PUBLIC SUMMARY DOCUMENT
Product: Tacrolimus, capsules 500 microgram, 1 mg and 5 mg, Prograf®
Sponsor: Janssen-Cilag Pty Ltd
Date of PBAC Consideration: March 2008

1. Purpose of Application

The submission sought an extension to the current Section 85 and Section 100 (Highly Specialised Drugs Program) listings to include lung allograft rejection.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

Tacrolimus had not previously been considered by the PBAC for PBS subsidised treatment following lung transplantation.

The PBAC first recommended tacrolimus for the prevention and treatment of rejection in primary liver transplant recipients at its meeting held in June 1997. Listing was recommended on the basis that tacrolimus is more effective and less costly compared to cyclosporin.

The PBAC considered an application to extend the listing of tacrolimus to include use in renal transplantation at its September 1999 meeting. The Committee accepted that tacrolimus had demonstrated an advantage in biopsy-proven graft rejection.

At the November 2007 meeting, the PBAC recommended an extension to the current Section 100 and Section 85 listings for tacrolimus to include cardiac allograft rejection on a cost-effectiveness basis over cyclosporin.

3. Registration Status

Tacrolimus was registered by the TGA on 25 August 1997 and is indicated for use as an adjunct to liver, kidney, heart or lung allograft transplantation in adults and children.

4. Listing Requested and PBAC's View

The requested extensions to the current listings are shown in **bold**:

Section 85 listing
Authority Required
Maintenance therapy, following initiation and stabilisation of treatment with tacrolimus and where therapy remains under the supervision and direction of the transplant unit reviewing that patient, of patients with:
(a) liver transplants. The name of the specialised transplant unit reviewing treatment and the date of the latest review at the specialised transplant unit must be included in the authority application; or
(b) renal transplants. The name of the specialised transplant unit reviewing treatment and the date of the latest review at the specialised transplant unit must be included in the authority application; or

(c) cardiac transplants. The name of the specialised transplant unit reviewing treatment and the date of the latest review at the specialised transplant unit must be included in the authority application; or
(d) lung transplants. The name of the specialised transplant unit reviewing treatment and the date of the latest review at the specialised transplant unit must be included in the authority application.

Section 100 (Highly Specialised Drugs Program) listing
Private Hospital Authority Required
Management of rejection, under the supervision and direction of a transplant unit, in patients receiving this drug for:
(a) prophylaxis and treatment of liver allograft rejection. Management includes initiation, stabilisation and review of therapy as required; or
(b) prophylaxis and treatment of renal allograft rejection. Management includes initiation, stabilisation and review of therapy as required; or
(c) prophylaxis and treatment of cardiac allograft rejection. Management includes initiation, stabilisation and review of therapy as required; or
(d) prophylaxis and treatment of lung allograft rejection. Management includes initiation, stabilisation and review of therapy as required.

The PBAC had no objections to the requested wording of the restriction.

5. Clinical Place for the Proposed Therapy

Tacrolimus would provide another option for maintenance of immunosuppression following lung transplantation.

6. Comparator

The submission nominates cyclosporin as the main comparator. This was accepted by the PBAC.

7. Clinical Trials

The submission presented three key randomised trials, EAILTx (2007), Hachem (2007), Zuckermann (2003) and one supporting randomised trial, Keenan (1995) comparing tacrolimus with cyclosporin in patients post lung transplant. The submission also presented the pooled results of the EAILTx (2007) and Zuckermann (2003) trials.

Details of the trials presented are in the table below.

Trial/First Author	Publication Title	Citation
EAILTx Glanville AR	A prospective randomised international multi-centre investigator driven study comparing TAC and CSA (+MMF/Steroids) after lung transplantation. 3 year follow-up analysis.	Presented at the International Society of Heart and Lung Transplantation 27th Anniversary Meeting and Scientific Sessions April 25-28, 2007.
Hachem RR	A randomised controlled trial of tacrolimus versus cyclosporine after lung transplantation.	Journal of Heart and Lung Transplantation 2007;26(10):1012-1018.
Zuckermann A	Cyclosporin A versus tacrolimus in combination with mycophenolate mofetil and steroids as primary immunosuppression after lung	Journal of Thoracic and Cardiovascular Surgery 2003; 125(4):891-900.

	transplantation: one-year results of a 2-center prospective randomised trial.	
Keenan RJ	Clinical trial of tacrolimus versus cyclosporin in lung transplantation.	Annals of Thoracic Surgery 1995; 60(3):580-584.

The PBAC considered the studies presented to be robust.

