

DATA SHEET

NAME OF MEDICINE

AVAGE[®] (tazarotene 1.0 mg/g) topical cream.

PRESENTATION

Topical cream: tazarotene 1.0 mg/g white to off white cream in collapsible aluminium tubes with tamper-evident opening and screw cap.

AVAGE[®] contains tazarotene (1.0 mg/g), benzyl alcohol, sodium thiosulfate, disodium edetate, liquid paraffin, medium chain triglycerides, carbomer 1342, sorbitan mono-oleate, carbomer 934P, sodium hydroxide and purified water.

USES

Actions

Tazarotene is a member of the acetylenic class of retinoids.

Tazarotene is a retinoid pro-drug which is converted to its active form, M1 ("tazarotenic acid"), 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 . Within the RAR family, "tazarotenic acid" shows selectivity for RAR β and RAR γ . "Tazarotenic acid" does not bind to or activate the RXR family of receptors. In addition, both cellular and *in vivo* studies show that, like tretinoin, tazarotene modulates cell differentiation and proliferation in a wide range of tissues.

Tazarotene has been shown to be inactive in a series of animal tests for effects on CNS activity, analgesia, body temperature, digestive tract function, respiratory function, circulatory function and kidney function.

Photodamage:

Ultraviolet irradiation from the sun has deleterious effects in human skin, including sunburn, immune suppression, cancer and premature aging (photoaging). Sunburn and immune suppression occur acutely in response to excessive exposure to the sun, whereas skin cancer and photoaging result from accumulated damage caused by repeated exposures. Skin cancer, the most prevalent form of cancer in humans, typically occurs in skin that is photoaged. Photoaged skin is characterized by wrinkles, laxity, uneven pigmentation, brown spots, and a leathery appearance. In contrast, chronologically aged skin that has been protected from the sun is thin and has reduced elasticity, but is otherwise smooth and unblemished.

Histological and ultrastructural studies have shown that alterations in photoaged skin are found in the dermal connective tissue. The extracellular matrix of the dermis is composed primarily of type I collagen, with lesser amounts of type III collagen, elastin, proteoglycans and fibronectin. Collagen fibres are responsible for the strength and resiliency of the skin. Dermal changes induced by ultraviolet irradiation are principally manifested histologically as the disorganisation of collagen fibrils and the accumulation of abnormal elastin-containing material. Biochemical evidence of connective tissue alterations in photoaged skin includes reduced levels of types I and III collagen precursors and cross-links, an increased ratio of type III to type I collagen, and an increased level of elastin.

The mechanism of tazarotene action in photodamage is unknown. Improvement in the appearance of photodamaged patients appears to occur in association with increased epidermal thickness, decrease in percentage area of melanin, and compaction of the stratum corneum. A study of the histological safety of tazarotene cream 1.0 mg/g applied

to photodamaged but otherwise normal skin for 24 weeks showed that tazarotene is not associated with the formation or worsening of keratinocytic atypia or melanocytic atypia. Tazarotene cream 1.0 mg/g was associated with significant improvements in the distribution/severity of melanocytic atypia when compared with vehicle. Furthermore, tazarotene cream 1.0 mg/g was shown to be associated with (i) significant increases in epidermal thickness and (ii) significantly greater proportions of patients who showed an increase from baseline in the number of granular cell layers. Tazarotene cream 1.0 mg/g was also associated with significantly greater proportions of patients who showed an increase from baseline in epidermal edema. The clinical significance of these changes is unknown.

PHARMACOKINETICS

Absorption and half-life

When tazarotene was administered intravenously to healthy volunteers (N=8), it had a half-life of 6 hours. The half-life of the active metabolite, tazarotenic acid, was 14 hours.

The half-life of tazarotenic acid following topical application of tazarotene gel or cream was similar in normal subjects and patients with psoriasis or acne, approximately 18 hours.

In a pharmacokinetic study in psoriatic patients, tazarotene 0.1% cream was applied once daily to the psoriatic lesions (5-35% of body surface area) at a standard (clinical) dosing of 2 mg/cm² or an exaggerated dosing of 10 mg/cm² to different groups of patients for 14 days. At 14 days, the systemic bioavailability was approximately 3% and 2% of the applied dose, respectively.

