AUSTRALIAN PRODUCT INFORMATION – ZORAC® (TAZAROTENE)

1 NAME OF THE MEDICINE

Tazarotene

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ZORAC® 0.05% w/w cream contains 0.5 mg/g of tazarotene

ZORAC® 0.1% w/w cream contains 1 mg/g of tazarotene

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

ZORAC® is a topical cream

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the topical treatment of plaque psoriasis. For the topical treatment of facial acne (0.1% w/w concentration only; see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.2 DOSE AND METHOD OF 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.

Psoriasis
Apply ZORAC® cream once a day, in the evening, to psoriatic lesions, using enough ($2mg/cm^2$) to cover only the lesions with a thin film.

Treatment may start with ZORAC® 0.05% w/w cream, with the strength increased to 0.1% if tolerated and medically indicated. ZORAC® 0.1% w/w cream was generally more effective than the 0.05% w/w concentration in reducing the severity of the individual signs of disease.

If irritation becomes problematic, the dosage may be altered by choosing the lower drug concentration or 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.

Acne
Cleanse the skin thoroughly. After the skin is dry, apply a thin film of ZORAC® 0.1% w/w cream 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® cream to the face.

4.3 CONTRAINDICATIONS

ZORAC® cream is contraindicated in individuals who have shown hypersensitivity to any of its components. ZORAC® cream is contraindicated in pregnancy and in women planning a pregnancy.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 has not been studied in patients with actinic keratosis or basal cell carcinoma.

ZORAC® cream should be administered with caution if the patient is also taking drugs known to be photosensitisers (e.g. 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 the elderly

No data available.

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.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug interaction studies have been conducted.

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® cream is begun.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No impairment of fertility occurred in male or female rats following topical application of tazarotene at dermal doses of up to 0.125 mg/kg/day (associated with plasma AUC of 1.2 times that maximally anticipated in patients treated with 2 mg/cm^2 of 0.1% w/w ZORAC® cream over 15% body surface area). However, following oral administration, decreases in sperm count, sperm density and relative weights of the seminal vesicles and prostate gland, were evident in male rats dosed at 3 mg/kg/day, with a No Observable Effect Level (NOEL) of 1 mg/kg/day. Reductions in implantations, live litter size and foetal body weight were observed in female rats dosed at 2 mg/kg/day, with a NOEL of 1 mg/kg/day. The NOEL of 1 mg/kg/day in male and female rats was associated with a plasma AUC value of 3.7 and 6.7 times, respectively, that maximally anticipated in patients treated with 2 mg/cm^2 of 0.1% w/w ZORAC® cream over 15% body surface area.

Use in pregnancy

Pregnancy Category D
As with other retinoids, tazarotene may cause foetal harm when used during pregnancy.

Tazarotene is teratogenic in rats and rabbits. Following topical dermal application at 0.25 mg/kg/day during organogenesis, tazarotene was associated with reduced foetal body weight and reduced skeletal ossification in rats and an increased incidence of known retinoid

malformations (including spina bifida, hydrocephaly and heart anomalies) in rabbits. Following oral administration at doses greater than 0.1 and 0.05 mg/kg/day in rats and rabbits, respectively, tazarotene caused developmental delays in rats and teratogenic effects and post-implantation loss in both rats and rabbits.

There are no adequate and well controlled studies of ZORAC® cream treatment in pregnant women. Tazarotene is contraindicated in women who are or may become pregnant. If ZORAC® cream is used during pregnancy or if the patient becomes pregnant while using ZORAC® cream, 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 contraception when ZORAC® cream is used.

It is difficult to determine the exact time frame in which a patient's system would be completely free of tazarotenic acid, the active form of tazarotene. However, if the patient has normal hepatic and renal function, based on the 18-hour half-life, one could assume that nearly all of the active metabolite would be gone after approximately 7 days following the last application. In seven days, over 9 half-lives will have been completed. It takes about 5 half-lives for 97% of a drug to be eliminated and 7 half-lives for about 99% of a drug to be eliminated. In human pharmacokinetic studies, no active metabolite of tazarotene could be detected after 7 days.

Use in lactation.
Tazarotene and/or its metabolites have been detected in the milk of lactating rats following topical administration with a tazarotene gel formulation. It is not known whether tazarotene and/or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if tazarotene cream is used in a breastfeeding woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Pre-marketing clinical trials:
In human dermal safety studies, tazarotene 0.1% w/w and 0.05% w/w creams were moderately irritating under the exaggerated conditions of the studies but did not induce contact sensitisation, phototoxicity or photoallergy. 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.

