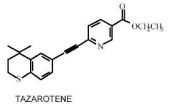
AVAGE - tazarotene cream
Allergan, Inc.

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

DESCRIPTION

AVAGE® Cream is a white cream and contains the compound tazarotene; this formulation of tazarotene cream is also marketed for the treatment of plaque psoriasis and acne vulgaris as TAZORAC® (tazarotene) Cream, 0.1%. 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 0.1% (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.
The mechanism of tazarotene action in the amelioration of fine wrinkling, facial mottled hypo- and hyperpigmentation, and benign facial lentigines is unknown. A histological study of tazarotene cream 0.1% applied in subjects with fine wrinkling and mottled hyperpigmentation but otherwise normal skin for 24 weeks showed that tazarotene cream was associated with significantly greater proportions of patients who had an increase from baseline in the number of granular cell layers and in epidermal edema. The clinical significance of these changes 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.
Tazarotene cream 0.1% was topically applied once daily to either the face (6 females and 2 males) or to 15% of body surface area (8 females and 8 males) over four weeks in patients with fine wrinkling and mottled hyperpigmentation. In the "face-only" dosing group, the maximum average C_{max} and $AUC_{0\text{-}24\ hr}$ values of tazarotenic acid occurred on Day 15 with mean ± SD values of C_{max} and $AUC_{0\text{-}24\ hr}$ of tazarotenic acid being 0.236 ± 0.255 ng/mL (N = 8) and 2.44 ± 1.38 ng·hr/mL (N = 8), respectively. The mean C_{max} and $AUC_{0\text{-}24\ hr}$ values of tazarotenic acid from patients in the 15% body surface area dosing group were approximately 10 times higher than those from patients in the face-only dosing group. The single highest C_{max} throughout the study period was 3.43 ng/ml on day 29 from patients in the 15% body surface area dosing group. Gender had no influence on the systemic bioavailability of tazarotenic acid.
Blood samples were collected from one of the two phase 3 studies to evaluate the systemic exposure following application of tazarotene cream 0.1% once daily for 24 weeks (double-blind period) followed by 28 weeks (open-label) under clinical conditions. The mean plasma tazarotenic acid concentrations following topical treatment with tazarotene cream 0.1% over 52 weeks ranged between 0.092 ± 0.073 ng/mL and 0.127± 0.142 ng/ml. The single highest observed tazarotenic acid concentration throughout the 52-week study was 0.705 ng/mL (observed at week 36). Systemic availability of tazarotenic acid was minimal and remained steady following once daily application of tazarotene cream 0.1% to the faces of patients in the study for up to 52 weeks.

Clinical Studies:

In two double-blind controlled studies in which tazarotene cream 0.1% was compared with its vehicle, applications were made once daily for 24 weeks to the facial skin of subjects with mild to severe fine wrinkling, facial mottled hypo- and hyperpigmentation, and benign facial lentigines due to overexposure to the sun. Treatment was as an adjunct to a comprehensive skin care and sun avoidance program which included use of sunscreens, protective clothing, and non-prescription emollient cream. At two to four week intervals the severity of fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines were graded on a scale of 0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe. The results of both studies demonstrate that tazarotene cream 0.1% was

significantly superior to its vehicle for fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines expressed as the proportion of subjects with an improvement of at least one grade from baseline.
Approximately 97% of subjects in clinical trials were white (Caucasian) with 80% of subjects in the clinical studies having Fitzpatrick skin type classifications I-III. The distribution of subject skin types were: Type I –12%; Type II – 26%; Type III – 40% and Type IV 22%. Patients with skin types V and VI were not studied. Insufficient non-white patients (Asian, Hispanic, or other) were studied to make an adequate determination of efficacy of AVAGE® Cream in such patients.
Percentage of Patients with Improvement in Fine Wrinkling after 24 Weeks of Treatment

	Study A		Study B	
	Taz. 0.1% N=283	Vehicle N=280	Taz. 0.1% N=284	Vehicle N=284
2 or more Grades Improvement	5%	1%	13%	5%
1 Grade Improvement	35%	15%	45%	18%
No Change	59%	83%	42%	76%
Worsened	1%	1%	0%	1%

Fine Wrinkling was graded on a 5-point scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) using a photonumeric guideline for investigators.

Percentage of Patients with Improvement in Mottled Hyperpigmentation after 24 Weeks of Treatment

	Study A		Study B	
	Taz. 0.1% N=283	Vehicle N=280	Taz. 0.1% N=284	Vehicle N=284
2 or more Grades Improvement	17%	1%	28%	10%
1 Grade Improvement	42%	17%	54%	30%
No Change	41%	80%	18%	59%
Worsened	<1%	3%	<1%	1%

Mottled Hyperpigmentation was graded on a 5-point scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) using a photonumeric guideline for investigators.

