

PUBLIC SUMMARY DOCUMENT

Product: ALEFACEPT, powder for injection, 7.5 mg and 15 mg, Amevive[®]

Sponsor: Biogen Idec Australia Pty Ltd

Date of PBAC Consideration: November 2005

1. Purpose of Application

This application sought Section 100 (High Specialised Drug) authority required listing for the treatment of severe chronic plaque psoriasis in adult patients who have a Psoriasis Area and Severity Index (PASI) score ≥ 15 and are refractory, intolerant or contraindicated to currently available therapies. Highly Specialised Drugs (HSDs) are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to prescribing through public and private hospitals which have appropriate specialist facilities.

2. Background

The PBAC at its meeting in July 2004 rejected a Section 85 authority required application to list alefacept for the treatment by a dermatologist of adults 18 years and over and who have been diagnosed with severe chronic plaque psoriasis who meet certain criteria, including CD4+ lymphocyte counts and baseline PASI scores because the incremental cost-effectiveness ratios were considered both unacceptably high and uncertain.

The Section 85 authority required application for the listing of alefacept was re-submitted by the sponsor for consideration by the PBAC at its March 2005 meeting taking into account the outcomes of a December 2004 Stakeholder Meeting between sponsors, clinicians and the PBAC.

Although the PBAC accepted both that there was a demonstrated clinical need for the drug and it was demonstrated to be effective, the Committee, nevertheless, rejected the application for uncertain and unacceptable cost-effectiveness reasons.

3. Registration Status

Alefacept was registered by the TGA on 7 May 2004 for the "Treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for phototherapy or systemic therapy. Safety and efficacy beyond two courses have not been demonstrated."

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drug)

Public and Private Hospital Authority required

The submission requested an authority required listing (private and public hospitals) as a section 100 item (Highly Specialised Drug). Under the requested listing, initial treatment would have been limited to patients with severe chronic plaque psoriasis who met certain criteria including a failure to achieve an adequate response to specified psoriasis therapies and a PASI score ≥ 15 . Eligibility for continuing PBS-subsidised treatment would have been contingent on the achievement and maintenance of a reduction of at least 50% in the PASI score.

See Recommendations and Reasons for the PBAC's view.

5. Clinical Place for the Proposed Therapy

Alefacept would provide an alternative treatment option for severe psoriasis for patients who are unresponsive or contraindicated to existing therapies.

6. Comparator

The submission nominated placebo as the comparator. The PBAC considered this appropriate given the requested restriction of alefacept as a last-line therapy.

7. Clinical Trials

The submission relied on data presented in previous submissions from two key randomised trials comparing alefacept (trial 711 of IV and trial 712 of IM) with placebo in patients with moderate-severe chronic plaque psoriasis. Alefacept was given for 12 weeks with a further 12 weeks' follow-up. A meta-analysis was presented for the two trials and a sub-group analysis of refractory patients fitting the requested restriction (eg with psoriasis area and severity index (PASI) ≥ 15 at baseline).

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

Trial/First author	Protocol/Publication title	Publication citation
C99-711 Krueger GG	A randomized, double-blind, placebo-controlled phase III study evaluating efficacy and tolerability of two courses of alefacept in patients with chronic plaque psoriasis.	J Am Acad Dermatol 47:821–833
C99-711 Krueger G 2003.	Clinical response to alefacept: results of a phase 3 study of intravenous administration of alefacept in patients with chronic plaque psoriasis.	J Eur Acad Dermatol Venereol 17 Suppl 2:17–24
C99-711 Gordon KB 2003.	Treatment of psoriasis with alefacept: correlation of clinical improvement with reductions of memory T-cell counts.	Arch Dermatol 139:1563–1570
C99-711 Feldman SR 2004.	Improved health-related quality of life following a randomized controlled trial of alefacept treatment in patients with chronic plaque psoriasis.	Br J Dermatol 150:317–326
C99-712 Ortonne JP 2003	Alefacept-induced decreases in circulating blood lymphocyte counts correlate with clinical response in patients with chronic plaque psoriasis.	<i>Eur J Dermatol</i> 13:117–123
C99-712 Finlay AY	Intramuscular alefacept improves health-related quality of life in patients with chronic plaque psoriasis.	<i>Dermatology</i> 206:307–315
C99-712 Lebwohl M 2003.	An international, randomized, double-blind, placebo-controlled phase 3 trial of intramuscular alefacept in patients with chronic plaque psoriasis.	<i>Arch Dermatol</i> 139:719–727
C99-712 Ortonne JP. 2003.	Clinical response to alefacept: results of a phase 3 study of intramuscular administration of alefacept in patients with chronic plaque psoriasis.	<i>J Eur Acad Dermatol Venereol</i> 17 Suppl 2:12–16

8. Results of Trials

The key results are presented in the table below.

