DATA SHEET

NAME OF MEDICINE
ZORAC® (tazarotene 1.0 mg/g and 0.5 mg/g) topical cream.

PRESENTATION
Topical cream: tazarotene 1.0 mg/g and 0.5 mg/g white to off white cream in collapsible aluminium tubes with tamper-evident opening and screw cap.

ZORAC® contains tazarotene (0.5 mg/g and 1.0 mg/g), benzyl alcohol, sodium thiosulfate, disodium edetate, liquid paraffin, medium chain triglycerides, carbomer 1342, sorbitan monoleate, Carbomer Homopolymer Type B, 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. "Tarazotenic acid" binds to and regulates gene expression through all three members of the RAR family of retinoid nuclear receptors, RARα, RARβ and RARγ. Within the RAR family, "tazarotenic acid" shows selectivity for RARβ and RARγ. "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.

Psoriasis: The exact mechanism of tazarotene action in psoriasis is unknown. Improvement 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 keratin16.

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, and in the psoriatic plaque, 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 buildup is an element of psoriatic scale formation. Tazarotene also induces the expression of TIG3 (tazarotene-induced gene 3), a tumour suppressor, which may inhibit epidermal hyperproliferation in treated plaques. Tazarotene, therefore, has multiple effects on keratinocyte differentiation and proliferation, as well as on inflammatory processes which contribute to the pathogenesis of psoriasis.

Acne: Although the exact mechanism of action of tazarotene in acne remains undefined, retinoids are recognised as fundamental mediators of cell differentiation and proliferation.
Directly or indirectly, tazarotene is thought to act against several of the factors that contribute to acne vulgaris. Its primary mechanism of action is to normalise the keratinisation pattern in acne and decrease the coherence of follicular keratinocytes, thus achieving a comedolytic effect against existing comedones and preventing the development of new microcomedones. Tazarotene may also have direct or indirect activity against inflammatory acne.

**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 plaque psoriasis. For the topical treatment of acne vulgaris (1.0 mg/g concentration only).

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 (in psoriasis only) or temporarily reducing the frequency of application (in psoriasis and acne). 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.

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.

For psoriasis: Apply ZORAC® once a day, in the evening, to psoriatic lesions, using enough (2mg/cm²) to cover only the lesions with a thin film.

For acne: Cleanse the skin thoroughly. After the skin is dry, apply a thin film of ZORAC® 1.0 mg/g once a day, in the evening to the skin where acne lesions appear. Use enough to cover the entire affected area. If any makeup is present it should be removed before applying ZORAC® to the face.

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

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

WARNINGS AND PRECAUTIONS

General:
ZORAC® cream should only be applied to affected areas. For external use only. 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.

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

Patients should be warned to use sunscreens (minimum SPF of 15) and protective clothing when using ZORAC® cream. Patients with sunburn should be advised not to use ZORAC® 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 ZORAC® cream.
ZORAC® 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 ZORAC® cream.

Use in pregnancy: Category D.
Teratogenic effects: In rats, tazarotene 0.5 mg/g gel administered topically during gestation days 6 through 17 at 0.25 mg/kg/day resulted in reduced foetal 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 ZORAC® cream will be used to treat, topical ZORAC® 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 ZORAC® (tazarotene) gel and cream 0.5 mg/g, 1.0 mg/g. 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 tumour formation is unknown.

Exposure of tazarotene cream treated areas to the sun should be avoided.

**Paediatric Use:** The safety and efficacy of tazarotene in psoriasis have not been established in patients under the age of 18 years. The safety and efficacy of tazarotene in acne have not been established in patients under the age of 12 years.

**ADVERSE EFFECTS**

**Pre-marketing clinical trials:**
In human dermal safety studies, tazarotene 1.0 mg/g and 0.5 mg/g creams were moderately irritating under the exaggerated conditions of the studies but did not induce contact sensitisation, phototoxicity or photoallergy.

**Psoriasis:**
In the two pivotal clinical trials 432 and 428 patients were exposed to tazarotene creams 1.0 mg/g and 0.5 mg/g strengths respectively. The most frequently reported treatment-related adverse events in both strengths were pruritus (22.7%), erythema (16.0%), burning skin (13.7%) and skin irritation (9.3%). The most frequently reported adverse events were in the skin and appendages group with 55.3% of patients reporting in the 0.5 mg/g tazarotene group, 47.7% reporting in the 1.0 mg/g group and 25.1% of the patients reporting in the vehicle group.

The following undesirable effects were reported as definitely, probably or possibly related to treatment were reported during clinical trials with ZORAC® cream. The majority of the events during the treatment period were mild to moderate in severity.

**Very common (>10%):**
*Skin and appendages:* pruritus, erythema and burning skin.

**Common (>1 and <10%):**
*Skin and appendages:* irritation skin, desquamation, stinging skin, irritant contact dermatitis, dermatitis, pain skin, psoriasis worsened, eczema, rash, hypertriglyridaemia, dry skin and skin inflammation.