In the 24 week studies, efficacy was also demonstrated in mottled hypopigmentation and benign facial lentigines, which were secondary endpoints in those studies.
The duration of the mitigating effects on facial fine wrinkling, mottled hyper- and hypopigmentation, and benign facial lentigines following discontinuation of AVAGE® (TAZAROTENE) Cream 0.1% has not been studied.

INDICATIONS AND USAGE:
(To understand fully the indication for this product, please read the entire INDICATIONS AND USAGE section of the labeling.)
AVAGE® (TAZAROTENE) Cream 0.1% is indicated as an adjunctive agent for use in the mitigation (palliation) of facial fine wrinkling, facial mottled hyper- and hypopigmentation, and benign facial lentigines in patients who use comprehensive skin care and sunlight avoidance programs. **AVAGE® (TAZAROTENE) Cream 0.1% DOES NOTELIMINATEor PREVENT WRINKLES, REPAIR SUN-DAMAGED SKIN, REVERSE PHOTOAGING, or RESTORE MORE YOUTHFUL or YOUNGER SKIN.**

- AVAGE® (TAZAROTENE) Cream 0.1% has NOT DEMONSTRATED A MITIGATING EFFECT on significant signs of chronic sunlight exposure such as coarse or deep wrinkling, tactile roughness, telangiectasia, skin laxity, keratinocytic atypia, melanocytic atypia, or dermal elastosis.

- AVAGE® (TAZAROTENE) Cream 0.1% should be used under medical supervision as an adjunct to a comprehensive skin care and sunlight avoidance program that includes the use of effective sunscreens (minimum SPF of 15) and protective clothing.

- Neither the safety nor the effectiveness of AVAGE® (TAZAROTENE) Cream 0.1% for the prevention or treatment of actinic keratoses, skin neoplasms, or lentigo maligna has been established.

- Neither the safety nor the efficacy of using AVAGE® (TAZAROTENE) Cream 0.1% daily for greater than 52 weeks has been established, and daily use beyond 52 weeks has not been systematically and histologically investigated in adequate and well-controlled trials. (See **WARNINGS** section.)

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 2.4 and 26 times, respectively, the maximum AUC_{0-24h} in patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for fine wrinkling and mottled hyperpigmentation.
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 2.1 and 52 times, respectively, the maximum AUC_{0-24h} in patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for fine wrinkling and mottled hyperpigmentation.
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 6.7 times the maximum AUC_{0-24h} in patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for signs of fine wrinkling and mottled hyperpigmentation.
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. As a retinoid, tazarotene is a teratogenic substance, and it is not known what level of exposure is required for teratogenicity in humans. However, there may be less systemic exposure in the treatment of the face alone, due to less surface area for application (see CLINICAL PHARMACOLOGY: Pharmacokinetics).
There were thirteen reported pregnancies in patients who participated in clinical trials for topical tazarotene. Nine of the patients were found to have been treated with topical tazarotene, and the other four had been treated with vehicle. One of the patients who was treated with tazarotene cream elected to terminate the pregnancy for non-medical reasons unrelated to treatment. The other eight pregnant women who were inadvertently exposed to topical tazarotene during clinical trials subsequently delivered apparently 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.
AVAGE® 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 AVAGE® 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 AVAGE® Cream therapy, which should begin during a normal menstrual period (See also PRECAUTIONS: Pregnancy: Teratogenic Effects).
AVAGE® 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 AVAGE® 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 AVAGE® Cream therapy, which should begin during a normal menstrual period.

PRECAUTIONS:

General:
AVAGE® Cream should be applied only to the affected areas. For external use only. Avoid contact with eyes 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 AVAGE® Cream. Patients must be warned to use sunscreens (minimum SPF of 15) and protective clothing when using AVAGE® Cream. Patients with sunburn should be advised not to use AVAGE® 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 AVAGE® Cream and ensure that the precautions outlined in the Information for Patients subsection are observed.
AVAGE® 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. Weather extremes, such as wind or cold, may be more irritating to patients using AVAGE® Cream.
Some facial pigmented lesions are not lentigines, but rather lentigo maligna, a type of melanoma. Facial pigmented lesions of concern should be carefully assessed by a qualified physician (e.g. dermatologist) before application of AVAGE® (TAZAROTENE) Cream. Lentigo maligna should not be treated with AVAGE® (TAZAROTENE) Cream.