8. Results of Trials

Acute rejection

Zuckermann (2003) did not show a statistically significant difference at 12 months for freedom from acute rejection ≥A2 (mild) or clinically confirmed but a statistically significant difference was observed in EAILTx (2007). There was a high rate of switching to the alternative treatment arm in both trials. In the Zuckermann (2003) trial by year 1, 10.8% in the cyclosporin arm had switched to tacrolimus treatment whereas 0% in the tacrolimus arm switched. In the EAILTx (2007) trial, by year 3, 36.3% in the cyclosporin arm switched to tacrolimus treatment and 2.4% in the tacrolimus arm switched to cyclosporin treatment. The switching occurred due to adverse events and acute rejection. Hachem (2007), at 2 years, shows statistically significant differences favouring tacrolimus.

The submission pooled the 1 year results from the Zuckermann (2003) and EAILTx (2007) trials. The pooled data showed a statistically significant difference in freedom from acute rejection ≥ A2 in favour of tacrolimus. The results are summarised in the table below.

Measures of effect, freedom from acute rejection ≥ grade A2 or clinically confirmed

	Tacrolimus	**Cyclosporin**	**Relative risk (95% CI)**	**Risk difference (95% CI)**
1 year				
Zuckermann (2003)	17/37 (46%)	13/37 (35%)	1.31 (0.75, 2.29)	0.11 (-0.11, 0.33)
EAILTx (2007)	79/128 (62%)	63/127 (50%)	1.24 (1.00, 1.55)	0.12 (0.00, 0.24)
Pooled result from random effects model			1.25 (1.02, 1.54) P=0.03	0.12 (0.01, 0.22) P=0.03

Bronchiolitis Obliterans Syndrome (BOS)

The tables below summarise the results and pooled results from Zuckerman (2003) and EAILTx (2007) trials relating to BOS.

The incidence of BOS at 1 year in both trials was not statistically different, at 3 years the Zuckermann (2003) trial reached a statistically significant difference with the incidence of BOS at 10% in the tacrolimus arm and 41% in the cyclosporin arm. The EAILTx (2007) trial did not reach statistical significance at 3 years, but the incidence of BOS was 10.7% in the tacrolimus arm and 19.6% in the cyclosporin arm. The pooled data showed a statistically significant difference in the incidence of BOS favouring tacrolimus.

Incidence of BOS in the Zuckermann (2003) and EAILTx (2007) trials - individual trial and pooled results

	Tacrolimus	Cyclosporin	Relative risk (95% CI)	Risk difference (95% CI)
1 year				
Zuckermann (2003)	3/37 (8%)	3/37 (8%)	1.00 (0.22, 4.64)	0.00 (-0.12, 0.12)
EAILTx (2007)	11/128 (8.6%)	17/127 (13.4%)	0.64 (0.31, 1.32)	-0.05 (-0.12, 0.03)
Pooled result from random effects model			0.70 (0.36, 1.33) p=0.27	-0.03 (-0.10, 0.03) p=0.30
3 years				
Zuckermann (2003)	4/37 (10%)	15/37 (41%)	0.27 (0.10, 0.73)	-0.30 (-0.48, -0.11)
EAILTx (2007)	12/112 (10.7%)	21/107 (19.6%)	0.55 (0.22, 1.05)	-0.09 (-0.18, 0.01)
Pooled result from random effects model			0.42 (0.22, 0.83) p=0.01	-0.18 (-0.38, 0.03) p=0.09

Survival

Survival was a secondary outcome of the Zuckermann (2003) and EAILTx (2007) trials. Overall survival was not reported in the Hachem (2007) trial. Overall patient survival is not statistically significantly different at year 1 or year 3 between tacrolimus and cyclosporin. The table below summarises the results at 1 and 3 years and the pooled results.

Overall patient survival Zuckermann (2003) and EAILTx (2007)

	Tacrolimus	Cyclosporin	Relative risk (95% CI)	Risk difference (95% CI)
1 year				
Zuckermann (2003)	26/37 (71%)	30/37 (82%)	0.87 (0.67, 1.13)	-0.11 (-0.30, 0.09)
EAILTx (2007)	109/128 (85%)	114/127 (90%)	0.95 (0.86, 1.04)	-0.05 (-0.13, 0.04)
Pooled result from random effects model			0.94 (0.86, 1.03) p=0.16	-0.06 (-0.13, 0.02) p=0.15
3 years				
Zuckermann (2003)	25/37 (68%)	21/37 (57%)	1.19 (0.83, 1.70)	0.11 (-0.11, 0.33)
EAILTx (2007)	88/112 (79%)	87/107 (81%)	0.97 (0.85, 1.10)	-0.03 (-0.13, 0.08)
Pooled result from random effects model			1.01 (0.85, 1.19) p=0.95	0.01 (-0.11, 0.12) p=0.92

The submission claimed that tacrolimus had a different but non-inferior toxicity profile when compared to cyclosporin. The submission concluded that tacrolimus was less likely to cause hypertension and dyslypidaemia, but may cause more diabetes mellitus than cyclosporin.