Table of adverse events seen in Acne clinical trials with ZORAC® cream		
Adverse Event	**ZORAC® 0.1% w/w cream (N = 424)**	**Vehicle (N = 423)**
Desquamation	124 (29.2%)	11 (2.6%)
Dry Skin	114 (26.9%)	10 (2.4%)
Erythema	87 (20.5%)	8 (1.9%)
Burning Sensation on Skin	59 (13.9%)	3 (0.7%)
Pruritus	19 (4.5%)	6 (1.4%)

Skin Irritation	17 (4.0%)	1 (0.2%)
Face Pain	8 (1.9%)	2 (0.5%)
Stinging Sensation on Skin	7 (1.7%)	1 (0.2%)
Skin Discolouration	4 (0.9%)	0 (0.0%)
Acne	3 (0.7%)	2 (0.5%)
Pain	3 (0.7%)	0 (0.0%)
Rash	3 (0.7%)	0 (0.0%)

Adverse events (<0.5%) include, cheilitis, excoriated skin, headache, eczema, sun-induced erythema, hypesthesia, infection, papules, pharyngitis, skin pain, skin tightness and worsened acne.

Table of adverse events seen in Psoriasis clinical trials with ZORAC® cream			
Adverse Event	**ZORAC® 0.05% w/w cream (N = 428)**	**ZORAC® 0.1% w/w cream (N = 432)**	**Vehicle (N = 443)**
Pruritus	80 (18.7%)	98 (22.7%)	47 (10.6%)
Erythema	54 (12.6%)	69 (16.0%)	10 (2.3%)
Burning Skin	50 (11.7%)	59 (13.7%)	21 (4.7%)
Skin Irritation	31 (7.2%)	40 (9.3%)	7 (1.6%)
Desquamation	11 (2.6%)	14 (3.2%)	4 (0.9%)
Stinging Skin	5 (1.2%)	13 (3.0%)	3 (0.7%)
Dermatitis	5 (1.2%)	12 (2.8%)	1 (0.2%)
Dermatitis Contact Irritant	8 (1.9%)	12 (2.8%)	1 (0.2%)
Skin Pain	11 (2.6%)	10 (2.3%)	7 (1.6%)
Psoriasis Worsened	10 (2.3%)	10 (2.3%)	6 (1.4%)
Eczema	3 (0.7%)	10 (2.3%)	0 (0%)
Rash	9 (2.1%)	9 (2.1%)	2 (0.5%)
Hypertriglyceridaemia	10 (2.3%)	7 (1.6%)	6 (1.4%)
Dry Skin	3 (0.7%)	6 (1.4%)	1 (0.2%)
Oedema Peripheral	3 (0.7%)	5 (1.2%)	0 (0%)
Inflammation Skin	2 (0.5%)	5 (1.2%)	0 (0%)
Excoriation	1 (0.2%)	4 (0.9%)	1 (0.2%)
Pain	1 (0.2%)	3 (0.7%)	0 (0%)
Skin Discharge	1 (0.2%)	3 (0.7%)	0 (0%)
Skin Erosion	0 (0%)	3 (0.7%)	0 (0%)
Skin Fissure	4 (0.9%)	3 (0.7%)	2 (0.5%)
Skin Hem	2 (0.5%)	3 (0.7%)	0 (0%)

Adverse events (<0.5%) include: arm pain, leg pain, oedema, chills, headache, infection, abdominal pain, knee pain, pelvic pain, nausea, mouth ulcer, SGOT Inc, SGPT Inc, insomnia, rash pustular, urticaria, hruritus scalp, hypercholesterolaemia, myalgia, dermatitis atopic, rash vesicular bullous, skin reaction, rosacea, eyelid erythema, eyelid irritation, foot pain, hyperlipemia, skin oedema focal, skin tightness, ear infection, genital oedema, cellulites, bilirubinaemia, hyperglycaemia, joint disease, tingling, skin discolouration and eye irritation.

Post-marketing experience

There have been isolated reports of patients using ZORAC® cream experiencing bullous eruptions (with or without fever).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Excessive topical use of ZORAC® 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Tazarotene is a member of the acetylenic class of retinoids.

Tazarotene is a retinoid prodrug which is converted to its biologically active form tazarotenic acid by deesterification in animals and man. Tazarotenic acid binds to and regulates gene expression through all three members of the RAR family of retinoid nuclear receptors, RAR α, RARβ and RARγ. Within the RAR family, tazarotenic acid shows relative 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 catalyzes 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 buildup is an element of psoriatic scale formation. Tazarotene also induces the expression of TIG3 (tazarotene-induced gene 3), a putative 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 may be to normalize the keratinization 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.