Information for Patients:
AVAGE® (TAZAROTENE) Cream 0.1% is to be used as described below when used for treatment of facial fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines, unless otherwise directed by your physician:

1. It is for use on the face.

2. Avoid contact with the eyes and mouth. AVAGE® (TAZAROTENE) Cream 0.1% may cause severe redness, itching, burning, stinging, and peeling.

3. Before applying AVAGE® (TAZAROTENE) Cream 0.1% once per day, gently wash your face with a mild soap. Make sure skin is dry before applying AVAGE® (TAZAROTENE) Cream 0.1%. Apply only a small pea sized amount (about 1/4 inch or 5 millimeter diameter) of AVAGE® (TAZAROTENE) Cream 0.1% to your face at one time. This should be enough to lightly cover the entire face.

4. For best results, you are advised that if emollients or moisturizers are used, they can be applied either before or after tazarotene cream, ensuring that the first cream or lotion has absorbed into the skin and dried completely.

5. In the morning, apply a moisturizing sunscreen, SPF 15 or greater.

6. AVAGE® (TAZAROTENE) Cream 0.1% is a serious medication. Do not use AVAGE® (TAZAROTENE) Cream 0.1% if you are pregnant or attempting to become pregnant. If you become pregnant while using AVAGE® (TAZAROTENE) Cream 0.1%, please contact your physician immediately.

7. Avoid sunlight and other medicines that may increase your sensitivity to sunlight. For the mitigation of fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines, avoidance of excessive sun exposure and the use of sunscreens with protective measures (hat, visor) are recommended.

8. AVAGE® (TAZAROTENE) Cream 0.1% does not remove or prevent wrinkles or repair sun-damaged skin.

Please refer to the Patient Package Insert for additional patient information.

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 AVAGE® 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 1.4 times the maximum $AUC_{0\text{-}24h}$ in patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for fine wrinkling and mottled hyperpigmentation.
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 7.8 times the maximum $AUC_{0\text{-}24h}$ in patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for fine wrinkling and mottled hyperpigmentation.
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 1.2 times the maximum

$AUC_{0\text{-}24h}$ in patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for fine wrinkling and mottled hyperpigmentation.
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 3.7 times the maximum $AUC_{0\text{-}24h}$ in patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for fine wrinkling and mottled hyperpigmentation.
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 6.7 times the maximum $AUC_{0\text{-}24h}$ in patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for signs of fine wrinkling and mottled hyperpigmentation.
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 1.2 times the maximum $AUC_{0\text{-}24h}$ in patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area for fine wrinkling and mottled hyperpigmentation.

Pregnancy:

Teratogenic Effects: Pregnancy Category X:
See CONTRAINDICATIONS section. Women of child-bearing potential should use adequate birth-control measures when AVAGE® 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 AVAGE® Cream therapy, which should begin during a normal menstrual period. There are no adequate and well-controlled studies in pregnant women. As a retinoid, tazarotene is a teratogenic substance, and it is not known what level of exposure is required for teratogenicity in humans. However, there may be less systemic exposure in the treatment of the face alone, due to less surface area for application (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 under the age of 17 years with facial fine wrinkling, facial mottled hypo- and hyperpigmentation, and benign facial lentigines.

Geriatric Use:
In the studies of facial fine wrinkling, facial mottled hypo- and hyperpigmentation, and benign facial lentigines , 44 male patients and 180 female patients out of the total population of 1131 patients were older than 65 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS:
In human dermal safety studies, tazarotene 0.05% and 0.1% creams did not induce allergic contact sensitization, phototoxicity or photoallergy.
The most frequent treatment-related adverse reactions (≥5%) reported during the clinical trials with AVAGE® (TAZAROTENE) Cream 0.1% in the treatment of facial fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines were limited to the skin. Those occurring in >10%, in descending order, included: desquamation, erythema, burning sensation, and dry skin. Events occurring in ≥1% to ≤10% of patients, in descending order included: skin irritation, pruritus, irritant contact dermatitis, stinging, acne, rash or cheilitis. Common adverse events observed in the clinical trials are presented in the following table:
TABLE OF ADVERSE EVENTS SEEN IN CLINICAL TRIALS WITH AVAGE® (TAZAROTENE) Cream 0.1%

Adverse Event	**AVAGE N=567**	**Vehicle N=564**
Desquamation	40%	3%
Erythema	34%	3%
Burning Sensation	26%	<1%
Dry skin	16%	3%

Irritation Skin	10%	1%
Pruritus	10%	1%
Irritant Contact Dermatitis	8%	1%
Stinging	3%	<1%
Acne	3%	3%
Rash	3%	1%
Cheilitis	1%	0%

A few patients reported adverse events at Week 0; however, for patients who were treated with AVAGE® the highest number of new reports for each adverse event was at Week 2.
When combining data from the two pivotal studies, 5.3% of patients in the tazarotene cream group and 0.9% of patients in the vehicle group discontinued due to adverse events.
Overall, 20/567 (3.5%) patients in the AVAGE® (TAZAROTENE) Cream 0.1% group and 16/564 (2.8%) patients in the vehicle group reported adverse events (including edema, irritation, and inflammation) directly related to the eye or eyelid. The majority of these conditions were mild.

