in your psoriasis as early as one week after starting **TAZORAC**[®] treatment. Continue to use **TAZORAC**[®] as directed by your doctor. Contact your doctor if your psoriasis becomes worse.

Acne:

Usual adult dose and dose for children above the age of 12:

Clean your skin gently. After it is dry, apply **TAZORAC**[®] 0.1% once a day in the evening to the affected areas. Use enough cream to cover the entire affected area with a thin film.

Follow your doctor's directions for other routine skin care and the use of make-up. Talk to your doctor about the use of cosmetics, especially those that dry your skin.

Your acne may begin to improve as early as 4 weeks after starting **TAZORAC**[®] treatment. Continue to use **TAZORAC**[®] as directed by your doctor.

Contact your doctor if your acne becomes worse.

Photodamage – The signs and symptoms of premature aging due to overexposure to the sun:

Usual adult dose and dose for children above the age of 12:

Remove makeup (if present) before applying **TAZORAC**[®]. If you wash your face prior to applying **TAZORAC**[®], you should allow your skin to dry first. Apply a pea-sized amount to lightly cover the entire face. Apply with special care around eyelids if desired. Do not spot treat. **TAZORAC**[®] should be applied once per day.

When treating the eyelid, wrinkles around the eye (Crow's feet) and mouth, special care must be taken to minimize contact with the eyes, lips and mucous-producing areas.

Follow your doctor's directions for other routine skin care and the use of make-up. It is recommended to use a sunscreen with an SPF of at least 15 during the day, but you should talk to your doctor about the use of sunscreens, moisturizers, and cosmetics. In general, facial moisturizers may be used as frequently as desired. If emollients or moisturizers are used, they can be applied either before or after tazarotene cream, but whichever one is applied first should be allowed to absorb into the skin before the next one is applied.

Although results will vary, you may begin to see improvement in about 2 weeks for mottled pigmentation, 8 weeks for fine wrinkling and varying times for other signs and symptoms. Continue to use **TAZORAC**[®] as directed by your doctor. Contact your doctor if your photodamage becomes worse.

General directions for use:

Your doctor may have told you to use **TAZORAC**[®] in a different way to that recommended in this leaflet. If so, follow your doctor's instructions about when and how to use the cream. Read the directions on your prescription label carefully. Ask your doctor or pharmacist to explain anything that you do not understand.

Remove the cap and check that the seal is not broken before you first use the cream. To break the seal, use the back of the cap.

Do not cover treatment areas with dressings or bandages. Excessive use of **TAZORAC**[®] will not provide faster or better results, and severe irritation or discomfort could occur.

TAZORAC[®] was prescribed by your doctor to treat your specific medical problem and is for your use only. Do not share it with others. It may harm them even if their skin problem appears to be the same as yours.

Overdose:

In case of oral ingestion or drug overdose, contact your doctor, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget a dose of **TAZORAC**[®], do not try to make it up, simply return to your normal application schedule as soon as you can.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Very common	Occurs in more than 1 out of 10 patients
Common	Occurs in between 1 and 10 out of every 100 patients

Like all medicines, **TAZORAC**[®] can have side effects. Most of the side effects are not serious. If these persist or cause you concern, consult your doctor.

Psoriasis:

Very common

- Burning and redness of the skin
- Itchy and irritated skin

Common

- Inflammation and pain of the skin
- Peeling of the skin
- Worsening of psoriasis
- Eczema
- Rash
- Stinging sensation of the skin

Acne:

Very common

- Burning, peeling and redness of the skin
- Dry skin

Common

- Itchy and irritated skin
- Stinging

Photodamage:

Very common

- Burning, peeling and redness of the skin
- Dry skin
- Inflammation of the skin

Common

- Itchy and irritated skin
- Stinging sensation of the skin
- Acne
- Rash

*This is not a complete list of side effects. For any unexpected effects while taking **TAZORAC**[®], contact your doctor or pharmacist.*

HOW TO STORE IT

TAZORAC[®] should be stored at room temperature (15 - 25°C).

Do not use **TAZORAC**[®] after the expiration date found on the crimp of the tube.

Keep the tube tightly closed when not in use. Store it in a safe place where children cannot reach it or see it.

Reporting Side Effects

You can help improve the safe use of health products for Canadians reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form

and sending it by:

- Fax to 1-866-678-6789 (toll-free), or
- Mail to:

Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Allergan Inc, at: 1-800-668-6424

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