Clinical trials

Psoriasis
In two 12 week vehicle-controlled clinical studies in patients with stable plaque psoriasis (excluding those with deteriorating disease), tazarotene 0.05% w/w and 0.1% w/w creams were significantly more effective than vehicle in reducing the severity of plaque psoriasis. The primary endpoint, clinical success, was defined as an Overall Lesional Assessment (OLA) of none, minimal or mild. It was rated on a 6-point scale from none (0) to very severe (5) and included the three key signs of psoriasis: plaque elevation, scaling and erythema.

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 0.1% w/w cream were generally superior (numerically) to those with the 0.05% w/w cream. During these studies, the number of patients with none, minimal or mild overall disease was significantly greater with tazarotene 0.05% w/w and 0.1% w/w cream vs vehicle at most follow-up visits.

Improvements in plaque elevation, scaling and erythema were generally significantly greater with tazarotene cream 0.1% w/w and 0.05% w/w cream than with vehicle. Tazarotene 0.1% w/w cream was generally more effective than the 0.05% concentration in reducing the severity of the individual signs of disease. However, tazarotene 0.1% w/w cream was associated with a somewhat greater degree of local irritation than the 0.05% w/w cream.

Patient numbers and percentages for OLA 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

	TAZ 0.05% w/w cream					**TAZ 0.1% w/w cream**					**Vehicle cream**				
	Study 1 N = 218			**Study 2** N = 210		**Study 1** N = 221			**Study 2** N = 211		**Study 1** N = 229			**Study 2** N = 214	
Score	BL	Wk 12	Wk 24	BL	Wk 12	BL	Wk 12	Wk 24	BL	Wk 12	BL	Wk12	Wk 24	BL	Wk 12
None (0)	0	1 (0.5%)	1 (0.5%)	0	2 (1%)	0	0	0	0	6 (3%)	0	0	1 (0.4%)	0	1 (0.5%)
Minimal (1)	0	11 (5%)	12 (6%)	0	7 (3%)	0	12 (5%)	14 (6%)	0	11 (5%)	0	7 (3%)	6 (3%)	0	1 (0.5%)
Mild (2)	0	79 (36%)	60 (28%)	0	76 (36%)	0	75 (34%)	53 (24%)	0	90 (43%)	0	49 (21%)	43 (19%)	0	54 (25%)
Moderate (3)	141 (65%)	86 (39%)	90 (41%)	100 (48%)	74 (35%)	122 (55%)	97 (44%)	107 (48%)	96 (45%)	62 (29%)	139 (61%)	119 (52%)	114 (50%)	97 (45%)	99 (46%)
Severe (4)	69 (32%)	39 (18%)	51 (23%)	80 (38%)	36 (17%)	91 (41%)	36 (16%)	46 (21%)	86 (41%)	29 (14%)	81 (35%)	51 (22%)	61 (27%)	93 (44%)	47 (22%)
Very Severe (5)	8 (4%)	2 (0.9%)	4 (2%)	30 (14%)	15 (7%)	8 (4%)	1 (0.5%)	1 (0.5%)	29 (14%)	13 (6%)	9 (4%)	3 (1%)	4 (2%)	24 (11%)	12 (6%)
"Clinical Success"	0	91 (42%*)	73 (33%*)	0	85 (40%)*	0	87 (39%*)	67 (30%*)	0	107 (51%*)	0	56 (24%)	50 (22%)	0	56 (26%)

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

Taz = tazarotene cream
Clinical Success defined as an OLA 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.

The secondary evaluation criteria were plaque elevation (which is the most distinctive feature of plaque psoriasis) scaling, erythema and treatment success at week 12.

