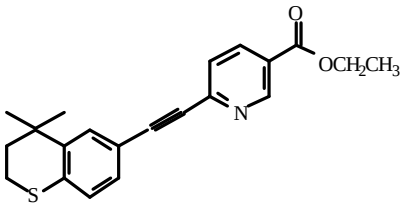
Allergan, Inc.

TAZORAC® (tazarotene) Cream, 0.05%
TAZORAC® (tazarotene) Cream, 0.1%

FOR TOPICAL USE ONLY. NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

DESCRIPTION

TAZORAC® Cream is a white cream and contains the compound tazarotene. Tazarotene is a member of the acetylenic class of retinoids and is represented by the following structural formula:



TAZAROTENE

Formula: $C_{21}H_{21}NO_2S$ Molecular Weight: 351.46
Chemical Name: Ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl] nicotinate

Contains:
Active: Tazarotene 0.05% or 0.1% (w/w)
Preservative: Benzyl alcohol 1.0% (w/w)
Inactives: Carbomer 934P, carbomer 1342, edetate disodium, medium chain triglycerides, mineral oil, purified water, sodium thiosulfate, sorbitan monooleate and sodium hydroxide to adjust the pH.

CLINICAL PHARMACOLOGY:

Tazarotene is a retinoid prodrug which is converted to its active form, the cognate carboxylic acid of tazarotene (AGN 190299), by rapid deesterification in animals and man. AGN 190299 ("tazarotenic acid") binds to all three members of the retinoic acid receptor (RAR) family: RARα, RARβ, and RARγ, but shows relative selectivity for RARβ, and RARγ and may modify gene expression. The clinical significance of these findings is unknown.

Psoriasis: The mechanism of tazarotene action in psoriasis is not defined. Topical tazarotene blocks induction of mouse epidermal ornithine decarboxylase (ODC) activity, which is associated with cell proliferation and hyperplasia. In cell culture and *in vitro* models of skin, tazarotene suppresses expression of MRP8, a marker of inflammation present in the epidermis of psoriasis patients at high levels. In human keratinocyte cultures, it inhibits cornified envelope formation, whose build-up is an element of the psoriatic scale. Tazarotene also induces the expression of a gene which may be a growth suppressor in human keratinocytes and which may inhibit epidermal hyperproliferation in treated plaques. However, the clinical significance of these findings is unknown.

Acne: The mechanism of tazarotene action in acne vulgaris is not defined. However, the basis of tazarotene's therapeutic effect in acne may be due to its anti-hyperproliferative, normalizing-of-differentiation and anti-inflammatory effects. Tazarotene inhibited corneocyte accumulation in rhino mouse skin and cross-linked envelope formation in cultured human keratinocytes. The clinical significance of these findings is unknown.

Pharmacokinetics:
Following topical application, tazarotene undergoes esterase hydrolysis to form its active metabolite, tazarotenic acid. Little parent compound could be detected in the plasma. Tazarotenic acid was highly bound to plasma proteins (>99%). Tazarotene and tazarotenic acid were metabolized to sulfoxides, sulfones and other polar metabolites which were eliminated through urinary and fecal pathways. The half-life of tazarotenic acid was approximately 18 hours, following topical application of tazarotene to normal, acne or psoriatic skin.

In a multiple dose study with a once daily dose for 14 consecutive days in 9 psoriatic patients (male=5; female=4), measured doses of tazarotene 0.1% cream were applied by medical staff to involved skin without occlusion (5 to 35% of total body surface area: mean± SD: 14 ± 11%). The C_{max} of tazarotenic acid was 2.31 ± 2.78 ng/mL occurring 8 hours after the final dose, and the $AUC_{0\text{-}24\,h}$ was 31.2 ± 35.2 ng·hr/mL on day 15 in the five patients who were administered clinical doses of 2 mg cream/cm^2.

During clinical trials with 0.05% or 0.1% tazarotene cream treatment for plaque psoriasis, three out of 139 patients with their systemic exposure monitored had detectable plasma tazarotene concentrations, with the highest value at 0.09 ng/mL. Tazarotenic acid was detected in 78 out of 139 patients (LLOQ = 0.05 ng/mL). Three patients using tazarotene cream 0.1% had plasma tazarotenic acid concentrations greater than 1 ng/mL. The highest value was 2.4 ng/mL. However, because of the variations in the time of blood sampling, the area of psoriasis involvement, and the dose of tazarotene applied, actual maximal plasma levels are unknown.

