PUBLIC SUMMARY DOCUMENT
Product: Mycophenolate sodium, tablet (enteric coated), 180 mg and 360 mg (mycophenolic acid), Myfortic®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: July 2012

1. Purpose of Application

Re-submission to extend the current Section 100 (Highly Specialised Drugs Program) Private Hospital Authority Required and Public Hospital Authority Required (STREAMLINED) and General Schedule Authority Required listings to include the treatment, initiated by or in consultation with a nephrologist, of patients with biopsy-proven WHO Class III, IV or V lupus nephritis.

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

This is the second consideration of this indication by the PBAC.

The first submission was considered at the November 2011 PBAC meeting. The PBAC noted that the Expert Advisory Panel had identified the need for mycophenolate therapy for the treatment of lupus nephritis due to the relatively high prevalence in the ATSI population and had written to the sponsors of mycophenolate to ask them to seek TGA registration and PBS listing for this indication. The PBAC deferred its decision on a submission for mycophenolate sodium (MPS) for the treatment of lupus nephritis (LN) until further discussion with the sponsor had taken place regarding a different approach to the economic modelling as well as further clarification regarding the status of the TGA consideration of MPS for the treatment of LN.

3. Registration Status

At the time of the July 2012 PBAC consideration, mycophenolate sodium was not yet registered for the induction and maintenance treatment of adult patients with WHO Class III, IV or V lupus nephritis.

The proposed indication was subsequently registered by the TGA on 7 September 2012 as follows:

Myfortic is indicated for induction and maintenance treatment of adult patients with WHO Class III, IV or V lupus nephritis.

4. Listing Requested and PBAC's View

Section 100
Public Hospital Authority Required (STREAMLINED)
Private Hospital Authority Required
Caution: Careful monitoring of patients is mandatory

Initiation of therapy with mycophenolate sodium by a nephrologist, or in consultation with a nephrologist, of a patient with biopsy-proven WHO Class III, IV or V lupus nephritis. The name of the consulting nephrologist must be included in the authority application.

Note:
A maximum quantity and number of repeats to provide for an initial course (24 weeks) of mycophenolate sodium will be authorised. Assessment of response to therapy must be made 22 to 24 weeks after the first dose.

Section 100
Public Hospital Authority Required (STREAMLINED)
Private Hospital Authority Required
Caution: Careful monitoring of patients is mandatory

Maintenance therapy, following initiation of and documented response to treatment with mycophenolate sodium and where therapy remains under the supervision and direction of a nephrologist reviewing the patient, of patients with biopsy-proven WHO Class III, IV or V lupus nephritis. The name of the nephrologist reviewing treatment and the date of the latest review, which must be within the last 12 months, must be included in the authority application.

Section 85- Authority Required
Caution: Careful monitoring of patients is mandatory

Maintenance therapy, following initiation of and documented response to treatment with mycophenolate sodium and where therapy remains under the supervision and direction of a nephrologist reviewing the patient, of patients with biopsy-proven WHO Class III, IV or V lupus nephritis. The name of the nephrologist reviewing treatment and the date of the latest review, which must be within the last 12 months, must be included in the authority application.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Lupus nephritis (LN) is a common renal manifestation of systemic lupus erythematosus (SLE) which may present as the sole clinical manifestation of SLE, or more commonly as part of multi-organ involvement. Mortality in SLE patients is highest amongst patients with renal involvement and progression to renal failure is strongly predictive of death. After diagnosis of LN stage III to V, patients may receive induction therapy with intravenous cyclophosphamide for 6 months then maintenance therapy with azathioprine.

The submission proposed that the place in therapy of mycophenolate sodium is as an alternative PBS-subsidised therapy to intravenous cyclophosphamide for induction and oral azathioprine for maintenance treatment of LN.

6. Comparator

The submission nominated intravenous cyclophosphamide (IVCP) as the comparator for the induction phase and azathioprine (AZA) as the comparator for the maintenance phase.

The PBAC reaffirmed the November 2011 recommendation that the appropriate comparators were IV cyclophosphamide for the induction phase and azathioprine for the maintenance phase.

7. Clinical Trials

There are no direct randomised controlled trials comparing MPS with either comparator. Therefore the re-submission, consistent with the previous submission, assumed that MPS is equivalent to mycophenolate mofetil (MMF), and therefore presented comparative trials of MMF versus IVCP in induction therapy and MMF versus AZA in maintenance therapy.