*Metabolic:* peripheral oedema.
Uncommon (<1%):
Skin and appendages: skin fissure, excoriation, bleeding skin, skin discharge, skin erosion, bullous vesicular rash, atopic dermatitis, pustular rash, rosacea, skin reaction, skin tightness, skin discolouration and urticaria.

Body: pain, arm pain, leg pain, infection, knee pain, abdominal pain, chills, headache, pelvic pain, pruritus scalp and foot pain.

Metabolic and nutritional: oedema, SGOT increased, SGPT increased, hypercholesterolaemia, hyperglycemia and biliary stasis.

Special senses: eyelid erythema, eyelid irritation, eye irritation and ear infection.

Digestive: mouth ulcer and nausea.

Musculoskeletal: myalgia and joint disease.

Nervous system: insomnia and tingling.

In psoriasis it may be difficult to distinguish some of the common adverse events of tazarotene (such as pruritus, erythema, burning skin, skin irritation and desquamation) from the signs and symptoms of the disease.

Acne:
In the two pivotal clinical trials 424 patients were exposed to the tazarotene 1.0 mg/g with the most frequently reported treatment-related adverse events being desquamation (29.2%), dry skin (26.9%), erythema (20.5%) and burning sensation on the skin (13.9%).

The most frequently reported adverse events were in the skin and appendages group with 54.2% of patients reporting in the tazarotene 1.0 mg/g group and 9.7% of the patients reporting in the vehicle group.

The following undesirable effects definitely, probably or possibly related to treatment were reported during clinical trials with ZORAC® cream. The majority of the events during the treatment period were mild to moderate in severity.

Very common (>10%):
Skin and appendages: desquamation, dry skin, erythema and burning skin.

Common (<10%):
Skin and appendages: pruritus, irritation skin and stinging skin.

Body: face pain

Uncommon (<1%):
Skin and appendages: acne, skin discolouration, rash, acne worsened, erythema sun-induced, excoriations, eczema, pain skin, papules and skin tightness.
Body: pain, infection and headache.

Digestive: cheilitis.

Respiratory: pharyngitis

Nervous system: hypesthesia

Post-marketing experience:

There have been isolated reports of patients using ZORAC® 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 ZORAC® is begun.

OVERDOSAGE

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. 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

15x3.5g, 15g, 30g and 60g tubes.

FURTHER INFORMATION

CLINICAL STUDIES

Psoriasis

In two 12 week vehicle-controlled clinical studies, tazarotene 0.5 m/g and 1.0 mg/g creams were significantly more effective than vehicle in reducing the severity of plaque psoriasis. Tazarotene creams demonstrated effectiveness as early as 1 week after starting treatment, and initial treatment success (global response to treatment of moderate, marked, almost cleared or completely cleared) was reached significantly earlier than vehicle. Treatment success rates with the 1.0 mg/g cream were generally superior (numerically) to those with the 0.5 mg/g cream. During these studies, the number of patients with none, minimal or mild overall disease was significantly greater with tazarotene 0.5 mg/g and 1.0 mg/g vs vehicle at most follow-up visits.
Improvements in plaque elevation, scaling and erythema were generally significantly greater with tazarotene cream 1.0 mg/g and 0.5 mg/g than with vehicle. Tazarotene cream 1.0 mg/g was generally more effective than the 0.5 mg/g concentration in reducing the severity of the individual signs of disease. However, tazarotene 1.0 mg/g was associated with a somewhat greater degree of local irritation than the 0.5 mg/g cream.

**Mean Decrease in Plaque Elevation, Scaling and Erythema from Baseline to Week 12 in two controlled clinical studies**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Taz 0.1% N = 221</td>
<td>Taz 0.05% N = 218</td>
</tr>
<tr>
<td>Plaque elevation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>all treated</td>
<td>-0.83</td>
<td>-0.75</td>
</tr>
<tr>
<td>knee/elbow</td>
<td>-0.96</td>
<td>-0.91</td>
</tr>
<tr>
<td>trunk/limb</td>
<td>-1.08</td>
<td>-0.83</td>
</tr>
<tr>
<td>Scaling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>all treated</td>
<td>-0.73</td>
<td>-0.67</td>
</tr>
<tr>
<td>knee/elbow</td>
<td>-0.76</td>
<td>-0.78</td>
</tr>
<tr>
<td>trunk/limb</td>
<td>-0.84</td>
<td>-0.75</td>
</tr>
<tr>
<td>Erythema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>all treated</td>
<td>-0.42</td>
<td>-0.40</td>
</tr>
<tr>
<td>knee/elbow</td>
<td>-0.57</td>
<td>-0.44</td>
</tr>
<tr>
<td>trunk/limb</td>
<td>-0.49</td>
<td>-0.49</td>
</tr>
</tbody>
</table>