OVERDOSAGE:
Excessive topical use of AVAGE® Cream 0.1% may lead to marked redness, peeling, or discomfort (see PRECAUTIONS: General). AVAGE® Cream 0.1% is 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 an interval the patient can tolerate, therapy can be resumed, or the 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.
Apply a pea-sized amount once a day at bedtime to lightly cover the entire face including the eyelids if desired. Facial moisturizers may be used as frequently as desired. If any makeup is present it should be removed before applying AVAGE® (TAZAROTENE) Cream 0.1% to the face. If the face is washed or a bath or shower is taken prior to application, the skin should be dry before applying the cream. If emollients or moisturizers are used, they can be applied either before or after application of tazarotene cream ensuring that the first cream or lotion has absorbed into the skin and has dried completely. Frequency of application should be closely monitored by careful observation of the clinical therapeutic response and skin tolerance. If the frequency of dosing is reduced, it should be noted that efficacy at a reduced frequency of application has not been established. The duration of the mitigating effects on facial fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines following discontinuation of AVAGE® (TAZAROTENE) Cream 0.1% has not been studied.

HOW SUPPLIED:
AVAGE® Cream is available in a concentrations of 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 a 30g size.
AVAGE® Cream 0.1%
30 gm NDC 0023-9236-30
Store at 25°C (77°F).
Excursions permitted from -5° to 30°C (23° to 86°F).
Rx only

U.S. Patent Number 5,089,509
9087X
ALLERGAN
Irvine, California 92612, USA May 2004

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

PATIENT INFORMATION
AVAGE® (TAZAROTENE) Cream 0.1%
Use only on the face.
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 the most important information I should know about AVAGE® Cream?

- **AVAGE® Cream can cause birth defects in unborn children of women who are pregnant when they use the product. If you are a woman who can become pregnant, you must not be pregnant when you start using AVAGE® Cream, and you must avoid pregnancy while you use it.** See the sections "Who should not use AVAGE® Cream?""How should I use AVAGE® Cream?" and "What should I avoid while using AVAGE® Cream?" for more information.

- Avoid sunlight and other medicines that may increase your sensitivity to sunlight (See "Who should not use AVAGE® Cream?" and "What should I avoid while using AVAGE® Cream?")

- AVAGE® Cream does not remove wrinkles or repair sun-damaged skin. (See "What is AVAGE® Cream?" for more details.)

What is AVAGE® Cream?
AVAGE® Cream is a prescription medicine that may reduce fine facial wrinkles and certain types of dark and light spots on your face.

- AVAGE® is for patients who are using a total skin care program and avoiding sunlight. AVAGE®Cream **does not** remove wrinkles, repair sun-damaged skin, reverse skin aging from the sun (photoaging), or bring back more youthful or younger skin. AVAGE® does not work for everyone who uses it. It may work better for some patients than for others.

- The active ingredient in AVAGE® Cream is tazarotene.

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

- **you are pregnant, plan to become pregnant, or may become pregnant.** AVAGE® Cream may harm your unborn child. Women who can become pregnant must have proof they are not pregnant from a reliable pregnancy test, done within 2 weeks before starting AVAGE® Cream. Talk with your doctor about effective birth control if you are a woman who is able to become pregnant.

- **you have sunburn or eczema**. If you have sunburn, wait until full recovery before using AVAGE® Cream. AVAGE® Cream may cause severe irritation if used on eczema. Wait until your doctor tells you your eczema has cleared up before starting AVAGE® treatment.

- **you are allergic to the ingredients in AVAGE® Cream.** The active ingredient is tazarotene. See the end of this information for a list of inactive ingredients.

Tell your doctor before using AVAGE® if

- you are breast feeding. We do not know if AVAGE® Cream can pass through your milk and harm the baby.

- you are sensitive to sunlight. AVAGE® may not be right for you or you may need extra protection from sunlight.

- you take certain other medicines, vitamins, and supplements that increase your sensitivity to sunlight. These include Vitamin A and medicines that are called thiazides, tertracyclines, fluoroquinolones, phenothiazines, and sulfonamides. Therefore, tell your doctor if you take any prescription or non-prescription medicines, vitamins, or supplements. This will help your doctor decide if you can take AVAGE® Cream.

