

DATA SHEET

NAME OF MEDICINE

ZORAC® topical gel [tazarotene].

PRESENTATION

Gel: 0.1% and 0.05% translucent, aqueous gel in collapsible aluminium tubes with tamper-evident opening and screw cap.

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 the skin. “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.

Among its specific pharmacological activities, topical tazarotene blocks induction of epidermal ornithine decarboxylase (ODC) activity in the hairless mouse by the tumour promoter 12-O-tetradecanoylphorbol 13-acetate (TPA). ODC catalyses the first step in polyamine synthesis and is associated with cell proliferation and hyperplasia; both ODC activity and hyperplasia are elevated in the epidermal layer of the psoriatic plaque.

In cultured human keratinocytes, tazarotene suppresses expression of MRP8, an inflammatory marker present in psoriatic epidermis at high levels and blocks the synthesis of cornified envelopes and envelope precursors. Cornified envelope build-up is an element of psoriatic scale and acne comedo formation. Tazarotene, therefore, has multiple effects on keratinocyte differentiation and proliferation, as well as on inflammatory processes which contribute to the pathogenesis of psoriasis and acne.

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.

Psoriasis: The exact mechanism of tazarotene action in psoriasis is unknown. Improvements in psoriatic patients appears to occur in association with restoration of normal cutaneous morphology, reduction of the inflammatory markers ICAM-1 and HLA-DR, and the diminution of markers of epidermal hyperplasia and abnormal differentiation such as elevated keratinocyte transglutaminase, involucrin and keratin.

Acne: The exact mechanism of action of tazarotene in acne is unknown. Directly or indirectly, tazarotene topical gel is thought to act against several of the factors that contribute to acne vulgaris. Animal and *in vitro* studies suggest that a primary mechanism of action may be to normalize follicular keratinisation and decrease the coherence of follicular keratinocytes, thus achieving a comedolytic effect against existing comedones and preventing the development of new microcomedones. Tazarotene also has activity against inflammatory acne.

Pharmacokinetics

Absorption: Controlled pharmacokinetic studies with 0.1% ¹⁴C Tazarotene gel indicate less than 1% of the dose is absorbed when applied topically (unoccluded) to psoriatic plaques.

After a 7-day dermal dosing period with tazarotene 0.1% gel to normal skin over 20% of the body surface area (0.1 mg/kg/day), the mean maximum plasma concentration was 0.72 ± 0.58 ng/mL at 9 hours and the area under the plasma concentration time curve over a 24-hour time period was 10.1 ± 7.2 ng hr/mL.

During clinical trials for treatment of acne and psoriasis with 0.1% and 0.05% gels, plasma concentrations of tazarotene were detected sporadically in only 2% of patients at very low levels (<0.23 ng/mL).

In the same studies, plasma concentrations of the primary metabolite “tazarotene acid” ranged from <0.05 ng/mL (below the limit of quantitation) to 6.1 ng/mL. The majority of patients with detectable levels of “tazarotene acid” had concentrations less than 1 ng/mL. Nine per cent of patients had plasma concentrations of “tazarotene acid” greater than 1 ng/mL, but none experienced any treatment-related systemic adverse events.

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

Distribution: Dosing topically under occlusion, on normal skin, approximately 5% and 0.5% of the dose were recovered in the stratum corneum and epidermis-dermis layers, respectively, whereas in psoriatic patients, 1.4% of the dermal dose applied without occlusion was recovered in the stratum corneum and 2.4% in the epidermis-dermis layers.

Tazarotene and “tazarotenic acid” are extensively bound (more than 99%) to human plasma albumin.

Metabolism: after topical administration to healthy subjects, ¹⁴C-tazarotene underwent esterase hydrolysis to “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. Following a topical nonoccluded dose of 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 drug removal, with equal excretion of the radioactivity in urine and faeces.

Indications

For the topical treatment of plaque psoriasis. For the topical treatment of acne vulgaris.

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 choosing the lower drug concentration or temporarily reducing the frequency of application.

For psoriasis:

Apply ZORAC® once a day, in the evening, to psoriatic lesions, using enough to cover only the lesions with thin film. If a bath or shower is taken prior to application, the skin should be dry before applying the gel. If emollients are used, they should be applied and allowed to absorb into the skin before application of ZORAC®. Because unaffected skin may be more susceptible to irritation, application of tazarotene to these areas should be carefully avoided. In clinical trials, ZORAC® was used for a period of 12 weeks.

For acne:

Cleanse the skin thoroughly. After the skin is dry, apply a thin film of ZORAC® once a day, in the evening, to the skin where acne lesions appear. Use enough to cover the entire affected area. In clinical trials, ZORAC® was used for a period of 12 weeks.

CONTRAINDICATIONS

ZORAC® is contraindicated in individuals who have shown hypersensitivity to any of its components. ZORAC® is contraindicated in pregnancy.

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

WARNINGS AND PRECAUTIONS

ZORAC® should only be applied to affected areas. Avoid contact with eyes, eyelids 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.

The safety of use over more than 20% of body surface area has not been established.

