PUBLIC SUMMARY DOCUMENT
Product: TACROLIMUS, capsules, 500 micrograms, 1 mg and 5 mg, Prograf®
Sponsor: Janssen-Cilag Pty Ltd
Date of PBAC Consideration: November 2007

1. Purpose of Application

The submission sought an extension to the current Section 85 and Section 100 (Highly Specialised Drugs Program) listings to include cardiac 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 for PBS-subsidy for the treatment following cardiac 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. In September 1999, the PBAC recommended extending the listing to include prevention of kidney transplant rejection due to an advantage of tacrolimus over cyclosporin in biopsy-proven graft rejection.

3. Registration Status

Tacrolimus is indicated for use as an adjunct to liver, kidney, lung or heart 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.

Section 100 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.

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Tacrolimus would provide another option for maintenance of immunosuppression following heart transplant.

6. Comparator

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

7. Clinical Trials

The submission was based on three direct randomised comparative trials of tacrolimus (TAC) versus cyclosporin (CYA) in immunosuppression post heart transplantation used in combination with mycophenolate mofetil (MMF) and oral corticosteroids (steroids).

Kobash06 was nominated by the submission as the key trial and trials Mehra02 and Meiser04 were nominated as supportive trials. These trials have been published as follows:

Table B.2.1: Trials and associated reports presented in the submission

Trial/First author	Protocol title	Publication citation
Kobash06 Kobashigawa et al 2006	Tacrolimus with mycophenolate mofetil (MMF) or sirolimus vs. cyclosporin with MMF in cardiac transplant: 1-year report.	American Journal of Transplantation; 2006: 6:1377-1386.
Mehra02 Mehra et al 2001 Mehra et al 2002	A randomised comparison of an immunosuppressive strategy using tacrolimus and cyclosporin in black heart transplant recipients. Ethnic disparity in clinical outcome after heart transplantation is arrogated using tacrolimus and mycophenolate mofetil-based Immunosuppression.	Transplantation Proceedings 2001; 33:1606-1607 Transplantation 2002: 74:1568-1573.
Meiser04 Meiser et al 2004	Tacrolimus or cyclosporin: Which is the better partner for mycophenolate mofetil in heart transplant recipients?	Transplantation 2004; 78(4): 591-598

8. Results of Trials

The results of primary efficacy outcomes for Kobash06, Mehra02 and Meiser04 are summarised in the tables and figure below.

Summary of outcomes in graft rejection – key trial Kobash06

Trials	Outcomes	TAC/MMF n/N (%)	CYA/MMF n/N (%)	Risk difference (95% CI)	P value
Kobash06	Number of patients with acute rejection grade ≥3A or HDC requiring treatment				
	- 6 mths	24[a]/107 (22.4%)	36[a]/114 (31.6%)	0.0914 (-0.025, 0.208)	0.126
	- 12 mths	25/107 (23.4%)	42/114 (36.8%)	-0.135 (-0.254, -0.015)	0.029
	Treated acute rejection episodes (at 1 yr)	45/107 (42.1%)	68/115 (59.1%)	-0.171 (-0.300, -0.041)	0.011
	HDC (at 1 yr)	4/107 (3.7%)	9/115 (7.8%)	-0.041 (-0.102, 0.002)	0.195

Abbreviations: TAC=tacrolimus; CYA=cyclosporin; MMF=mycophenolate mofetil; HDC=haemodynamic compromise, Grade=refers to ISHLT cardiac biopsy grading

The protocol defined primary outcome of the key trial Kobash06 was the number of patients with acute rejection at 6 months. After the completion of the study, the primary analysis set was redefined so that patient and graft survival at 12 months, biopsy-verified acute rejection ≥3A and biopsy-verified acute rejection ≥3A with HDC were highlighted as the primary efficacy endpoints.

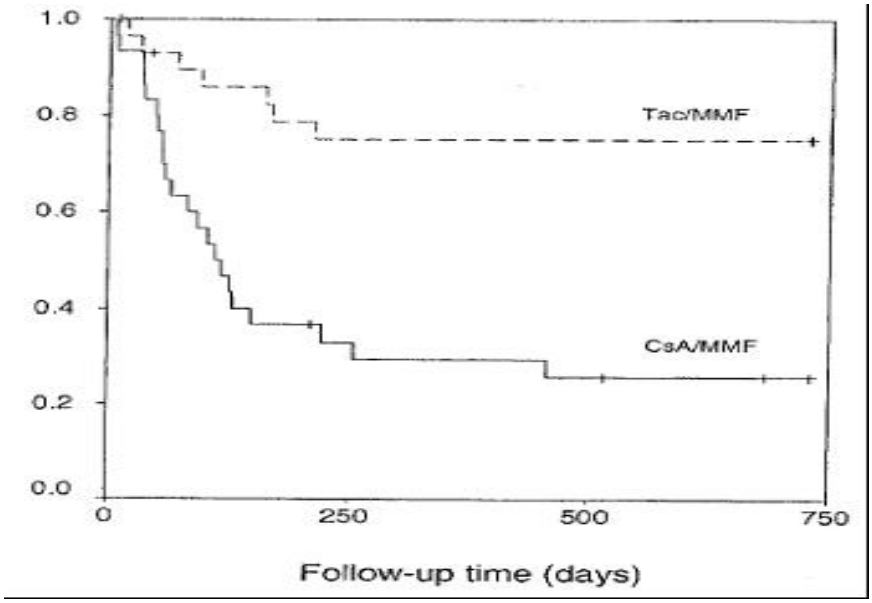
In Kobash06 the differences in patients with treated acute rejection grade ≥3A or HDC requiring treatment at 12 months and treated acute rejection episodes at 12 months reached statistical significance. A number of other outcomes also suggested a trend in the favour of treatment with tacrolimus.

