

PRODUCT MONOGRAPH

Pr **TAZORAC**[®]

Tazarotene gel 0.05% and 0.1% w/w

Anti-Psoriasis and Anti-Acne Agent

Allergan Inc.
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Date of Preparation:
February 17, 1997

Date of Revision:
June 29, 2015

Submission Control No: 183295

PRODUCT MONOGRAPH

Pr TAZORAC®

Tazarotene gel 0.05% and 0.1% w/w

THERAPEUTIC CLASSIFICATION

Anti-Psoriatic, Anti-Acne Agent

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.

In two large vehicle-controlled clinical studies, tazarotene 0.1% and 0.05% gels applied once daily were significantly more effective than vehicle in reducing the severity of the clinical signs of plaque psoriasis. Tazarotene gels demonstrated effectiveness as early as 1 week after starting treatment, with initial treatment success (good or excellent response or complete clearing) reached significantly earlier than with vehicle. The 0.1% gel was more effective than the 0.05% gel, but the 0.05% gel was associated with less local irritation than the 0.1% gel. In one of these studies, patients were also evaluated for 12 weeks following cessation of therapy, and it was found that subjects treated with the 0.1% and 0.05% tazarotene gels continued to show a therapeutic effect during the 12-week post-treatment period.

Acne: Tazarotene is thought to act against several of the factors that contribute to acne vulgaris. Animal and *in vitro* studies show that tazarotene inhibits corneocyte accumulation in rhino mouse skin (*in vivo*) and cross-linked envelope formation in cultured human keratinocytes (*in vitro*). The primary mechanisms of action in humans are believed to be the normalizing of keratinization and a decrease in the coherence of follicular keratinocytes. Both mechanisms contribute to a comedolytic effect against existing comedones and prevention of the development of new microcomedones. Tazarotene also exhibits activity against inflammatory acne.

In two large vehicle-controlled studies, tazarotene 0.1% and 0.05% gels applied once daily were significantly more effective than their vehicle in the treatment of acne vulgaris. The 0.1% gel was more effective than the 0.05% gel, but the 0.05% gel was associated with less local irritation than the 0.1% gel.

Pharmacokinetics: Controlled clinical pharmacokinetic studies with 0.1% ¹⁴C tazarotene gel indicate that less than 1% of the dose is systemically absorbed when applied topically (unoccluded) to psoriatic plaques, and approximately 5% of the dose is absorbed after application to normal skin under occlusion. After a 7-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 mean maximum plasma concentration was 0.72 ± 0.58 ng/mL at 9 hours, and the area under the plasma concentration time curve over a 24-hour time period was 10.1 ± 7.2 ng•hr/mL. A clinical pharmacokinetic study conducted in five psoriatic patients where treatment conditions were maximized to ensure sufficiently high plasma concentrations, showed that tazarotene absorption through the skin increased over the two week course of the study. The maximal plasma concentration was 12.0 ± 7.6 ng/mL at 6 hours, and the area under the plasma concentration time curve over a 24 hour time period was 105 ± 55 ng•hr/mL. This increased absorption through the skin in psoriatic may be due not only to a reduction of thick scale prior to normalization of indurated plaques, but also in part to a possible thinning of the stratum corneum. Following topical dosing of tazarotene, the half-life of “tazarotenic acid”, the primary active metabolite, was approximately 18 hours. The terminal half-lives of tazarotene and “tazarotenic acid” were 6 and 14 hours respectively, following intravenous dosing to normal volunteers.

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. Following topical dosing with ¹⁴C-tazarotene under occlusion to healthy subjects, 2.6% and 2.7% of the dose were excreted in urine and feces, respectively, over a 7-day period. Following a topical unoccluded dose to psoriatic patients, 0.3% of the dose was excreted in the urine and 0.4% excreted in the feces. Greater than 75% of total drug excretion was completed within 72 hours after drug removal, with equal excretion of radioactivity in urine and feces. The drug's rapid systemic metabolism limits the propensity for tissue distribution and body exposure to tazarotene.

INDICATIONS AND CLINICAL USE

TAZORAC[®] Gel (tazarotene 0.05% and 0.1% w/w) is indicated for topical application in the treatment of :

- 1) plaque psoriasis, and
- 2) acne vulgaris.