In the same pharmacokinetic study, the mean (range) plasma tazarotenic acid C_{max} value was 2.31 ng/ml (range 1.02 – 6.85 ng/ml) at the standard dosing rate. Values of C_{max} at the exaggerated dosing level were higher, but not proportionately so. Values of C_{max} in a pharmacokinetic study in acne patients were lower than in the psoriatic study, even at an exaggerated dosing schedule.

Following topical application, tazarotene rapidly undergoes esterase hydrolysis to form its active metabolite, tazarotenic acid. Little parent compound can be detected in the plasma. Across all pharmacokinetic and therapeutic drug level monitoring studies, there is no evidence to suggest that plasma tazarotenic acid concentrations are dependent on gender, age, or body weight.

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

Metabolism: After tazarotene gel was topically applied to healthy subjects, ¹⁴C-tazarotene underwent esterase hydrolysis to produce tazarotenic acid, and oxidative metabolism to inactive sulfoxide and sulfone derivatives. Secondary metabolites of tazarotenic acid (the sulfoxide, the sulfone and an oxygenated derivative of tazarotenic acid) were detected in human urine and faeces.

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

Excretion: Tazarotene was not excreted unchanged. After dermal dosing with ¹⁴C-tazarotene gel under occlusion to healthy volunteers, 2.6% of the dose was excreted in urine and 2.7% of the dose was excreted in faeces over a 7-day period. Following a topical non-occluded dose to psoriatic patients, 0.3% of the dose was excreted in the urine and 0.4% excreted in the faeces. Greater than 75% of total drug excretion was completed within

72 hours after removal of residual gel from the skin surface using gauze pads wetted with isopropanol. There was equal excretion of the radioactivity in urine and faeces.

INDICATIONS

For the topical treatment of the signs and symptoms of premature aging of the skin due to overexposure to the sun.

DOSAGE AND ADMINISTRATION

For dermatological (cutaneous) use only.

General: Application may cause a transitory feeling of burning or stinging. If irritation becomes problematic, the dosage may be altered by temporarily reducing the frequency of application. Efficacy has not been established for less than once-daily dosing frequencies. Application should be closely monitored by careful observation of the clinical therapeutic response and skin tolerance.

Apply AVAGE[®] cream once per day, in the evening, using a pea-sized amount to lightly cover the entire face. Facial moisturisers may be used as frequently as desired. If any makeup is present it should be removed before applying AVAGE[®] cream 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 moisturisers are used, they can be applied either before or after tazarotene cream, but whichever one is applied first should be allowed to absorb into the skin before the next one is applied.

CONTRAINDICATIONS

AVAGE[®] cream is contraindicated in individuals who have shown hypersensitivity to any of its components. AVAGE[®] cream is contraindicated in pregnancy.

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

WARNINGS AND PRECAUTIONS

General:

AVAGE[®] cream should only be applied to affected areas. For external use only. Avoid contact with eyes and mouth. If contact with eyes occurs, rinse thoroughly with water.

Some individuals may experience excessive itching, 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 adjusted to a level or interval the patient can tolerate.

Patients should be advised to avoid excessive exposure to UV light (use of a solarium or PUVA therapy) during treatment with AVAGE[®] cream.

Patients should be warned to use sunscreens (minimum SPF of 15) and protective measures (hat, visor) 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.

AVAGE[®] cream should be administered with caution if the patient is also taking drugs known to be photosensitisers (eg. thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented photosensitivity.

Weather extremes, such as wind or cold, may be more irritating to patients using AVAGE® cream.

Use in pregnancy: Category D.

Teratogenic effects: 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.

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.

In view of the condition that AVAGE® will be used to treat, topical AVAGE® cream should not be used by women who are pregnant or who intend to become pregnant during treatment. Female patients should be advised to use adequate contraceptive measures during treatment.

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.

There have been spontaneous post-marketing reports of pregnancy occurring during use of topical tazarotene (gel and cream). No reports of teratogenicity or other adverse pregnancy outcomes have been attributed to use of the drug.