Mean decrease in plaque elevation, scaling and erythema from baseline to week 12 in two controlled clinical studies

Lesion	Study 1				Study 2			
	Taz 0.1% N = 221	Taz 0.05% N = 218	Vehicle N = 229	P-value[b]	Taz 0.1% N = 211	Taz 0.05% N = 210	Vehicle N = 214	P-value[b]
Plaque elevation[a]								
all treated	-0.83	-0.75	-0.48	< **0.001**[d]	-1.08	-0.90	-0.61	< **0.001**[e]
knee/elbow	-0.96	-0.91	-0.57	< **0.001**[d]	-1.21	-1.04	-0.68	< **0.001**[e]
trunk/limb	-1.08	-0.83	-0.59	< **0.001**[e]	-1.25	-0.98	-0.69	< **0.001**[e]
Scaling[a]								
all treated	-0.73	-0.67	-0.46	< **0.001**[d]	-1.03	-0.80	-0.70	< **0.001**[f]
knee/elbow	-0.76	-0.78	-0.62	**0.049**[d]	-1.13	-0.98	-0.76	< **0.001**[d]
trunk/limb	-0.84	-0.75	-0.66	**0.038**[c]	-1.06	-0.90	-0.79	**0.010**[c]
Erythema[a]								
all treated	-0.42	-0.40	-0.37	0.539	-0.78	-0.62	-0.47	< **0.001**[f]
knee/elbow	-0.57	-0.44	-0.38	**0.005**[f]	-0.82	-0.66	-0.44	< **0.001**[e]
trunk/limb	-0.49	-0.49	-0.42	0.276	-0.82	-0.65	-0.46	< **0.001**[e]
Treatment Success rate[a]								
all treated	48.9%	42.7%	30.1%	< **0.001**[d]	58.8%	47.6%	36.9%	< **0.001**[e]
knee/elbow	53.4%	45.4%	30.6%	< **0.001**[d]	62.6%	53.3%	39.3%	< **0.001**[d]
trunk/limb	51.1%	45.4%	32.3%	< **0.001**[d]	56.9%	49.1%	37.9%	< **0.001**[d]

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%.

Acne

In two 12 week vehicle-controlled studies, tazarotene 0.1% w/w 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 0.1% w/w cream demonstrated effectiveness in reducing the total number of lesions as early as 4 weeks after starting treatment.

The primary efficacy variable in the studies was the percentage reduction from baseline in the total number of facial lesions (the sum of all non-inflammatory and inflammatory lesions). The reduction in the total number of lesions provided an objective measure of improvement in the key characteristic of acne. Secondary variables were the reductions in non-inflammatory (sum of open and closed comedones) and inflammatory (sum of papules, pustules, and nodules) lesions separately, providing information about the responses of the different types of acne lesions. The secondary efficacy variables also included an overall acne assessment (none, minimal, mild, moderate, severe and very severe) and a global response to treatment (completely cleared, almost cleared, marked response, moderate response, slight response, condition unchanged and condition worsened).

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 0.1% w/w cream than with vehicle.

Tazarotene 0.1% w/w cream 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.

Baseline and median percent change from baseline in total lesion count, inflammatory lesion count and non-inflammatory lesion count in two acne clinical trials

	Study 1		Study 2	
Lesion type	**Total**		**Total**	
	Taz 0.1% w/w cream	**Vehicle**	**Taz 0.1% w/w cream**	**Vehicle**
Study week	**N = 218**	**N = 218**	**N = 206**	**N = 205**
0[a]	**81.50**	**80.50**	**86.50**	**88.00**
4[b]	**-21.51***	**-14.52**	**-15.33**	**-9.23**
8[b]	**-36.27***	**-20.93**	**-33.33***	**-15.53**
12[b]	**-43.90***	**-23.97**	**-41.76***	**-20.92**

Taz = tazarotene cream. N = number of patients at baseline; subsequent sample sizes may vary due to missing values.
[a] week 0 = median lesion count at baseline
[b] weeks 4, 8, 12 = median percent change from baseline
*Denotes statistically significant difference compared with vehicle

Median percentage changes from baseline in efficacy variables in two acne clinical trials

		Study 1			Study 2		
Efficacy Measure	**Study week**	**Taz 0.1% N = 218**	**Vehicle N = 218**	**P-value**	**Taz 0.1% N = 206**	**Vehicle N = 205**	**P-value**
Total Inflammatory Lesions	0	24.50	24.00	-	21.00	21.00	-
	4	-16.33%	-14.29%	0.712[a]	0.00%	-15.38%	**0.007[a]**
	8	-29.71%	-23.21%	0.103[a]	-30.22%	-23.30%	0.241[a]
	12	-40.69%	-27.43%	**0.010[a]**	-44.49%	-25.00%	**0.001[a]**
Total Non-Inflammatory Lesions	0	55.00	52.00	-	63.00	64.00	-
	4	-20.57%	-13.89%	**0.039[a]**	-23.33%	-6.67%	**0.001[a]**
	8	-39.36%	-21.68%	**<0.001[a]**	-34.22%	-12.77%	**<0.001[a]**
	12	-46.32%	-26.67%	**<0.001[a]**	-41.32%	-20.83%	**<0.001[a]**
Incidence of Clinical Improvement[c]	4	25.94%	22.64%	0.429[b]	22.96%	30.65%	0.086[b]
	8	36.36%	26.70%	**0.029[b]**	40.63%	36.98%	0.410[b]
	12	49.08%	33.49%	**0.001[b]**	48.06%	32.68%	**0.001[b]**
Global Response to treatment[d] - Treatment Success[e]	4	24.06%	13.68%	**0.004[b]**	15.82%	14.57%	0.687[b]
	8	44.98%	23.30%	**<0.001[b]**	36.98%	21.88%	**0.001[b]**
	12	59.17%	33.94%	**<0.001[b]**	48.54%	26.83%	**<0.001[b]**