CONTRAINDICATIONS

TAZORAC[®] is contraindicated in individuals who have shown hypersensitivity to retinoic 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 or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Topical retinoids should not be used on eczematous skin, as they may cause severe irritation.

Keep away from the eyes, nose, mouth, and other mucous membranes. In the event of contact with the eye, flush with cold water.

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 has not been established for less than once-daily dosing frequencies.

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).

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. As with other retinoids, teratogenic effects were seen when tazarotene was given orally to rats and rabbits at doses of 0.25 mg/kg/day and 0.2 mg/kg/day, respectively. Very low drug exposure to the fetus was observed after oral administration of ¹⁴C-tazarotene to pregnant rats and rabbits. 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. There are no adequate and well-controlled studies in pregnant women.

PRECAUTIONS

General: For external use only.

Excessive use should be avoided.

TAZORAC[®] should be applied only to the affected areas.

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided unless deemed medically necessary, and in such cases, exposure should be minimized during the use of TAZORAC[®]. Patients must be warned to use sunscreens (minimum SPF of 15) and protective clothing when using TAZORAC[®]. Patients with sunburn should be advised not to use TAZORAC[®] until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using TAZORAC[®]. The safety of use over more than 20% of body surface area has not been established.

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

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

In patients with psoriasis, application to normal skin should be avoided.

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.

Drug Interactions: Concomitant dermatologic medications and cosmetics that have a strong drying effect 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.

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 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 gels, 0.05% and 0.1% for plaque psoriasis, 163 were over the age of 65. Subjects over 65 years of age experienced more adverse events and lower treatment success rates after 12 weeks of use of TAZORAC[®] Gel compared with those 65 years of age and younger. Currently there is no other reliable clinical experience on the differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals should not be ruled out. Tazarotene gel for the treatment of acne has not been clinically evaluated in persons over the age of 65.

ADVERSE REACTIONS

Psoriasis: The most frequent adverse reactions (≥5%) reported during clinical trials with tazarotene gel included pruritus, burning, erythema, skin irritation, skin pain, and worsening of psoriasis. Reported less frequently (1% - <5%) were desquamation, rash, contact irritant dermatitis, skin inflammation, stinging, and dry skin. Rarely reported reactions (<1%) included fissuring of the skin, bleeding, skin discharge, increased skin fragility, and localized edema. The incidence and severity of adverse reactions appeared to be dose related.

Increases in “psoriasis worsening” and “sun-induced erythema” were noted in some patients over the 4th to 12th months as compared to the first three months of a 1 year study.

Acne: The most frequent adverse reactions ($\geq 5\%$) reported during clinical trials with tazarotene gels in the treatment of acne included burning, desquamation, dry skin, erythema, and pruritus. Reported less frequently (1% - $< 5\%$) were skin irritation, and stinging. The following reactions were reported rarely ($< 1\%$) by study subjects: skin pain, skin tightness, fissuring of the skin, cheilitis, skin discoloration, worsening of acne, contact irritant dermatitis, and localized edema. The incidence and severity of adverse reactions appeared to be dose related.

In human topical safety studies, tazarotene 0.1% and 0.05% gels did not induce contact sensitization, phototoxicity or photoallergy. (See TOXICOLOGY.)

Postmarketing Experience: The following adverse reactions have been identified during postmarketing use of TAZORAC[®] in clinical practice. Because they are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or establish a causal relationship.

The reactions include: blister, rash, skin discoloration (including skin hyperpigmentation or skin hypopigmentation), pain

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.
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DOSAGE AND ADMINISTRATION

For dermatological (topical) use only.

General: Application may cause excessive irritation in the skin of certain sensitive individuals. In cases where it has been necessary to temporarily discontinue 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 start with TAZORAC[®] 0.05%, with strength increased to 0.1% if tolerated and medically indicated. Apply TAZORAC[®] once a day, in the evening, to psoriatic lesions, using enough (2 mg/cm²) to cover only the lesion with a thin film to no more than 20% of body surface area. If a bath or shower is taken prior to application, the skin should be dry before applying the gel. 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 tazarotene to these areas should be carefully avoided. TAZORAC[®] was investigated for up to 12 months during clinical trials for psoriasis.