Summary of trial outcomes in graft rejections - supporting studies

Trials	Outcomes	TAC/MMF n/N (%)	CYA/MMF n/N (%)	P value
Mehra02	Freedom from rejection requiring treatment at 1 year	13a/20 (64%)	8/22 (37%)	0.01
Meiser04	Freedom from acute rejection at two years	See figure below	See figure below	P=0.0001

Abbreviations: TAC=tacrolimus; CYA=cyclosporin; MMF=mycophenolate mofetil; Grade=refers to ISHLT cardiac biopsy grading;

Primary outcome of Meiser04: Freedom from acute rejection. Kaplan-Meier analysis for two years after transplantation



The patient/graft survival outcomes from the trials are summarised in table below.

Results of patient and graft survival in randomised trials.

Trial	Outcome	TAC/MMF n/N=(%)	CYA/MMF n/N (%)	P value
Mehra02	Patient or graft survival at one year	19/20 (95%)	16/22 (73%)	0.04
Meiser04	Overall patient survival at two years	28/30 (93.3%)	27/30 (90.0%)	0.65

Abbreviations: N=number treated; Rand N=number randomised; TAC=tacrolimus; CYA=cyclosporin; MMF=mycophenolate mofetil;

No difference was observed in patient graft survival at one year in the key trial Kobash06.

Overall treatment related discontinuations due to any target adverse event were more common in cyclosporin treated patients compared to tacrolimus treated patients (21.7% vs 8.4%, p=0.006). Discontinuations due to refractory rejection were statistically higher in cyclosporin treated patients compared to tacrolimus treated patients (11.3% vs0%, p=0.0003).

Renal function outcomes varied across the trials, however overall renal toxicity appeared to be similar between tacrolimus and cyclosporin treated patients. Diabetogenicity was generally comparable between the tacrolimus and cyclosporin treated patients however numerically more patients treated with tacrolimus experienced glucose intolerance. In general, more cases of hyperlipidaemia were reported for cyclosporin compared with tacrolimus treated patients. Hypertension was generally more common in cyclosporin treated patients. Cosmesis was better for patients treated with tacrolimus: significantly less hirsutism and gingival hypertrophy were detected in Kobash06. All other safety profiles were similar between tacrolimus and cyclosporin.

Overall, the toxicity profile favoured tacrolimus.

9. Clinical Claim

The submission claimed that tacrolimus has superior effectiveness (in terms of the composite primary endpoint of biopsy-verified grade ≥3A or haemodynamic compromise acute rejection as well as secondary endpoint of any treated acute rejection) and non-inferior safety when compared with cyclosporin (both in combination with mycophenolate mofetil) following heart transplantation. Overall, the PBAC agreed that the totality of the data presented supports tacrolimus being more effective in terms of rejection rates and in having less toxicity than cyclosporin. (*see Recommendation and Reasons*).

10. Economic Analysis

The submission presented a modelled economic evaluation. A cost-analysis approach was undertaken which assumed a time horizon of 12 months and included drug costs and costs associated with rejection and adverse events.

The submission estimated that treatment with tacrolimus compared with cyclosporin based regimens may be associated with a small cost saving per patient per year.

For the PBAC's view of the economic analysis, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the number of patients would be less than 10,000 per year in at least the first four years of listing. The estimated net cost to the PBS of listing tacrolimus for the new indication was less than $10 million per year in the first four years of listing.

12. Recommendation and Reasons

The PBAC recommended an extension to the current Section 100 and Section 85 listings for tacrolimus to include cardiac allograft rejection on the basis of acceptable cost-effectiveness over cyclosporin at the price proposed in the submission.

Although the PBAC considered that the key trial Kobash06 did not detect any statistically significant differences in the primary efficacy outcome of incidence of biopsy-verified grade ≥3A or haemodynamic compromise (HDC) acute rejection requiring treatment at 6 months, a statistically significant difference in this outcome favouring tacrolimus was detected at 12 months. The grade ≥3A with HDC outcome is a particularly relevant clinical outcome for the maintenance of the graft. The PBAC accepted the sponsor's explanation that the non significant difference observed at 6 months may have been due to a higher dropout rate due to adverse events in the cyclosporin arm (15%) compared to the tacrolimus arm (9%) which may have introduced a bias against tacrolimus as more switching occurred from cyclosporin to tacrolimus prior to any emergence of acute rejection.

Overall, the PBAC agreed that the totality of the data presented supports tacrolimus being more effective in terms of rejection rates and in having less toxicity than cyclosporin. The economic analysis suggests that the price differential per year for tacrolimus over cyclosporin yields acceptable value for money in a procedure which has limited availability and where any improvement in regard to rejection rates has substantial potential benefits.

The restriction wording will be as requested by the sponsor.

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 heart transplantation.