Tazarotene cream 0.1% was applied once daily to either the face (N = 8) or to 15% of body surface area (N = 10) of female patients with moderate to severe acne vulgaris. The mean C_{max} and AUC values of tazarotenic acid peaked at day 15 for both dosing groups during a 29 day treatment period. Mean C_{max} and $AUC_{0\text{-}24\,h}$ values of tazarotenic acid from patients in the 15% body surface area dosing group were more than 10 times higher than those from patients in the face-only dosing group. The single highest C_{max} throughout the study period was 1.91 ng/mL on day 15 in the exaggerated dosing group. In the face-only group, the mean ± SD values of C_{max} and $AUC_{0\text{-}24\,h}$ of tazarotenic acid on day 15 were 0.10 ± 0.06 ng/mL and 1.54 ± 1.01 ng.hr/mL, respectively, whereas in the 15% body surface area dosing group, the mean ± SD values of C_{max} and $AUC_{0\text{-}24\,h}$ of tazarotenic acid on day 15 were 1.20 ± 0.41 ng/mL and 17.01 ± 6.15 ng.hr/mL, respectively. The steady state pharmacokinetics of tazarotenic acid had been reached by day 8 in the face-only and by day 15 in the 15% body surface area dosing groups.

In a Phase 3 clinical trial, tazarotene 0.1% cream was applied once daily for 12 weeks to each of 48 patients (22 females and 26 males) with facial acne vulgaris. The mean ± 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.

Clinical Studies:

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 stable plaque psoriasis. Tazarotene cream 0.1% and tazarotene cream 0.05% demonstrated superiority over vehicle cream as early as 1 week and 2 weeks, respectively, after starting treatment.

In these studies, the primary efficacy endpoint was "clinical success," defined as the proportion of patients with none, minimal, or mild overall lesional assessment at Week 12, and shown in the following Table. "Clinical success" was also significantly greater with tazarotene 0.05% and 0.1% vs vehicle at most follow-up visits.

Patient Numbers and Percentages for Overall Lesional Assessment Scores and "Clinical Success" At Baseline (BL), End of Treatment (Week 12) and 12 Weeks After Stopping Therapy (Week 24)# in Two Controlled Clinical Trials for Psoriasis

	TAZORAC 0.05% Cream					TAZORAC 0.1% Cream					Vehicle cream				
	Study 1 N = 218			Study 2 N = 210		Study 1 N = 221			Study 2 N = 211		Study 1 N = 229			Study 2 N = 214	
Score	BL	Wk 12	Wk 24	BL	Wk 12	BL	Wk 12	Wk 24	BL	Wk 12	BL	Wk 12	Wk 24	BL	Wk 12
None (0)	0	1 (0.5%)	1 (0.5%)	0	2 (1%)	0	0	0	0	6 (3%)	0	0	1 (0.4%)	0	1 (0.5%)
Minimal (1)	0	11 (5%)	12 (6%)	0	7 (3%)	0	12 (5%)	14 (6%)	0	11 (5%)	0	7 (3%)	6 (3%)	0	1 (0.5%)
Mild (2)	0	79 (36%)	60 (28%)	0	76 (36%)	0	75 (34%)	53 (24%)	0	90 (43%)	0	49 (21%)	43 (19%)	0	54 (25%)
Moderate (3)	141 (65%)	86 (39%)	90 (41%)	100 (48%)	74 (35%)	122 (55%)	97 (44%)	107 (48%)	96 (45%)	62 (29%)	139 (61%)	119 (52%)	114 (50%)	97 (45%)	99 (46%)
Severe (4)	69 (32%)	39 (18%)	51 (23%)	80 (38%)	36 (17%)	91 (41%)	36 (16%)	46 (21%)	86 (41%)	29 (14%)	81 (35%)	51 (22%)	61 (27%)	93 (44%)	47 (22%)
Very Severe (5)	8 (4%)	2 (0.9%)	4 (2%)	30 (14%)	15 (7%)	8 (4%)	1 (0.5%)	1 (0.5)	29 (14%)	13 (6%)	9 (4%)	3 (1%)	4 (2%)	24 (11%)	12 (6%)
"Clinical Success"	0	91 (42%*)	73 (33%*)	0	85 (40%*)	0	87 (39%*)	67 (30%*)	0	107 (51%*)	0	56 (24%)	50 (22%)	0	56 (26%)