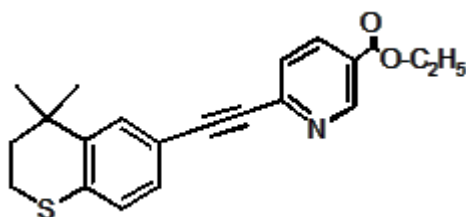
For acne: Cleanse the face gently. After the skin is dry, apply a thin film of TAZORAC[®] 0.1% (2 mg/cm²) once a day, in the evening, to the skin where acne lesions appear. Use enough to cover the entire affected area. TAZORAC[®] was investigated for up to 12 weeks during clinical trials for acne.

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 colourless to light yellow, translucent homogeneous gel containing tazarotene 0.1% or 0.05% (w/w); Non-Medicinal Ingredients: Benzyl alcohol 1.0% (w/w) as a preservative; ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene as antioxidants; Carbomer 934P, edetate disodium, hexylene glycol, purified water, poloxamer 407, polyethylene glycol 400, polysorbate 40, and tromethamine.

Stability and Storage Recommendations:

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

AVAILABILITY OF DOSAGE FORMS

TAZORAC[®] is available in concentrations of 0.1% and 0.05%. It is available in a collapsible aluminum tube, of 30 grams.

PHARMACOLOGY**Preclinical**Metabolism and Pharmacokinetics

Absorption: 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 various animal species are less than 20 minutes, with the exception of the miniswine, where the elimination half-life was 5.7 hours. Due to the rapid hydrolysis of tazarotene to “tazarotenic acid”, tazarotene was not detected in the rat following intravenous, oral, or topical administration, and “tazarotenic acid” was the only drug-derived species in the systemic circulation. The disposition of “tazarotenic acid” following an intravenous dose of tazarotene was formation rate-limited with a half-life of 1.3 to two hours in the mouse, rat, hamster, guinea pig, rabbit, and monkey.

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% gel was applied topically, ¹⁴C-tazarotene rapidly distributed into skin layers of rats and miniswine and attained high concentrations in the skin at the end of one day of dosing, e.g., 14.7 and 0.185 µg-eq/g in rats and 38.4 and 0.128 µg-eq/g in miniswine for the epidermis and dermis layers, respectively. In the miniswine, concentrations in the epidermis and dermis reached 13.0 µg-eq/g and 0.0310 µg-eq/g, respectively, two hours after a single topical application. These concentrations remained steady until dose removal 24 hours post drug application. The skin concentrations decreased, due to an increased percutaneous absorption rate over a seven day dosing regimen in the rat, but not in the miniswine.

Tissue distribution of ¹⁴C-tazarotene 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.

A clinical pharmacokinetic study conducted in five psoriatic patients where treatment conditions were maximized to ensure sufficiently high plasma concentrations, showed that tazarotene absorption through the skin increased over the two week course of the study. The maximal plasma concentration was 12.0 ± 7.6 ng/mL at 6 hours, and the area under the plasma concentration time curve over a 24 hour time period was 105 ± 55 ng•hr/mL. This increased absorption through the skin in psoriatic subjects was probably due to skin normalization (i.e., reduced severity of psoriasis). Following topical dosing of tazarotene, the half-life of “tazarotenic acid” was approximately 18 hours.

Following intravenous infusion of tazarotene 15 µg/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 treatment of acne and psoriasis with 0.1% or 0.05% gels, plasma concentrations of tazarotene were detected sporadically at very low levels (<0.23 ng/mL) in only 2% of patients assessed. In the same studies, plasma concentrations of “tazarotenic acid” ranged from <0.05 ng/mL (below the limit of quantitation) to 6.1 ng/mL in one patient. The majority of patients with detectable levels of “tazarotenic acid” had concentrations less than 1 ng/mL. Nine percent of patients tested had plasma concentrations of “tazarotenic acid” greater than 1 ng/mL, but none of these patients experienced any treatment-related systemic adverse events.

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 only metabolite of tazarotene known to have pharmacological activity.

Distribution: Dosing normal skin topically under occlusion, 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 ration 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 was metabolized to “tazarotenic acid” in the skin.

