PUBLIC SUMMARY DOCUMENT

Product: Tazarotene, cream, 500 micrograms per g (0.05%) and 1.0 mg per g (0.1%), 30 g, Zorac®

Sponsor: Genepharm Australasia Ltd

Date of PBAC Consideration: July 2007

1. Purpose of Application

The submission sought a restricted benefit listing for chronic stable plaque type psoriasis vulgaris.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Tazarotene (0.05% and 0.1%) cream was registered on 12 July 2005 for the treatment of plaque psoriasis and for the treatment of facial acne (0.1% cream only).

4. Listing Requested and PBAC's View

Restricted benefit

Chronic stable plaque type psoriasis vulgaris.

The PBAC did not comment on the requested restriction.

5. Clinical Place for the Proposed Therapy

Currently, there is no effective cure for psoriasis and all therapies suffer from reduced efficacy over time. Tazarotene will provide an alternative topical therapy in the first-line treatment of psoriasis in place of other topical therapies, or in combination with topical or systemic therapies.

6. Comparator

The submission nominated calcipotriol as the main comparator.

The PBAC agreed that, in the context of this submission, calcipotriol was the appropriate comparator.

7. Clinical Trials

The submission presented four head-to-head randomised controlled trials (RCTs) comparing tazarotene gel (with or without co-treatment) and calcipotriol.

Supportive evidence was provided by five trials comparing tazarotene gel to placebo and two trials comparing tazarotene cream to placebo.

These studies had been published at the time of submission, as follows:

Trial/First author	Protocol title/Publication title	Publication citation
Tazarotene gel vs. Calcipotriol		

Trial/First author	Protocol title/Publication title	Publication citation
Guenther LC et al (2000)	A comparison of tazarotene 0.1% Gel once daily plus mometasone furoate 0.1% cream once daily versus calcipotriene 0.005% ointment twice daily in the treatment of plaque psoriasis.	Clin. Ther. 2000; 22:1225–1238.
Schiener R et al (2000)	Calcipotriol vs. tazarotene as combination therapy with narrowband ultraviolet B (311 nm): efficacy in patients with severe psoriasis.	The British Journal of Dermatology 2000; 143:1275–1278.
Dando TM and Wellington K, 2005	Topical Tazarotene: A review of its Use in the Treatment of Plaque Psoriasis.	Am J Clin Dermatol 2005 6(4): 255–272.
Tzung TY et al (2005)	Comparison of Tazarotene 0.1% gel plus petrolatum once daily versus calcipotriol 0.005% ointment twice daily in the treatment of plaque psoriasis.	Acta Derm Venereol 2005; 85: 236–239.
Tazarotene gel studies		
Behrens S et al (1999)	Combination treatment of psoriasis with photochemotherapy and tazarotene gel, a receptor-selective topical retinoid.	The British Journal of Dermatology 1999; 141:177.
Behrens S et al (2000)	Combination phototherapy of psoriasis with narrow-band UVB irradiation and topical tazarotene gel .	J Am Acad Dermatol 2000; 42:493–5.
Koo YM et al (2000)	Tazarotene plus UVB phototherapy in the treatment of psoriasis	J Am Acad Dermatol 2000; 43:821–8.
Dando TM and Wellington K (2005)	Topical Tazarotene: A review of its Use in the Treatment of Plaque Psoriasis.	Am J Clin Dermatol 2005 6(4): 255–272.
Weinstein GD et al (1997)	Tazarotene gel, a new retinoid, for topical therapy of psoriasis: Vehicle-controlled study for safety, efficacy, and duration of therapeutic effect.	J Am Acad Dermatol 1997; 37:85–92.
Tazarotene cream studies		
Study A:190168-016C and Study B: 190168-017C Weinstein G D et al and the Tazarotene Cream Clinical Study Group, 2003.	Tazarotene cream in the treatment of psoriasis: Two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene creams 0.05% and 0.1% applied once daily for 12 weeks.	J Am Acad Dermatol 2003; 48:760–767

8. Results of Trials

The results of the key trials are summarised in the table below.

Percentage of patients achieving treatment success

Trial	Treatment	N[a]	Treatment success
Tazarotene gel vs. calcipotriol			
Guenther (2000)	Taz 0.1% + MF 0.1% Cal 0.005%	*60* *58*	*~60%*[b] *~60%*[b]
R168-145-8606	Taz0.1% Taz 0.05% Cal 0.005%	*95* *95* *88*	41%[c](12wk) 44%[c](12wk) 63%[c](12wk)
Tzung (2005)	Taz 0.1% + petrolatum Cal 0.005%	19[d] 19[d]	95%[e] *74%*[f] 90%[e] *85%*[f]

Taz: tazarotene, Cal: calcipotriol MF: mometasone furoate

[a] N is the number of evaluated patients, not necessarily the intention-to-treat population
[b] treatment success is ≥75% global improvement
[c] treatment success is ≥50% global improvement in appearance of lesions
[d] each patient received both treatments on one side only
[e] percent of patients with any improvement (this number could not be verified in the evaluation)
[f] The data presented in italics were extracted during evaluation, and were defined in the publication as at least marked improvement assessed by the patients themselves

Treatment success was similar between tazarotene + mometasone furoate and calcipotriol treatment in the trial from Guenther (2000), while calcipotriol appeared to be more effective than tazarotene in trials R168-145-8606 and Tzung (2005) (no statistics performed).