The PBAC has previously considered tacrolimus to have less toxicity than cyclosporin in the treatment of cardiac allograft rejection.

9. Clinical Claim

The submission described tacrolimus as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over cyclosporin.

The PBAC noted that statistically significant results favouring tacrolimus were observed in freedom from acute rejection ≥ A2 at 1 year and in incidence of bronchiolitis obliterans syndrome (BOS) at 3 years using the pooled data from the EAILTx (2007) and Zuckermann (2003) trials. The PBAC also noted that there was no significant difference in overall survival at 1 and 3 years.

10. Economic Analysis

The submission presented a stepped economic evaluation, based on pooled results from 2 of the key direct randomised trials (Zuckermann, 2003; EAILTx, 2007) and implementing a stepped modelled evaluation.

The types of economic evaluation presented are a cost-utility analysis and cost-effectiveness analyses.

The results of the Step 1 economic evaluation comparing tacrolimus with cyclosporin show the incremental cost per patient free from acute rejection over the one-year period to be less than $15,000. The results of the Steps 2 and 3 economic evaluation evaluating tacrolimus versus cyclosporin with regard to incidence of BOS show treatment with tacrolimus to be dominant, as it provides additional clinical benefit for lung transplant recipients and is less costly.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the number of patients receiving tacrolimus for this new indication would be less than 10,000 per year in the first 5 years of listing, with a financial saving to the PBS of less than $10 million per year in the first 5 years of listing.

12. Recommendation and Reasons

The PBAC recommended extending the listings for tacrolimus to include lung allograft rejection on the basis of acceptable cost effectiveness over cyclosporin.

The PBAC noted that statistically significant results favouring tacrolimus were observed in freedom from acute rejection ≥ A2 at 1 year and in incidence of bronchiolitis obliterans syndrome (BOS) at 3 years using the pooled data of the EAILTx (2007) and Zuckermann (2007) trials.

The PBAC noted that there was no significant difference in overall survival between tacrolimus and cyclosporin at 1 and 3 years.

In relation to adverse effects, the PBAC noted that the studies presented showed adverse effects associated with tacrolimus to be different to, but no worse than cyclosporin.

Recommendation

TACROLIMUS, capsule, 500 microgram, 1 mg and 5 mg.

Amend the current S100 and S85 listings to read as follows:
(NB: Retain current caution)

Restriction:	Section 100 (Highly Specialised Drugs Program) Private hospital Authority required Management of rejection, under the supervision and direction of a transplant unit, in patients receiving this drug for: (a) prophylaxis and treatment of liver allograft rejection. Management includes initiation, stabilisation and review of therapy as required; or (b) prophylaxis and treatment of renal allograft rejection. Management includes initiation, stabilisation and review of therapy as required; or (c) prophylaxis and treatment of cardiac allograft rejection. Management includes initiation, stabilisation and review of therapy as required; or (d) prophylaxis and treatment of lung allograft rejection. Management includes initiation, stabilisation and review of therapy as required.
Pack size:	100 (500 microgram and 1 mg strengths), 50 (5 mg strength)
	Section 85 Authority required Maintenance therapy, following initiation and stabilisation of treatment with tacrolimus and where therapy remains under the supervision and direction of the transplant unit reviewing that patient, of patients with: (a) liver transplants. The name of the specialised transplant unit reviewing treatment and the date of the latest review at the specialised transplant unit must be included in the authority application; or (b) renal transplants. The name of the specialised transplant unit reviewing treatment and the date of the latest review at the specialised transplant unit must be included in the authority application; or (c) cardiac transplants. The name of the specialised transplant unit reviewing treatment and the date of the latest review at the specialised transplant unit must be included in the authority application; or (d) lung transplants. The name of the specialised transplant unit reviewing treatment and the date of the latest review at the specialised transplant unit must be included in the authority application.
Maximum quantity:	100 (Capsules 500 micrograms and 1 mg) 50 (Capsule 5 mg)
Repeats:	3 (all strengths)

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 welcomes this decision by the PBAC to recommend listing of an alternative calcineurin inhibitor for Australian patients following lung transplantation.