After topical administration to healthy subjects, ¹⁴C-tazarotene 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 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

a. Mice

Topical application of 0.005% tazarotene gel at a daily dosage of 0.05 mg/kg to females and 0.01% tazarotene gel at a daily dosage of 0.10 mg/kg to males for 13 weeks produced no signs of dermal irritation. At doses of 0.25 and 0.50 mg/kg/day, a reversible and slight dermal irritation characterized by the presence of erythema and dryness clinically and acanthosis and hyperkeratosis histologically was observed. Laboratory tests revealed reduced serum albumin and cholesterol levels among animals which received a daily dosage of 0.25 mg/kg or higher. At dosages of 0.50 mg/kg/day or higher, reversible focal hyperplasia and acanthosis were observed infrequently in the forestomach. This change was considered to result from contact of the squamous epithelium of the forestomach with the test substance, via self-grooming of the treatment site leading to ingestion, and is irrelevant to human safety since a forestomach does not exist in humans. Mean blood levels of “tazarotenic acid” ranged from 13.4 ng/mL at the 0.05 mg/kg/day dose to 71.5 ng/mL at the highest dose of 1.0 mg/kg/day. A dose of 0.10 mg/kg/day with mean blood drug levels of 20 ng/mL produced no systemic toxicity and could unequivocally be considered as the no effect level.

b. Rats

Topical applications with 0.01% to 0.1% concentrations of tazarotene gels induced dose dependent local irritation which was characterized by erythema with or without edema, flaking, scab formation, thickening and hardening of the skin. Other adverse effects included reduced body weight gain, reduced serum albumin, calcium and cholesterol, increased serum alkaline phosphatase and triglycerides, and reduced mean corpuscular volume of erythrocytes and hematocrit. Organ weights affected by tazarotene treatment included a decreased spleen weight and increased adrenal weight. Altogether, females appeared to be more sensitive to tazarotene than males. There was no apparent difference in toxicity when gels containing the neutralizing agents trolamine or tromethamine were compared. Mean blood “tazarotenic acid” concentrations of 2.0 to 3.4 ng/mL (mean across both sexes) were observed in the 5-week topical evaluation at dosages of 0.125 and 0.25 mg/kg/day of both formulations.

c. Miniswine

Topical application of gels containing 0.025%, 0.05%, and 0.1% of tazarotene caused a reversible, concentration-dependent, minimal to marked dermal irritation. A high dose of 0.50 mg/kg/day produced dermal irritation in a 3-month study to the extent that this dose, for humane reasons, could not be used in the 12-month evaluation. Daily dosages of up to 0.50 mg/kg/day for 3 months and 0.25 mg/kg/day for 12 months did not induce any adverse systemic or skeletal effects in miniswine and are considered no effect levels. Mean blood concentrations of “tazarotenic acid” were 2.2 ng/mL following 3 months of treatment at 0.50 mg/kg/day and 1.1 ng/mL following 1 year of treatment at 0.25 mg/kg/day. Dermal irritation of the animal skin was a limiting factor for the highest dose that could be administered in these studies.

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 phosphatase. At a higher toxic dose, a reduction of body weight gain, indications of hepatic functional impairment such as increased bilirubin and aminotransferases, 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 hemorrhage 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 hematological 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 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 nor tretinoin were 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 was evaluated for potential sensitization, photoallergy, and phototoxicity following topical administration in guinea pigs. Primary eye irritation and comedogenicity were evaluated by topical administration in rabbits.

In guinea pig models, gel concentrations of 0%, 0.01%, 0.05% and 0.1%, were considered non-sensitizing and non-phototoxic; gel concentrations of 0%, 0.05% and 0.1% were considered non-photoallergenic.

A single ocular instillation of tazarotene gel to rabbits at concentrations of 0%, 0.05% or 0.1% caused transient discomfort and hyperemia of the conjunctiva. These ocular reactions, which reversed within 90 minutes, indicated that the placebo gel itself is irritating to the eye, and direct ocular contact should be avoided.

Tazarotene gels at 0%, 0.05% and 0.1% concentrations were considered non-comedogenic in the rabbit inner ear test model.

Human Safety Studies

Irritation: The 21-day cumulative irritation potential of two concentrations (0.1% and 0.05%) of tazarotene gel was determined. Thirty healthy male volunteers enrolled in the study, 29 of whom completed the study. Study formulations were applied to semi-occlusive patches to test areas on each volunteer's back for 21 consecutive days. Results indicated that both the 0.05% and 0.1% gels produced moderate irritation.