- you take any other prescription or non-prescription medicines, supplements or vitamins. Some of them may make you more sensitive to sunlight.

How should I use AVAGE® Cream?

- If you are able to become pregnant, take a reliable pregnancy test within 2 weeks before beginning to use AVAGE® Cream to be sure you are not pregnant. If you have menstrual periods, start taking AVAGE® Cream during a normal menstrual period. These actions help assure you are not pregnant when you begin use.

- If you get pregnant while using AVAGE® Cream, stop use and contact your doctor right away.

- Use AVAGE® Cream only under the guidance of your doctor as part of a total skin care program in which you avoid sunlight. This program should include avoiding sunlight as much as possible, using clothing to protect you from sunlight, using sunscreens with an SPF of 15 or higher, and using face creams that add moisture to your skin.

- Follow these directions:

1. Use AVAGE® Cream once a day in the evening.
2. In the evening, gently wash your face with mild soap. Pat your skin dry and wait 20-30 minutes before applying AVAGE® Cream.
3. Be sure your skin is dry before you use AVAGE® Cream.
4. Apply only a pea-sized amount (about ¼ inch or 5mm wide) to your face at one time. This should be enough to cover the wrinkled or discolored areas lightly. You can include your eyelids, if desired.
5. Wash your hands after applying the medicine. If the cream gets on areas you do not need to treat, wash it off.
6. In the morning, apply a moisturizing sunscreen of SPF 15 or greater.

- You can use a cream or lotion to soften or moisten your skin before or after you apply AVAGE® Cream. Just be sure there is no more of the first cream or lotion on your skin and your skin is dry before you apply the second product.

- Keep AVAGE® Cream out of your eyes and mouth. If it gets in your eyes, wash them off with large amounts of cool water. Contact your doctor if irritation continues.

- If you miss a dose, do not try to make it up. Continue with your normal schedule.

- In general, you can use facial moisturizers, such as lotions, oils, and creams, as often as you want. However, follow your doctor's advice for routine skin care and for using makeup, moisturizers, and sunscreens.

- Do not use more AVAGE® 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.

- Wear clothing that protects your skin from the sun, and use non-prescription creams to help keep your skin soft.

- Watch your reaction to AVAGE® Cream carefully if you are also using other skin products or processes with strong drying or irritating effects. These include products with high amounts of alcohol, astringents, spices, lime peel, medicated or abrasive soaps, medicated shampoos, and permanent wave solution. Avoid electrolysis, hair depilatories, waxes, and other products or processes that may dry or irritate your skin.

- If AVAGE® Cream is swallowed, contact your doctor or call your poison control center right away.

What should I avoid while using AVAGE® Cream?

- Do not become pregnant while using AVAGE® Cream. See the section “How should I use AVAGE® Cream?” for more information. Use effective birth control while using AVAGE® Cream, and be sure you are not pregnant before you start using AVAGE® Cream.

- If you become pregnant while using AVAGE® Cream, stop use and contact your doctor right away.

- AVAGE® Cream makes you more sensitive to sunlight. It works only in patients who follow a sun avoidance program. Therefore, avoid sunlight as much as possible. Use cover-up clothing and sunscreens of at least SPF 15 during the day when using AVAGE® Cream. Also, do not use sunlamps, unless your doctor tells you to.

- 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.

- Avoid cosmetics, medicines and supplements that may make you more sensitive to sunlight, including Vitamin A.

What are the possible side effects of AVAGE® Cream?

AVAGE® can cause increased skin irritation and increased chance of sunburn.
While you use AVAGE® Cream, strong wind or cold may irritate your skin more than usual.
The most common side effects of AVAGE® (TAZAROTENE) Cream 0.1% are peeling, redness, burning, dryness, and irritated and itching skin.
These are not all the side effects possible with AVAGE® Cream. For more information, ask your doctor or pharmacist.
Tell your doctor if side effects become problems. Your doctor may adjust your dose of AVAGE® Cream. However, the effectiveness of AVAGE® Cream when used less often than once a day has not been proven.
What are the ingredients of AVAGE® 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.
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. Medicines are sometimes prescribed for conditions not mentioned in patient information leaflets. Do not use AVAGE®

Cream for a condition for which it was not prescribed. Do not use AVAGE® Cream after the expiration date on the bottom seal of the tube.

Where can I get more information about AVAGE® Cream?

You can contact Allergan by calling 800-433-8871. You can ask your doctor or pharmacist for the information about AVAGE® Cream that is written for health professionals.

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