0 no plaque elevation above normal skin level; may have residual non-erythematous discoloration; no psoriatic scale
1 essentially flat with possible trace elevation; may have up to moderate erythema (red coloration); no psoriatic scale
2 slight but definite elevation of plaque above normal skin level; may have up to moderate erythema (red coloration); fine scales with some lesions partially covered
3 moderate elevation with rounded or sloped edges to plaque; moderate erythema (red coloration); somewhat coarser scales with most lesions partially covered
4 marked elevation with hard, sharp edges to plaque; severe erythema (very red coloration); thick scales with virtually all lesions covered and a rough surface
5 very marked elevation with very hard, sharp edges to plaque; very severe erythema (extreme red coloration); very coarse, thick scales with all lesions covered and a very rough surface

Clinical Success defined as an overall lesional assessment score of none, minimal, or mild.
Study 1 had post-treatment period observations for 12 weeks after stopping therapy, which were not part of Study 2
✳ Denotes statistically significant difference for "Clinical Success" compared with vehicle.

At the end of 12 weeks of treatment, tazarotene creams 0.05% and 0.1% were consistently superior to vehicle in reducing the plaque thickness of psoriasis. Improvements in erythema and scaling were generally significantly greater with tazarotene 0.05% and 0.1% than with vehicle. Tazarotene cream 0.1% was also generally more effective than the 0.05% concentration in reducing the severity of the individual signs of disease. However, tazarotene cream 0.1% was associated with a somewhat greater degree of local irritation than the 0.05% cream.

Mean Decreases in Plaque Elevation, Scaling and Erythema in Two Controlled Clinical Trials for Psoriasis

		TAZORAC® 0.05% Cream						TAZORAC® 0.1% Cream						Vehicle Cream					
Lesion		Trunk/Arm/ Leg lesions		Knee/Elbow lesions		All Treated		Trunk/Arm/ Leg lesions		Knee/Elbow lesions		All Treated		Trunk/Arm/ Leg lesions		Knee/Elbow lesions		All Treated	
		Study 1	Study 2	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2
		N=218	N=210	N=218	N=210	N=218	N=210	N=221	N=211	N=221	N=211	N=221	N=211	N=229	N=214	N=229	N=214	N=229	N=214
Plaque elevation	B#	**2.29**	**2.50**	**2.40**	**2.52**	**2.28**	**2.51**	**2.34**	**2.52**	**2.35**	**2.49**	**2.32**	**2.51**	**2.28**	**2.51**	**2.35**	**2.51**	**2.29**	**2.51**
	C-12	-0.83*	-0.98*	-0.91*	-1.04*	-0.75*	-0.90*	-1.08*	-1.25*	-0.96*	-1.21*	-0.83*	-1.08*	-0.59	-0.69	-0.57	-0.68	-0.48	-0.61
	C-24	-0.75*		-0.73*		-0.60*		-0.87*		-0.73*		-0.63*		-0.57		-0.49		-0.42	
Scaling	B#	**2.26**	**2.45**	**2.47**	**2.60**	**2.32**	**2.47**	**2.37**	**2.45**	**2.40**	**2.57**	**2.36**	**2.53**	**2.34**	**2.46**	**2.45**	**2.61**	**2.31**	**2.53**
	C-12	-0.75	-0.90	-0.78*	-0.98*	-0.67*	-0.80	-0.84*	-1.06*	-0.76*	-1.13*	-0.73*	-1.03*	-0.66	-0.79	-0.62	-0.76	-0.46	-0.70
	C-24	-0.68		-0.62*		-0.51*		-0.79*		-0.61*		-0.59*		-0.56		-0.45		-0.34	
Erythema	B#	**2.26**	**2.51**	**2.17**	**2.40**	**2.23**	**2.48**	**2.25**	**2.53**	**2.17**	**2.42**	**2.21**	**2.51**	**2.24**	**2.47**	**2.17**	**2.34**	**2.24**	**2.47**
	C-12	-0.49	-0.65*	-0.44	-0.66*	-0.40	-0.62	-0.49	-0.82*	-0.57*	-0.82*	-0.42	-0.78*	-0.42	-0.46	-0.38	-0.44	-0.37	-0.47
	C-24	-0.52		-0.44		-0.41		-0.55		-0.52*		-0.39		-0.43		-0.34		-0.33	