Mean change from baseline in erythema, pruritus, plaque elevation and scaling

Trial	Treatment	N[a]	Mean reduction from baseline ± SD		
			Erythema	Plaque elevation	Scaling
tazarotene gel vs. calcipotriol					
Guenther (2000)	Taz 0.1% + MF	60	60%	75%	72%
	Cal 0.005	60	52%	63%	62%
R168-145-8606	Taz 0.1%	95	0.8	1.3	1.3
	Taz 0.05%	95	0.7	1.2	1.0
	Cal 0.005%	88	1.1	1.7[bc]	1.7[bc]
Tzung (2005)	Taz 0.1% + Pet	19[d]	0.5 ± 0.71	0.2 ± 0.40	0.3 ± 0.43
	Cal 0.005%	19[d]	0.4 ± 0.7	0.2 ± 0.39	0.3 ± 0.49

Taz: tazarotene, Cal: calcipotriol, MF: mometasone furoate 0.1% cream, Pet: petrolatum, sd: standard deviation
[a] N = number of patients evaluated, not necessarily the intention-to-treat population
[b] p<0.05 vs. tazarotene 0.1%
[c] p<0.05 vs. tazarotene 0.05%
[d] each patient received both treatments on one side only

9. Clinical Claim

The submission claimed that there was no difference between patients (or lesions/sides) treated with tazarotene compared with calcipotriol.

The submission also claimed that tazarotene was no worse than calcipotriol in terms of safety.

The PBAC considered that the large number of significant and fundamental deficiencies identified in the submission makes it highly uncertain whether this preparation is as effective or as safe as the comparator, *see Recommendation and Reasons*.

10. Economic Analysis

The submission presented a preliminary economic evaluation using a cost minimisation approach. The resources included were drug costs. In the context of cost-minimisation, the submission did not present an equi-effective dose.

The preliminary economic evaluation used a hypothetical patient presenting a plaque psoriasis lesion requiring 1 g per application.

The submission stated that over 30 days, tazarotene treatment offered a cost saving over calcipotriol. Three sensitivity analyses were performed, using different scenarios, and all three resulted in a higher cost with tazarotene treatment compared to calcipotriol treatment.

In view of PBAC's conclusions regarding the comparative efficacy of tazarotene and calcipotriol, the economic analysis was not considered valid by the Committee.

The submission did not present a modelled economic evaluation.

11. Estimated PBS Usage and Financial Implications

The financial cost/year to the PBS (excluding co-payments) minus any savings in use of other drugs was estimated by the submission to be up to < $10 million in Year 3. With the overall market expected to grow or grow more rapidly as a result of listing tazarotene, the PBAC considered this to be a likely under-estimate in the submission as the number of anti-psoriatic treatments on the PBS is limited and therefore the shift from the private market could be underestimated. There is also potential for usage beyond the requested restriction (i.e. acne).

12. Recommendation and Reasons

The PBAC agreed that, in the context of this submission, calcipotriol was the appropriate comparator. However the key trials used tazarotene gel, whereas the product proposed for listing is a cream. Although there are trials comparing the cream with placebo, and the gel with placebo, the submission did not attempt an analysis to demonstrate that the gel is no worse than the cream. Also, the gel seemed to perform better than the cream in regard to erythema, plaque elevation and scaling. In view of the known impact of the base on the efficacy of topical applications, the PBAC considered this to be a significant issue for this submission.

In the Guenther (2002) trial, treatment success with tazarotene and calcipotriol was noted to be similar, but the trial used a combination of the tazarotene gel plus mometasone versus calcipotriol. The PBAC considered this to be an inappropriate comparison since the impact of the corticosteroid was not balanced across both arms. It was further noted that calcipotriol appeared to be more effective than tazarotene in trial R168-145-8606. The Tzung (2005) trial was small and the data inconclusive as to the relative efficacy. The PBAC agreed that based on these trials, tazarotene may be inferior to calcipotriol, but the data were considered insufficient to form firm conclusions regarding comparative efficacy.

The results from the fourth comparative trial, Schiener (2000), suggested that the psoriasis area and severity index (PASI) scores were similar for calcipotriol and tazarotene, both in combination with UVB. However, the PBAC noted that the confidence intervals were very wide and therefore the study was underpowered to test non-inferiority. Additionally, no information was provided on whether there was a difference in UVB dose between the two study arms.

The Committee considered the adverse event data provided to be sparse, and to indicate that tazarotene may have a higher incidence of adverse events than its comparator, calcipotriol. The tazarotene gel and cream studies reported dose-related increases in erythema, pruritus, irritation, burning and withdrawals due to adverse events.

The PBAC concluded that the large number of significant and fundamental deficiencies identified in the submission makes it highly uncertain whether this preparation is as effective or as safe as the comparator.

The PBAC therefore rejected the submission because of uncertain clinical benefit in comparison with calcipotriol.

Recommendation
Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Genepharm is working with the original manufacturer of Zorac; Allegan Inc. US to review all available and new clinical data and is confident that such data can be resubmitted to PBAC in the near future. Genepharm is confident that any resubmission will demonstrate the efficacy and cost minimisation criteria required by PBAC when considering to list a new product on the PBS. We consider that the Australian public would benefit from the listing of Zorac in Australia; the number one retinoid in the United States; and we look forward to having another opportunity to demonstrate this to PBAC.