Patients should be advised to avoid excessive exposure to UV light (use of a solarium or PUVA therapy) during treatment with ZORAC®. Treated areas should be protected when exposed to sunlight.

ZORAC® 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 photosensitisation.

ZORAC® gel is presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery.

Use in pregnancy: Pregnancy Category D.

Tazarotene was found to be non-teratogenic and non-foetotoxic when applied topically at the maximum tolerable doses in rats and rabbits. However tazarotene, like other retinoids, is known to be teratogenic when administered at sufficiently high oral doses. In view of the condition that ZORAC® will be used for treatment, topical ZORAC® gel should not be used by women who are pregnant or who intend to become pregnant during treatment.

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 ZORAC® gel is used.

The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered.

Use of Lactation: It is not known whether this drug is excreted in human milk. As many drugs are excreted in human milk, caution should be exercised if tazarotene is administered to a nursing woman.

Impairment of Fertility (Segment 1): 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 and oral administration to rats showed no indications of increased carcinogenic risks related to treatment.

Marked skin irritation, possibly contributing to enhancement of photocarcinogenesis, was observed in hairless mice following chronic dermal dosing with intercurrent exposure to ultraviolet radiation at tazarotene concentrations of 0.001%, 0.005% and 0.01% for up to 40 weeks.

Relevance of these studies in humans has not been established.

Paediatric Use: The safety and efficacy of tazarotene have not been established in patients under the age of 12 years.

ADVERSE EFFECTS

Pre-marketing clinical trials:

Psoriasis:

The most frequent adverse reactions ($\geq 5\%$) reported during clinical trials with ZORAC® in the treatment of psoriasis included pruritus, burning/stinging, erythema, skin irritation, skin pain, worsening of psoriasis and rash. Reported less frequently (1% - 5%) were desquamation, contact irritant dermatitis, dry skin, skin inflammation, local oedema and fissuring of the skin. The following reactions were reported rarely ($<1\%$) by study subjects: bleeding, excoriation, skin discharge, vasodilation, skin erosion and increased skin fragility. The incidence and severity of adverse reactions appear to be dose related.

Acne:

The most frequent adverse reactions ($\geq 5\%$) reported during initial clinical trials with ZORAC® in the treatment of acne included burning/stinging, desquamation, dry skin, erythema and pruritus.

Reported less frequently (1-5%) were skin irritation and skin pain.

The following reactions were reported rarely ($<1\%$) by subjects: skin tightness, fissuring of the skin, cheilitis, skin discolouration, worsening of acne, contact irritant, dermatitis and localised oedema.

The incidence and severity of adverse reactions appear to be dose related, and dryness can be simply controlled by the use of a non-comedogenic moisturiser.

In human dermal safety studies, tazarotene 0.1% and 0.05% gels were moderately irritating under exaggerated conditions of the studies but did not induce contact sensitisation, phototoxicity or photoallergy.

Post-marketing experience:

There have been isolated reports of patients using ZORAC® experiencing bullous eruptions (with or without fever). In postmarketing comparative clinical trials, ZORAC® was as well tolerated as other retinoid treatments, with adverse effects occurring only at trace levels (average severity less than mild).

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 ZORAC® is begun.

OVERDOSEAGE

Excessive topical use of ZORAC® 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.

PHARMACEUTICAL PRECAUTIONS

Storage: Store at or below 25°C. DO NOT REFRIGERATE OR FREEZE.

Shelf life: 36 months in the unopened container.

Once the tube has been opened, it may be used for up to 12 months. After that, any unused contents should be discarded.

Keep tube tightly closed when not in use.

MEDICINE CLASSIFICATION

Prescription medicine

PACKAGE QUANTITIES

10g or 15g (Physician's sample), 30g and 100g tubes.

FURTHER INFORMATION

Psoriasis Clinical trials:

In two vehicle-controlled clinical studies, tazarotene 0.1% and 0.05% gels were significantly more effective than vehicle in reducing the severity of the clinical signs of plaque psoriasis. Tazarotene gels demonstrated effectiveness as early as 1 week after starting treatment, and initial treatment success (good or excellent response or complete clearing) was reached significantly earlier than vehicle.

Treatment success rates with the 0.1% gel were generally superior (numerically) to those with the 0.05% gel. However, tazarotene 0.1% was associated with a somewhat greater degree of local irritation than the 0.05% gel. In one of these studies, patients were also evaluated for 12 weeks following cessation of therapy and it was found that subjects treated with the 0.1% and 0.05% tazarotene gels continued to show a therapeutic effect during the 12 week post-treatment period.

Acne Clinical Trials:

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

In a 12 week study comparing tretinoin 0.025% gel once daily to tazarotene 0.1% gel once daily, tazarotene was significantly more effective in reducing non-inflammatory acne lesions, and tended to be more effective in reducing inflammatory acne lesions than tretinoin.

Ingredients:

ZORAC® contains tazarotene (0.5 mg/g and 1 mg/g) as the active ingredient. It also contains benzyl alcohol, ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene, edetate disodium, polyethylene glycol 400, hexylene glycol, carbomer 934P, tromethamine, poloxamer 407, polysorbate 40 and purified water.

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