Plaque elevation, scaling and erythema scored on a 0-4 scale with 0=none, 1=mild, 2=moderate, 3=severe and 4=very severe.
#B=Mean Baseline Severity:
C-12=Mean Change from Baseline at end of 12 weeks of therapy:
C-24=Mean Change from Baseline at week 24 (12 weeks after the end of therapy).
***Denotes statistically significant difference compared with vehicle**

Acne:
In two large vehicle-controlled studies, patients (age 12 or over) with facial acne vulgaris of a severity suitable for monotherapy with a topical agent were enrolled. After face cleansing in the evening, tazarotene cream 0.1% was applied once daily to the entire face as a thin layer. Tazarotene was significantly more effective than vehicle in the treatment of facial acne vulgaris. Efficacy results after 12 weeks of treatment are shown in the following Table:

Efficacy Results after Twelve Weeks of Treatment in Two Controlled Clinical Trials for Acne

	TAZORAC® 0.1% Cream		Vehicle Cream	
	Study 1 N=218	Study 2 N=206	Study 1 N=218	Study 2 N=205
Median Percent Reduction in				
• **Noninflammatory lesions**	**46%***	**41%***	**27%**	**21%**
• **Inflammatory lesions**	**41%***	**44%***	**27%**	**25%**
• **Total lesions**	**44%***	**42%***	**24%**	**21%**
Percent of Subjects with No Acne or Minimal Acne	**18%***	**20%***	**11%**	**6%**
Percent of Subjects with No Acne, Minimal Acne, or Mild Acne	**55%***	**53%***	**36%**	**36%**

*Denotes statistically significant difference compared with vehicle.

INDICATIONS AND USAGE:

TAZORAC® (tazarotene) Cream 0.05% and 0.1% are indicated for the topical treatment of patients with plaque psoriasis.

TAZORAC® (tazarotene) Cream 0.1% is also indicated for the topical treatment of patients with acne vulgaris.

CONTRAINDICATIONS:
Retinoids may cause fetal harm when administered to a pregnant woman.

In rats, tazarotene 0.05% gel administered **topically** during gestation days 6 through 17 at 0.25 mg/kg/day resulted in reduced fetal body weights and reduced skeletal ossification. Rabbits dosed **topically** with 0.25 mg/kg/day tazarotene gel during gestation days 6 through 18 were

noted with single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies.

Systemic exposure (AUC_{0-24h}) to tazarotenic acid at topical doses of 0.25 mg/kg/day tazarotene in a gel formulation in rats and rabbits represented 1.2 and 13 times, respectively, that in a psoriatic patient treated with 0.1% tazarotene cream at 2 mg/cm^2 over 35% body surface area in a controlled pharmacokinetic study, and 4.0 and 44 times the maximum AUC_{0-24h} in acne patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area.

As with other retinoids, when tazarotene was given **orally** to experimental animals, developmental delays were seen in rats; and teratogenic effects and post-implantation loss were observed in rats and rabbits at doses producing 1.1 and 26 times, respectively, the systemic exposure (AUC_{0-24h}) seen in a psoriatic patient treated topically with 0.1% tazarotene cream at 2 mg/cm^2 over 35 % body surface area in a controlled pharmacokinetic study and 3.5 and 85 times the maximum AUC_{0-24h} in acne patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15 % body surface area.

In a study of the effect of oral tazarotene on fertility and early embryonic development in rats, decreased number of implantation sites, decreased litter size, decreased number of live fetuses, and decreased fetal body weights, all classic developmental effects of retinoids, were observed when female rats were administered 2 mg/kg/day from 15 days before mating through gestation day 7. A low incidence of retinoid-related malformations at that dose were reported to be related to treatment. That dose produced an AUC_{0-24h} that was 3.4 times that observed in a psoriatic patient treated with 0.1% tazarotene cream at 2 mg/cm^2 over 35% body surface area and 11 times the maximum AUC_{0-24h} in acne patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area.

Systemic exposure to tazarotenic acid is dependent upon the extent of the body surface area treated. IN PATIENTS TREATED TOPICALLY OVER SUFFICIENT BODY SURFACE AREA, EXPOSURE COULD BE IN THE SAME ORDER OF MAGNITUDE AS IN THESE ORALLY TREATED ANIMALS. 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: Pharmacokinetics).