Taz=tazarotene cream

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

a Plaque elevation, scaling and erythema rated on a 5-point scale from none (0) to very severe (4).
b Among-group p-values the Cochran-Mantel-Haenszel test using modified ridit scores; pairwise comparisons from Fisher’s protected LSD test.
c Pairwise comparisons favoured tazarotene 0.1% vs. vehicle.
d Pairwise comparisons favoured tazarotene 0.1% and 0.05% vs. vehicle.
e Pairwise comparisons favoured tazarotene 0.1% and 0.05% vs. vehicle and tazarotene 0.1% vs. 0.05%.
f Pairwise comparisons favoured tazarotene 0.1% vs. vehicle and tazarotene 0.1% vs. 0.05%.

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 0.5 mg/g and 1.0 mg/g creams continued to show a therapeutic effect during the 12 week post-treatment period.

Pairwise comparisons were statistically significant favouring tazarotene creams vs. vehicle at each post-treatment visit, with no significant differences between tazarotene 1.0 mg/g and tazarotene 0.5 mg/g. At week 24, the clinical success rate was 30.3% (67/221) with tazarotene 1.0 mg/g, 33.5% (73/218) with tazarotene 0.5 mg/g and 21.8% (50/229) with vehicle. Similarly, there were statistically significant improvements from baseline in plaque elevation, scaling and global response favouring tazarotene creams during the 12 weeks of post-treatment follow-up but not for erythema.
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

<table>
<thead>
<tr>
<th>Score</th>
<th>None</th>
<th>Minimal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
<th>Clinical Success</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BL Wk 12 Wk 24</td>
<td>BL Wk 12 Wk 24</td>
<td>BL Wk 12 Wk 24</td>
<td>BL Wk 12 Wk 24</td>
<td>BL Wk 12 Wk 24</td>
<td>BL Wk 12 Wk 24</td>
<td>BL Wk 12 Wk 24</td>
</tr>
<tr>
<td>None (0)</td>
<td>1 (0.5%)</td>
<td>2 (1%)</td>
<td>0</td>
<td>2</td>
<td>6 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Minimal (1)</td>
<td>11 (5%)</td>
<td>12 (6%)</td>
<td>7 (3%)</td>
<td>12 (5%)</td>
<td>14 (6%)</td>
<td>11 (5%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Mild (2)</td>
<td>79 (36%)</td>
<td>60 (28%)</td>
<td>76 (36%)</td>
<td>75 (34%)</td>
<td>53 (24%)</td>
<td>90 (43%)</td>
<td>49 (21%)</td>
</tr>
<tr>
<td>Moderate (3)</td>
<td>141 (65%)</td>
<td>99 (41%)</td>
<td>100 (44%)</td>
<td>74 (30%)</td>
<td>122 (55%)</td>
<td>97 (44%)</td>
<td>96 (45%)</td>
</tr>
<tr>
<td>Severe (4)</td>
<td>69 (32%)</td>
<td>51 (23%)</td>
<td>80 (36%)</td>
<td>36 (17%)</td>
<td>91 (41%)</td>
<td>46 (21%)</td>
<td>86 (41%)</td>
</tr>
<tr>
<td>Very Severe (5)</td>
<td>8 (4%)</td>
<td>4 (2%)</td>
<td>30 (14%)</td>
<td>15 (7%)</td>
<td>8 (4%)</td>
<td>1 (0.5%)</td>
<td>29 (14%)</td>
</tr>
</tbody>
</table>

Acne

In two 12 week vehicle-controlled studies, tazarotene 1.0 mg/g cream was significantly more effective than vehicle in reducing the total number of lesions, the number of inflammatory lesions and the number of non-inflammatory lesions. Tazarotene cream 1.0 mg/g demonstrated effectiveness in reducing the total number of lesions as early as 4 weeks after starting treatment.

After 12 weeks, the number of patients whose overall acne assessment improved from baseline by one or more grades (clinical improvement rate) was significantly greater with tazarotene cream 1.0 mg/g than with vehicle. Tazarotene cream 1.0 mg/g was also associated with a significantly higher treatment success rate, based upon numbers of patients with a moderate response to treatment or better, than vehicle cream.

Tazarotene cream 1.0 mg/g was associated with a somewhat greater degree of local irritation than the 0.5 mg/g cream. In general, the rates of irritation adverse events reported during psoriasis studies with ZORAC® 1.0 mg/g cream were 1 to 4 percentage points higher than those reported for ZORAC® 0.5 mg/g cream.

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**Abbreviations:**
- Taz=tazarotene cream
- 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.