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

In general, the rates of irritation adverse events reported during psoriasis studies with ZORAC® 0.1% w/w cream were 1 to 4 percentage points higher than those reported for ZORAC® 0.05% w/w cream.

In acne, tazarotene cream has only been studied in the treatment of facial lesions.

No studies of treatment duration longer than 12 weeks have been conducted to assess the efficacy and safety of tazarotene cream in acne and psoriasis.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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.

In a pharmacokinetic study in psoriatic patients, tazarotene 0.1% w/w cream was applied once daily to the psoriatic lesions (5-35% of body surface area) at a standard (clinical) dosing of 2 mg/cm^2 or an exaggerated dosing of 10 mg/cm^2 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 which is linear binding. The blood-to-plasma ratio of ^{14}C-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, ^{14}C-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
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.

Tazarotene was not excreted unchanged. After dermal dosing with ^{14}C-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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Tazarotene was negative in a standard battery of *in vitro* and *in vivo* genotoxicity tests.

Carcinogenicity
The carcinogenic potential of tazarotene was studied in mice following topical dermal application and in rats following oral administration. No increase in tumour incidence was apparent in either mice or rats at plasma AUC levels of up to 7.8 and 1.4 times respectively, that maximally anticipated in patients treated with 2 mg/cm^2 of ZORAC® 0.1% w/w cream over 15% body surface area.

A reduction in median time to onset of ultraviolet radiation-induced tumour formation was observed in hairless mice following topical dermal application of a tazarotene gel formulation. The cause of this effect is unknown. The potential photocarcinogenicity of the ZORAC® cream formulation has not been examined. Exposure of ZORAC® cream treated areas to the sun should be avoided.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Benzyl alcohol, sodium thiosulfate pentahydrate, disodium edetate, liquid paraffin, medium chain triglycerides, carbomer 1342, sorbitan mono-oleate, carbomer 934P, sodium hydroxide and purified water.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

3 years in the unopened container.
Keep tube tightly closed when not in use.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

1.0 mg/g and 0.5 mg/g white to off white cream in collapsible aluminum tubes with tamper-evident opening and screw cap in 3.5g, 30g and 60g sizes.

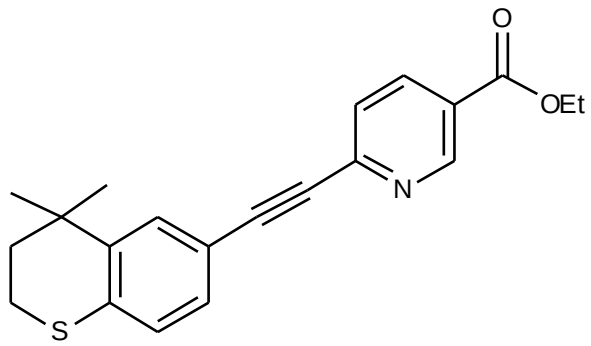
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Unused contents of the tube should be discarded 12 months after opening.

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure:



CAS number: 118292-40-3

Molecular weight: 351.46

Chemical Name: Ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate

Empirical formula: $C_{21}H_{21}NO_2S$

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

ZORAC® 0.05% w/w cream AUST R 101328
ZORAC® 0.1% w/w cream AUST R 101327

8 SPONSOR

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ABN 85 000 612 831

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9 DATE OF FIRST APPROVAL

12 July 2005

10 DATE OF REVISION

13 September 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
The PI has been reformatted in line with the TGA's approved form for PIs. Additional mandatory headings and standard text have been included to the PI line with the TGA's approved form for PIs. Minor editorial changes have been made throughout the PI to improve legibility.	
4.3	Inclusion of a further contraindication for women planning a pregnancy.