There were three reported pregnancies in patients who participated in the clinical trials on acne with tazarotene cream 0.1%. Two of the patients were found to have been treated with tazarotene cream and the other had been treated with vehicle. One of the patients who was treated with tazarotene cream elected to terminate the pregnancy. The other gave birth to an apparently normal, healthy child at 36 weeks gestation. Seven pregnant women who were inadvertently exposed to topical tazarotene during other clinical trials subsequently delivered healthy babies. As the exact timing and extent of exposure in relation to the gestation times are not certain, the significance of these findings is unknown.

TAZORAC® Cream 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. Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when TAZORAC® Cream is used. The possibility that a woman of child-bearing

potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for human chorionic gonadotropin (hCG) should be obtained within 2 weeks prior to TAZORAC® Cream therapy, which should begin during a normal menstrual period (see also PRECAUTIONS: Pregnancy: Teratogenic Effects).

TAZORAC® Cream is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS:

Pregnancy Category X. See CONTRAINDICATIONS section. Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when TAZORAC® Cream is used. The possibility that a woman of child-bearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for hCG should be obtained within 2 weeks prior to TAZORAC® Cream therapy, which should begin during a normal menstrual period.

PRECAUTIONS:

General: TAZORAC® Cream should be applied only to the affected areas. For external use only. Avoid contact with eyes, eyelids, and mouth. If contact with eyes occurs, rinse thoroughly with water.

Retinoids should not be used on eczematous skin, as they may cause severe irritation. 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® Cream. Patients must be warned to use sunscreens (minimum SPF of 15) and protective clothing when using TAZORAC® Cream. Patients with sunburn should be advised not to use TAZORAC® Cream 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® Cream and ensure that the precautions outlined in the Information for Patients subsection are observed.

TAZORAC® Cream 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.

Some individuals may experience excessive pruritus, burning, skin redness or peeling. If these effects occur, the medication should either be discontinued until the integrity of the skin is restored, or the dosing should be reduced to an interval the patient can tolerate. However, efficacy at reduced frequency of application has not been established. Alternatively, patients with psoriasis who are being treated with the 0.1% concentration can be switched to the lower concentration. Weather extremes, such as wind or cold, may be more irritating to patients using TAZORAC® Cream.

Information for Patients: See attached Patient Package Insert.

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® Cream is begun.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
A long term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to 0.6 times that seen in a psoriatic patient treated with 0.1% tazarotene cream at 2 mg/kg/cm^2 over 35% body surface area in a controlled pharmacokinetic study. This estimated systemic exposure in rats was 2.0 times the maximum $AUC_{0\text{-}24h}$ in acne patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area.

In evaluation of photo co-carcinogenicity, median time to onset of tumors was decreased, and the number of tumors increased in hairless mice following chronic topical dosing with intercurrent exposure to ultraviolet radiation at tazarotene concentrations of 0.001%, 0.005%, and 0.01% in a gel formulation for up to 40 weeks.

A long-term topical application study of up to 0.1% tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1.0 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals; untreated control animals were not completely evaluated. Systemic exposure ($AUC_{0\text{-}12h}$) at the highest dose was 3.9 times that ($AUC_{0\text{-}24h}$) seen in a psoriatic patient treated with 0.1% tazarotene cream at 2 mg/cm^2 over 35% body surface area in a controlled pharmacokinetic study, and 13 times the maximum $AUC_{0\text{-}24h}$ in acne patients treated with 2 mg/cm ^{2} of tazarotene cream 0.1% over 15 % body surface area.

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

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 up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat would be equivalent to 0.6 times that observed in a psoriatic patient treated with 0.1% tazarotene cream at 2 mg/cm^2 over 35% body surface area in a controlled pharmacokinetic study, and 2.0 times the maximum $AUC_{0\text{-}24h}$ in acne patients treated with 2 mg/cm ^{2} of tazarotene cream 0.1% over 15 % body surface area.

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1.0 mg/kg/day tazarotene. That dose produced an $AUC_{0\text{-}24h}$ that was 1.9 times that observed in a psoriatic patient treated with 0.1% tazarotene cream at 2 mg/cm^2 over 35% body surface area, and 6.3 times the maximum $AUC_{0\text{-}24h}$ in acne patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15 % body surface area.