Tazarotene 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 foetus. Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when tazarotene is used.

Use in Lactation: Although it is not known whether tazarotene is excreted in human milk, ¹⁴C-tazarotene has been detected in the milk of nursing rats dosed topically with tazarotene gel. As many drugs are excreted in human milk, caution should be exercised if tazarotene cream is administered to a nursing woman.

Impairment of Fertility. No impairment of fertility occurred in rats when males were treated for 70 days prior to mating and females were treated for 14 days prior to mating and continuing through gestation and lactation with maximum tolerated dermal doses of 0.125 mg/kg/day.

Mutagenesis/Carcinogenesis:

Tazarotene was found to be non-mutagenic and non-clastogenic in a battery of in vitro and in vivo tests.

Long term studies of tazarotene following topical applications in mice (88 weeks) and oral administration to rats (104 weeks), showed no indications of increased risks related to treatment.

A tazarotene gel dose-related reduction in median time to onset of ultraviolet radiation-induced tumour formation in hairless mice has been observed. Although this effect was accompanied by marked skin irritation which may be a contributing factor, the exact cause of the tumour formation is unknown.

Paediatric Use: The safety and efficacy of tazarotene in the treatment of signs and symptoms of premature aging of the skin due to overexposure to the sun have not been established in patients under the age of 18 years.

ADVERSE EFFECTS

Pre-marketing clinical trials:

In human dermal safety studies, tazarotene 1.0 mg/g was moderately irritating under the exaggerated conditions of the studies but did not induce contact sensitisation, phototoxicity or photoallergy.

In the two pivotal clinical trials 567 patients were exposed to tazarotene 1.0 mg/g with the most frequently reported treatment-related adverse events being desquamation (39.3%), erythema (33.2%), burning sensation (24.9%) and dry skin (15.9%). The most frequently reported adverse events were in the skin and appendages group with 71.3% of patients reporting in the tazarotene group and 11.3% of the patients in the vehicle group.

The following undesirable effects were reported as definitely, probably or possibly related to treatment were reported during clinical trials with AVAGE[®] cream. Most were in the skin and appendages group and were mild to moderate in severity.

Very common (>10%):

Skin and appendages: desquamation, erythema, burning sensation, dry skin.

Common (>1 and <10%):

Skin and appendages: skin irritation, pruritus, irritant contact dermatitis, stinging, acne and rash.

Digestive system: cheilitis

Metabolic and nutritional: oedema

Uncommon (<1%):

Skin and appendages: skin tightness, vesiculobullous rash, herpes simplex, papules, skin oedema, skin pain, dermatitis, skin discolouration, skin erosion, skin hypertrophy, skin reaction, sun-induced erythema, excoriation, fixed eruption, rosacea, skin inflammation, bleeding skin, hair disorder, seborrhoea, urticaria.

Special senses: eye irritation, eyelid oedema, eye oedema, hordeolum, allergic conjunctivitis, conjunctivitis, eyelid blisters, eyelid erythema, eyelid inflammation.

Body as a whole: pain, accidental injury, face pain and infection.

Cardiovascular: vasodilatation

Haemic and lymphatic: petechiae

Respiratory: pharyngitis

Urogenital system: metrorrhagia

Post-marketing experience:

There have been isolated reports of patients using AVAGE[®] experiencing bullous eruptions (with or without fever).

INTERACTIONS

Concomitant dermatological 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.

OVERDOSAGE

Excessive topical use of AVAGE[®] cream may lead to marked redness, peeling or discomfort.

Inadvertent 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.

PHARMACEUTICAL PRECAUTIONS

Storage: Store at or below 25°C.

Shelf life: 3 years.

Keep tube tightly closed when not in use.

UNUSED CONTENTS OF THE TUBE SHOULD BE DISCARDED 12 MONTHS AFTER OPENING.

MEDICINE CLASSIFICATION

Prescription Medicine

PACKAGE QUANTITIES

3.5 g (professional sample), 15g, 30g and 60g tubes.