$\geq 50\%$ reduction from baseline PASI any time after first dose

Analysis	Alefacept n/N (%)	Placebo n/N (%)	OR (95% CI)	RD (95% CI)	NNT (95% CI)
Total population					
Trial 711	204/374 (54.5)	44/188 (23.4)	3.93 (2.65, 5.83)	0.31 (0.23, 0.39)	3.2 (2.6, 4.3)
Trial 712	94/168 (56.0)	59/169 (34.9)	2.37 (1.53, 3.67)	0.21 (0.11, 0.31)	4.8 (3.2, 9.1)
Meta-analysis	301/542 (55.5)	103/357 (28.9)	3.16 (2.36, 4.23)	0.27 (0.21, 0.33)	3.7 (3.0, 4.8)

The previous submission also included data from patients refractory and/or contraindicated to cyclosporin, as well as supportive data from two longer term open label studies (714 and 724), both of which are unpublished.

For the purposes of the preliminary economic evaluation and the economic model, the refractory to cyclosporin sub-group was used. However, the PBAC noted based on the new restriction, the population should be refractory or intolerant or contraindicated to at least two of the following therapies: phototherapy, cyclosporin, or methotrexate.

The PBAC noted that the clinical data remained unchanged from the previous submission, including the resubmission's use of the results from the post hoc sub-group analysis, which was considered by the PBAC to be more favourable to alefacept than the results from the full intention-to-treat analysis.

There were significantly higher incidences of adverse events in the alefacept arms of trials 711 and 712. However, there were no significant differences in serious/severe adverse events, number of infections or number of malignancies. With continued treatment (714 and 724), no significant increases in total adverse events, serious/severe adverse events, number of infections or number of malignancies were identified. In 724, there were significantly fewer serious/severe adverse events compared to the placebo from its prior trial (711), during all three extra courses of alefacept treatment.

At similar doses, rates of adverse events, infections and malignancies remained stable throughout the studies.

9. Clinical Claim

The submission claimed that alefacept has significant advantages in effectiveness over the main comparator (which is placebo) but is associated with more toxicity

The PBAC had previously considered that although trial results confirmed alefacept was efficacious, the extent of benefit beyond two courses was not known.

10. Economic Analysis

The trial-based incremental discounted cost/extra discounted extra responder (PASI reduction of $\geq 50\%$ at any time during the trial) was estimated by the submission to be between \$15,000 to \$45,000 using the sub-group analysis and between \$15,000 to \$45,000 using the Intention to Treat (ITT) population.

An updated modelled economic evaluation was presented. The base case modelled incremental discounted cost/extra discounted quality adjusted life year (QALY) gained was between \$45,000 to \$75,000 using both the sub-group analysis the ITT population response rates.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the likely number of patients/year would be less than 10,000 in Year 2 of listing.

The submission estimated that the financial cost/year to the PBS would be between less than \$10 million in Year 2 of listing.

12. Recommendation and Reasons

The PBAC did not agree with the submission's request to list alefacept as a Highly Specialised Drug under Section 100 because most dermatologists work in private rooms and not in outpatients' clinics. The sponsor had stated that it would be prepared to accept Section 85 listing, and calculated cost-effectiveness ratios accordingly as a sensitivity analysis. The PBAC noted that listing under Section 85 would increase the costs of alefacept and, as a result, the cost-effectiveness ratios.

The PBAC considered there still remained outstanding issues with the requested restriction. However, as previously, the outstanding issues around the restriction were not the principle reason for the PBAC's decision to reject the submission.

Two sets of utility values were employed in the submission's calculations of cost-effectiveness. The first derived from a published American study by Zug *et al* (1995) and the second from a specifically commissioned Australian study (2004). The PBAC took the view that the utility estimates from Zug *et al* (1995), while not ideal, were more plausible than those from the Australian study.

The PBAC recalled that it had judged the base-case incremental cost per extra QALY gained in the previous submission, to be unacceptably high. Further, it recalled that this ratio had made a series of six assumptions that favoured alefacept and previous uncertainty over the series of assumptions remained. In addition, the model omitted the request to allow re-initiation of treatment 15 months after the last follow-up visit in patients who have failed to achieve a response to earlier alefacept treatment. Thus, the more realistic incremental cost per extra QALY gained was likely to be higher and less acceptable than the base-case.

The PBAC noted that the base-case incremental cost per extra QALY gained in this submission is numerically higher than the best-case scenario that was presented in the previous submission. The base case cost-effectiveness ratio would be higher under a Section 85 listing. The PBAC rejected the submission because of unacceptable and uncertain cost-effectiveness.

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

The sponsor regrets that Australian patients with a significant and well-recognised clinical need have again been denied PBS access to a safe and effective therapy that is widely available in other countries.