No effect on parameters of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through day 7 of gestation with oral doses of

tazarotene up to 2.0 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose (see CONTRAINDICATIONS). That dose produced an $AUC_{0\text{-}24h}$ that was 3.4 times that observed in a psoriatic patient treated with 0.1% tazarotene cream at 2 mg/cm^2 over 35% body surface area and 11 times the maximum $AUC_{0\text{-}24h}$ in acne patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area.

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. Based on data from another study, the systemic drug exposure in the rat would be equivalent to 0.6 times that observed in a psoriatic patient treated with 0.1% tazarotene cream at 2 mg/cm^2 over 35% body surface area, and 2.0 times the maximum $AUC_{0\text{-}24h}$ in acne patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area.

Pregnancy: Teratogenic Effects: Pregnancy Category X:
See CONTRAINDICATIONS section. Women of child-bearing potential should use adequate birth-control measures when TAZORAC® Cream 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 having a sensitivity down to at least 50 mIU/mL for hCG should be obtained within 2 weeks prior to TAZORAC® Cream therapy, which should begin during a normal menstrual period. There are no adequate and well-controlled studies in pregnant women. 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: Pharmacokinetics).

Nursing mothers:
After single topical doses of ^{14}C-tazarotene gel to the skin of lactating rats, radioactivity was detected in milk, suggesting that there would be transfer of drug-related material to the offspring via milk. It is not known whether this drug is excreted in human milk. Caution should be exercised when tazarotene is administered to a nursing woman.

Pediatric Use:
The safety and efficacy of tazarotene cream have not been established in patients with psoriasis under the age of 18 years or in patients with acne under the age of 12 years.

Geriatric Use: Of the total number of patients in clinical studies of tazarotene cream for plaque psoriasis, 120 were over the age of 65. No overall differences in safety or effectiveness were observed between these patients and younger patients. Currently there is no other clinical experience on the 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.

ADVERSE REACTIONS:

In human dermal safety studies, tazarotene 0.05% and 0.1% creams did not induce allergic contact sensitization, phototoxicity or photoallergy.

Psoriasis:
The most frequent adverse events reported with TAZORAC® 0.05% and 0.1% creams were limited to the skin. Those occurring in 10 to 23% of patients, in descending order, included pruritus, erythema, and burning. Events occurring in >1 to <10% of patients, in descending order, included irritation, desquamation, stinging, contact dermatitis, dermatitis, eczema, worsening of psoriasis, skin pain, rash, hypertriglyceridemia, dry skin, skin inflammation, and peripheral edema.

Tazarotene cream 0.1% was associated with a somewhat greater degree of local irritation than the 0.05% cream. In general, the rates of irritation adverse events reported during psoriasis studies with TAZORAC® 0.1% Cream were 1 to 4 percentage points higher than those reported for TAZORAC® 0.05% Cream.

Acne:
The most frequent adverse reactions reported during clinical trials with TAZORAC® Cream 0.1% in the treatment of acne, occurring in 10-30% of patients, in descending order included desquamation, dry skin, erythema, and burning sensation. Events occurring in 1 to 5% of patients included pruritus, irritation, face pain, and stinging.

OVERDOSAGE:
Excessive topical use of TAZORAC® Creams 0.05% and 0.1% may lead to marked redness, peeling, or discomfort (see PRECAUTIONS: General).

TAZORAC® Creams 0.05% and 0.1% are not for oral use. Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis A) or other retinoids. If oral ingestion occurs, the patient should be monitored and appropriate supportive measures should be administered as necessary.

DOSAGE AND ADMINISTRATION:

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% Cream, with strength increased to 0.1% if tolerated and medically indicated. Apply TAZORAC® Cream once per day, in the evening, to psoriatic lesions, using enough ($2mg/cm^2$) to cover only the lesion with a thin film. 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® Cream. Because unaffected skin may be more susceptible to irritation, application of TAZORAC® Cream to these areas should be carefully avoided.

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

HOW SUPPLIED:
TAZORAC® Cream is available in concentrations of 0.05% and 0.1%. It is available in a collapsible aluminum tube with a tamper-evident aluminum membrane over the opening and a white polypropylene screw cap, in 15g, 30g and 60g sizes.

	TAZORAC® Cream 0.05%	TAZORAC® Cream 0.1%
15 gm	NDC 0023-9155-15	NDC 0023-9156-15
30 gm	NDC 0023-9155-30	NDC 0023-9156-30
60 gm	NDC 0023-9155-60	NDC 0023-9156-60

Store at 25°C (77°F).
Excursions permitted from -5° to 30°C (23° to 86°F).