FURTHER INFORMATION

CLINICAL STUDIES

In two 24-week vehicle-controlled clinical studies, tazarotene cream 1.0 mg/g was significantly more effective than vehicle in reducing the severity of fine wrinkling, mottled hyperpigmentation, elastosis, lentigines, pore size, and irregular depigmentation and in showing improvement in Overall Integrated Assessment (OIA) of Photodamage. (OIA is an assessment by the investigator of the overall severity of facial photodamage).

The incidence rates of patients who improved by one grade or more from baseline were significantly higher for tazarotene cream 1.0 mg/g than vehicle as early as Week 2 for mottled hyperpigmentation and Week 8 for fine wrinkling. Improvement for lentigines was observed as early as Week 4, elastosis and pore size as early as Week 12, and irregular depigmentation as early as Week 16. Improvement in OIA was observed as early as Week 8. Tazarotene cream 1.0 mg/g was also associated with a significantly higher treatment success rate, (based upon the numbers of patients with a moderate response to treatment or better, than vehicle cream).

The distribution of patients' overall self-assessment of photodamage scores in the tazarotene-treated group demonstrated significantly greater improvement from baseline

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

Number (%) of Patients with Clinical Improvement by Visit in Fine Wrinkling and Mottled Hyperpigmentation (ITT Population)

Study week	Study 1				Study 2			
	Fine Wrinkling		Mottled Hyperpigmentation		Fine Wrinkling		Mottled Hyperpigmentation	
	Taz 0.1%	Vehicle	Taz 0.1%	Vehicle	Taz 0.1%	Vehicle	Taz 0.1%	Vehicle
	N=283	N=280	N=283	N=280	N=284	N=284	N=284	N=284
2	1.9%	0.8%	6.7%*	0.8%	4.2%*	1.2%	11.6%*	3.5%
4	8.2%	5.2%	22.1%*	6.0%	13.1%*	4.6%	31.5%*	14.9%
8	16.4%*	10.0%	38.9%*	12.2%	27.4%*	12.4%	56.8%*	24.4%
12	23.6%*	11.7%	48.4%*	16.8%	39.8%*	14.8%	69.5%*	32.5%
16	33.5%*	14.1%	56.3%*	18.5%	49.2%*	17.5%	78.1%*	38.3%
20	38.3%*	17.7%	59.2%*	20.9%	59.2%*	23.0%	84.9%*	42.6%
24	44.3%*	17.3%	63.5%*	19.3%	63.0%*	24.2%	86.6%*	42.9%
study endpoint	40.3%**	16.1%	59.0%*	17.9%	58.1%*	22.5%	81.7%*	39.4%

Clinical improvement is an improvement from baseline by at least 1 grade.

Study endpoint = last observation of each patient.

Taz = tazarotene cream. N = number of patients at baseline; subsequent sample sizes may vary due to missing values.

* Denotes statistically significant difference compared with vehicle, using Cochran-Mantel-Haenszel test.

** Denotes statistically significant difference at study endpoint, using Hochberg adjustment for multiplicity.

Number (%) of Patients with Clinical Improvement in Secondary Efficacy Variables^a at Study Endpoint

Variable	Study 1			Study 2		
	Taz 0.1%	Vehicle	p-value ^b	Taz 0.1%	Vehicle	p-value ^b
	N=283	N=280		N=284	N=284	
Lentigines	50.2%	15.7%	<0.001	54.6%	23.9%	<0.001
Elastosis	20.5%	4.6%	<0.001	28.5%	10.9%	<0.001
Tactile Roughness	44.2%	34.6%	0.005	44.4%	37.3%	0.055
Coarse Wrinkling	13.1%	5.7%	0.002	14.4%	10.2%	0.075
Telangiectasia	14.8%	11.8%	0.283	15.5%	13.0%	0.333
Pore Size	27.2%	9.6%	<0.001	39.8%	18.0%	<0.001
Irregular Depigmentation	19.8%	9.3%	<0.001	22.5%	13.4%	0.002
OIA	32.6%	8.2%	<0.001	53.5%	16.5%	<0.001

Key: a: Clinical improvement is an improvement from baseline of at least 1 grade.

b: P values based on CMH test.

N = number of patients at baseline; subsequent sample sizes may vary due to missing values.

Study endpoint = last observation of each patient

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