Contact Sensitization/Phototoxicity/Photosensitization: The contact sensitization potential of two concentrations (0.1% and 0.05%) of tazarotene gel was determined. Two-hundred-three healthy male and female volunteers enrolled in the study, and 181 subjects completed the study. Study formulations were applied to semi-occlusive patches to test areas on each volunteer's back. Nine induction 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 materials. The results showed that the tazarotene 0.1% and 0.05% gels caused very low levels of local irritation but did not induce any skin reactions indicative of contact sensitization. It was concluded that neither tazarotene 0.1% gel or tazarotene 0.05% gel demonstrated contact sensitization potential, and both gels had acceptable safety profiles.

The phototoxicity potential of two concentrations (0.1% and 0.05%) of tazarotene gel was determined in 10 healthy female volunteers. Study formulations were applied under semi-occlusive patches to test areas on the forearms of each volunteer. Twenty-four hours after application one forearm was irradiated with UVA light and the other forearm was used as the non-irradiated control. There were no skin reactions to the study formulations, nor any evidence of phototoxicity. It was concluded that the tazarotene 0.1% and 0.05% gels did not demonstrate phototoxicity potential, and both gels had acceptable safety profiles.

The photoallergic potential of two concentrations (0.1% and 0.05%) of tazarotene gel was determined. Twenty-eight healthy male and female volunteers enrolled in the study, and 22 subjects completed the study. Study formulations were applied under semi-occlusive patches to test areas on the forearms of each volunteer. Over a 3 week period, nine induction applications and irradiations with UVA light were made to the test areas. One forearm was irradiated with UVA light and the other forearm was used as the non-irradiated control. After a 2 week rest period, challenge patches were applied to sites previously unexposed to the test materials, and 24 hours later were irradiated with UVA light. Many volunteers had moderate or marked irritation during the induction phase of the study, but none of the study formulations induced photoallergic reactions. It was concluded that the tazarotene 0.1% and 0.05% gels did not demonstrate photoallergic potential, and both gels had acceptable safety profiles.

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INFORMATION FOR THE CONSUMER

Pr **TAZORAC® Gel**

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 and acne. It is applied to the skin.

What it does:

TAZORAC® is a preserved gel that contains tazarotene as the active ingredient which is a retinoid. The exact mechanisms of action for psoriasis and acne are 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® should not be used by women who are or may become pregnant. If this drug is used during pregnancy, treatment should be stopped and discussed with your doctor.

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 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; ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene as antioxidants; carbomer 934P, edetate disodium, hexylene glycol, purified water, poloxamer 407, polyethylene glycol 400, polysorbate 40, and tromethamine

What dosage forms it comes in:

Gel, 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 products that make your skin dry (see INTERACTIONS WITH THIS MEDICATION)
- if you have a skin condition called eczema. TAZORAC® may cause severe irritation if applied to eczematous skin

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. 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 exposure to sun, 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 you heal before using TAZORAC®.

INTERACTIONS WITH THIS MEDICATION

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

Medications that may interact with TAZORAC® include:

- medications that are applied to the skin and cosmetics that have a strong drying effect. It is also advisable to "rest" a patient's skin until the effects of such preparations subside before use of TAZORAC® begins.
- medications that make you sensitive to the sun (e.g. thiazides (diuretics), antibiotics (tetracyclines, fluoroquinolones), sulfonamides)).

PROPER USE OF THIS MEDICATION

For external use only.

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 gel to your psoriasis lesions once a day before going to bed.

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

If you need to treat your hands, avoid contact with your eyes. Usually, you will notice an improvement in your psoriasis after about one week. 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® once a day, before going to bed, to the areas where you have acne lesions. Use enough gel 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.

Usually, your acne will begin to improve in about 4 weeks. Continue to use TAZORAC® as directed by your doctor.

Contact your doctor if your acne 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 gel. Read the directions on your prescription label carefully. Ask your doctor or pharmacist to explain anything that you do not understand.

If you use a cream or lotion to lubricate your skin, apply it to your skin before applying TAZORAC®.

Remove the cap and check that the seal is not broken before you first use the gel. 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.

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

This medicine was prescribed 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
- Skin pain
- Worsening of psoriasis

Common

- Skin peeling
- Dry skin
- Skin swelling
- Rash
- Stinging sensation of the skin

Acne:

Very common

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

Common

- Irritation of the skin
- Stinging sensation of the skin

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 by 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

This leaflet was prepared by Allergan Inc.

Last revised: June 29, 2015

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