Rx only

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U.S. Patent Numbers 5,089,509 and 5,914,334
ALLERGAN
Irvine, California 92612, USA October 2001 (PM#) (copy code)
 Printed in USA

Pharmacist: Please cut or tear at dotted line and provide this patient package insert to your customer.

INFORMATION FOR PATIENTS
TAZORAC® (tazarotene) Cream 0.05%
TAZORAC® (tazarotene) Cream 0.1%

Read this leaflet carefully before you start to use your medicine. Read the information you get every time you get more medicine. There may be new information about the drug. This leaflet does not take the place of talks with your doctor. If you have any questions or are not sure about something , ask your doctor or pharmacist.

What is TAZORAC® Cream?
TAZORAC® (TAZ-or ac) Cream 0.05% and 0.1% are used to treat plaque psoriasis. In addition, TAZORAC® Cream 0.1% is used to treat acne. The active ingredient is tazarotene.

Who should not use TAZORAC® Cream?
Do not use TAZORAC® Cream if

- you are pregnant, plan to become pregnant, or may become pregnant because of the potential harm to an unborn child. Talk with your doctor about effective birth control if you are a woman who is able to become pregnant.
- you are breast feeding. We do not know if TAZORAC® Cream can pass through the milk to the baby. The potential harm to the baby is unknown.
- you have sunburn, eczema, or other continuing skin condition. If you have sunburn, wait until full recovery before using TAZORAC® Cream. TAZORAC® Cream may cause severe irritation if used on eczema.
- you are sensitive to sunlight, unless prescribed differently by your doctor.
- you take other drugs that increase your sensitivity to sunlight. These include medicines that are thiazides, tetracyclines, fluoroquinolones, phenothiazines, and sulfonamides. Therefore, tell your doctor if you take any medicines. This will help your doctor decide if you can take TAZORAC® Cream.
- you are allergic to the ingredients in TAZORAC® Cream. The active ingredient is tazarotene. The inactive ingredients are benzyl alcohol, carbomer 934P, carbomer l342, edetate disodium, medium chain triglycerides, mineral oil, purified water, sodium hydroxide, sodium thiosulfate, and sorbitan monooleate.

How should I use TAZORAC® Cream 0.1% or 0.05% for treatment of psoriasis?

- Read the directions on your prescription label carefully. Ask your doctor or pharmacist to explain anything you do not understand.
- Apply a thin film of the cream to your psoriasis areas once a day, in the evening.
- Carefully avoid application to apparently uninvolved skin. TAZORAC® Cream may be irritating to non-lesional skin.
- If you bathe or shower before using TAZORAC® Cream, be sure the skin is dry before you use TAZORAC® Cream.
- If you use a cream or lotion to soften or moisten your skin, apply TAZORAC® Cream after there is no more of the first cream or lotion on the skin.
- Wash your hands after applying the medicine, unless you are treating your hands for psoriasis. If the cream gets on areas you do not need to treat, wash it off.
- If you need to treat your hands, avoid hand contact with your eyes.
- Keep TAZORAC® Cream away from your eyes, eyelids, and mouth. If it gets in your eyes, wash them with large amounts of cool water. Contact your doctor if eye irritation continues.
- If you miss a dose, do not try to make it up. Continue with your normal schedule.
- If you are able to become pregnant, take a pregnancy test within 2 weeks prior to beginning to use TAZORAC® Cream to be sure you are not pregnant. If you have menstrual periods, begin taking TAZORAC® Cream during a normal menstrual period. These actions help assure that you are not pregnant when you begin use.
- If you become pregnant while using TAZORAC® Cream, stop use and contact your doctor right away.

Do not use more TAZORAC® Cream than instructed or more often than instructed. Using larger amounts of medicine than recommended will not lead to faster or better results and may cause more side effects.

Psoriasis plaques and scales will usually begin to improve in about one to two weeks. The redness may take longer to improve. Continue to use TAZORAC® Cream as directed by your doctor. Contact your doctor if your psoriasis becomes worse.

How should I use TAZORAC® Cream 0.1% for treatment of acne?