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**Acne**

In two 12 week vehicle-controlled studies, tazarotene 1.0 mg/g cream was significantly more effective than vehicle in reducing the total number of lesions, the number of inflammatory lesions and the number of non-inflammatory lesions. Tazarotene cream 1.0 mg/g demonstrated effectiveness in reducing the total number of lesions as early as 4 weeks after starting treatment.

After 12 weeks, the number of patients whose overall acne assessment improved from baseline by one or more grades (clinical improvement rate) was significantly greater with tazarotene cream 1.0 mg/g than with vehicle. Tazarotene cream 1.0 mg/g was also associated with a significantly higher treatment success rate, based upon numbers of patients with a moderate response to treatment or better, than vehicle cream.

Tazarotene cream 1.0 mg/g was associated with a somewhat greater degree of local irritation than the 0.5 mg/g cream. In general, the rates of irritation adverse events reported during psoriasis studies with ZORAC® 1.0 mg/g cream were 1 to 4 percentage points higher than those reported for ZORAC® 0.5 mg/g cream.
Baseline and Median Percent Change from Baseline in Total Lesion Count, Inflammatory Lesion Count and Non-Inflammatory Lesion Count in Two Acne Clinical Trials

<table>
<thead>
<tr>
<th>Lesion type</th>
<th>Study 1</th>
<th></th>
<th>Study 2</th>
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<th></th>
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<tr>
<td></td>
<td>Total</td>
<td>Inflammatory</td>
<td>Non-Inflammatory</td>
<td>Total</td>
<td>Inflammatory</td>
</tr>
<tr>
<td></td>
<td>Taz 0.1%</td>
<td>Vehicle</td>
<td>Taz 0.1%</td>
<td>Vehicle</td>
<td>Taz 0.1%</td>
</tr>
<tr>
<td>Study week</td>
<td>N=218</td>
<td>N=218</td>
<td>N=218</td>
<td>N=218</td>
<td>N=206</td>
</tr>
<tr>
<td>0</td>
<td>81.50</td>
<td>80.50</td>
<td>24.50</td>
<td>24.00</td>
<td>55.0</td>
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<tr>
<td>12</td>
<td>-43.90*</td>
<td>-23.97</td>
<td>-40.69*</td>
<td>-27.43</td>
<td>-46.32*</td>
</tr>
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</table>

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.
### Median Percentage Changes From Baseline in Efficacy Variables in Two Acne Clinical Trials

<table>
<thead>
<tr>
<th>Efficacy Measure</th>
<th>Study 1</th>
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<th>Study 2</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Study</td>
<td>Taz 0.1%</td>
<td>Vehicle</td>
<td>P-value</td>
</tr>
<tr>
<td></td>
<td>week</td>
<td>N=218</td>
<td>N=218</td>
<td></td>
</tr>
<tr>
<td>Total Lesion Count</td>
<td>0</td>
<td>81.50</td>
<td>80.50</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>-21.51%</td>
<td>-14.52%</td>
<td><strong>0.034</strong></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>-36.27%</td>
<td>-20.93%</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>-43.90%</td>
<td>-23.97%</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Total Inflammatory Lesions</td>
<td>0</td>
<td>24.50</td>
<td>24.00</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>-16.33%</td>
<td>-14.29%</td>
<td>0.712</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>-29.71%</td>
<td>-23.21%</td>
<td>0.103</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>-40.69%</td>
<td>-27.43%</td>
<td><strong>0.010</strong></td>
</tr>
<tr>
<td>Total Non-Inflammatory Lesions</td>
<td>0</td>
<td>55.00</td>
<td>52.00</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>-20.57%</td>
<td>-13.89%</td>
<td><strong>0.039</strong></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>-39.36%</td>
<td>-21.68%</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>-46.32%</td>
<td>-26.67%</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Incidence of Clinical Improvement c</td>
<td>4</td>
<td>25.94%</td>
<td>22.64%</td>
<td>0.429</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>36.36%</td>
<td>26.70%</td>
<td><strong>0.029</strong></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>49.08%</td>
<td>33.49%</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Global Response to treatment d - Treatment Success e</td>
<td>4</td>
<td>24.06%</td>
<td>13.68%</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>44.98%</td>
<td>23.30%</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>59.17%</td>
<td>33.94%</td>
<td><strong>&lt;0.001</strong></td>
</tr>
</tbody>
</table>

Key: N = number of patients at baseline; subsequent sample sizes may vary due to missing values.
- a P-values based on two-way analysis of variance using a rank transformation
- b P-values based on Cochran-Mantel-Haenszel test
- c Clinical improvement: percentage of patients whose overall acne assessment improved by at least one grade from baseline.
- d Completely cleared – 100% improved; almost cleared – approx. 90% improved; marked response – approx. 75% improvement; moderate response = approx. 50% improvement; slight response – approx. 25% improvement; condition unchanged; condition worsened
- e Treatment success: response of moderate, marked, almost cleared or completely cleared

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