- If you are able to become pregnant, take a pregnancy test within 2 weeks prior to beginning to use TAZORAC® Cream to be sure you are not pregnant. If you have menstrual periods, begin taking TAZORAC® Cream during a normal menstrual period. These actions help assure that you are not pregnant when you begin use.
- If you become pregnant while using TAZORAC® Cream, stop use and contact your doctor right away.
- Read the directions on your prescription label carefully. Ask your doctor or pharmacist to explain anything you do not understand.
- Cleanse the face gently.
- After the skin is dry, apply a thin layer of TAZORAC® Cream once per day, in the evening, to the skin where acne lesions appear.
- Use enough to cover the entire affected area. In acne, the whole of the skin prone to acne should be treated.
- Follow your doctor's directions for other routine skin care and the use of make-up. Talk to your doctor about the use of sunscreens and cosmetics.
- Wash your hands after applying the medicine. If the cream gets on areas you do not need to treat, wash it off.
- Keep TAZORAC® Cream away from your eyes, eyelids and mouth. If it gets in your eyes, wash them with large amounts of cool water. Contact your doctor if eye irritation continues.
- If you miss a dose, do not try to make it up. Continue with your normal schedule.
- Continue to use TAZORAC® Cream as directed by your doctor even though you may not begin to see improvement for at least four weeks. Contact your doctor if your acne becomes worse.

What should I avoid while using TAZORAC® Cream?

- If you are able to become pregnant, take a pregnancy test 2 weeks before beginning to use TAZORAC® Cream to be sure you are not pregnant. If you have menstrual periods, begin applying TAZORAC® Cream during a normal menstrual period. These actions help assure that you are not pregnant when you begin use.
- If you become pregnant while using TAZORAC® Cream, stop use and contact your doctor right away.
- Because of increased sensitivity to sun, avoid sunlight as much as possible while using TAZORAC® Cream. Use protective clothing and sunscreens of at least SPF 15 during the day when using TAZORAC® Cream. Also, do not use sunlamps, unless prescribed differently by your doctor.
- If you are sensitive to sunlight or in the sun a lot on your job, be especially careful to protect your skin. Use sunscreens and protective clothing. Stay out of the sun as much as possible.
- Do not cover treated areas with dressings or bandages.
- Do not use TAZORAC® Cream on skin that has eczema. TAZORAC® Cream may cause severe irritation on skin with eczema. Do not use TAZORAC® Cream until your doctor has told you that your eczema is fully recovered.

- Carefully avoid application to apparently uninvolved skin in psoriasis. TAZORAC® Cream may be more irritating to non-lesional skin. All skin involved with acne should be treated.

What other precautions should I take in using TAZORAC® Cream?
Watch your reaction to TAZORAC® Cream carefully if you are also using other skin products with a strong drying effect or high amounts of 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.

If TAZORAC® Cream is swallowed, contact your doctor or a poison control center.

If you are taking Vitamin A supplements, tell your doctor about your Vitamin A dose. TAZORAC® and Vitamin A belong to the same class of chemicals.

What are the possible side effects of TAZORAC® Cream?
For patients with psoriasis, the most common side effects of TAZORAC® Cream 0.05% and 0.1% are itching, red skin and burning or stinging.

For patients with acne, the most common side effects of TAZORAC® Cream 0.1% are peeling, dry skin, red skin, and burning.

Tell your doctor if these side effects become problems. Your doctor may wish to adjust your dose of TAZORAC® Cream. However, effectiveness of TAZORAC® Cream when used less often than once a day has not been proven.

While you take TAZORAC® Cream, weather extremes, such as wind or cold, may irritate your skin more than usual.

Storage Information
Keep the tube tightly closed when not in use. Store the tube out of the reach of children, at a temperature of 77°F (25°C). Storage temperature can range from 23° to 86°F (-5° to 30°C) for short periods of time.

General advice about prescription medicines
This medicine is for your use only. Never give it to other people. It may harm them even if their skin problem appears to be the same as yours. Do not use TAZORAC® Cream for a condition for which it was not prescribed. Do not use TAZORAC® Cream after the expiration date on the bottom seal of the tube.

Where can I get more information about TAZORAC® Cream?
You can contact Allergan by calling 800-433-8871. You can ask your doctor or pharmacist for the information about TAZORAC® Cream that is written for health professionals.

Where can I get more information about psoriasis?
You can get information from:

The National Psoriasis Foundation
6600 SW 92nd Avenue, Suite 300, Portland, OR 97223-7195
Telephone (800) 723-9166, or on the World Wide Web at http://www.psoriasis.org

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/s/

Jonathan Wilkin
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