The re-submission did not update its clinical trial search from the previous submission. Instead the submission provided the draft (Academic-In-Confidence) Cochrane Review of LN. The trials, all using MMF rather than MPS, identified and included in the Cochrane review formed the primary evidence base for the re-submission:

- Six head-to-head randomised trials comparing MMF to IVCP for induction treatment (Appel 2009 [ALMS-induction]; El-Shafey 2010; Ginzler 2005; Li 2009; Mulic-Bacic 2008; Ong 2005). All but two of these trials (Li 2009; Mulic-Bacic 2008) have previously been considered by the PBAC.
- Three head-to-head randomised trials comparing MMF to AZA for maintenance treatment (Contreras 2004; Houssiau 2010; Dooley 2011 [ALMS-maintenance]). All of these trials have previously been considered by the PBAC; Dooley (2011) is a full publication of the results reported in the abstract by Wofsy (2010).

Although all included trials enrolled patients with WHO Class III-V LN, they differed in terms of baseline patient characteristics and study design.

Details of the MPS and MMF trials and associated reports published at the time of submission are in the table below.

Trial ID / First author	Protocol title/ Publication title	Publication citation
Studies of MPS in LN		
Kitiyakara 2008	Treatment of lupus nephritis and primary glomerulonephritis with enteric-coated mycophenolate sodium.	Clinical Nephrology 2008;69(2):90-101.
Mak 2008	Efficacy of enteric-coated mycophenolate sodium in patients with active lupus nephritis.	Nephrology 2008;13:331-6.
Traitanon 2008	Efficacy of enteric-coated mycophenolate sodium in patients with resistant-type lupus nephritis: a prospective study.	Lupus 2008 Aug 1;17(8):744-51.
Vazquez 2006	Preliminary results in Lupus Nephritis patients treated with enteric coated mycophenolate sodium.	American Society of Nephrology meeting 2006.
Zeher 2011	Efficacy and safety of enteric-coated mycophenolate sodium in combination with two glucocorticoid regimens for the treatment of active lupus nephritis.	Lupus 2011; 20(14):1484-93
Induction trials of MMF versus IVCP		
Appel et al 2009 Sinclair A et al 2007	Mycophenolate Mofetil versus Cyclophosphamide for Induction Treatment of Lupus Nephritis. Mycophenolate mofetil as induction therapy for lupus nephritis: rationale and protocol for the randomised, controlled Aspreva Lupus Management Study (ALMS).	J Am Soc Nephrol 2009; 20(5):1103-12. Lupus 2007; 16:972-980.

Sundel RP, Lisk L, 2008	Mycophenolate mofetil compare with Intravenous Cyclophosphamide as Induction Treatment for Pediatric Lupus Nephritis: A Randomized Trial.	American College of Rheumatology - Annual Scientific Meeting [Poster 1247]. 2008.
El-Shafey et al 2010	Is mycophenolate mofetil superior to pulse intravenous cyclophosphamide for induction therapy of proliferate lupus nephritis in Egyptian patients.	Clincal Expertimential Nephrology 2010; 14:214-21.
Ginzler et al 2005	Mycophenolate Mofetil or Intravenous Cyclophosphamide for Lupus Nephritis.	New England Journal of Medicine 2005; 353(21):2219-28.
Li et al 2011 Li et al 2009	Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide. [ABSTRACT ONLY]	Nephrol Dial Transplant 2011; [Electronic publication Sep 11 ahead of print] J Am Soc Nephrol 2009;20:391A
Mulic-Bacic et al 2008	Mycophenolate mofetil or intravenous cyclophosphamide in treatment of lupus nephritis.	Annals of the Rheumatic Diseases 2008;67(Suppl II):S349
Ong et al 2005	Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis.	Nephrology 2005;10(5):504-10.
Maintenance trials of MMF versus AZA		
Contreras et al 2004	Sequential Therapies for Proliferative Lupus Nephritis.	New England Journal of Medicine 2004; 350(10):971-80.
Dooley et al 2011 Wofsy D et al 2010	Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. Asprev Lupus management study maintenance results. (Abstract CS12.6 /PO2.E.23).	New England Journal of Medicine 2011; 365(20):1886-1895. 9th International Congress on Lupus 2010.
Houssiau et al 2010	Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial.	Annals of the Rheumatic Diseases 2010;69(12):2083-9.

8. Results of Trials

STUDIES WITH MPS:

The number and proportion of patients experiencing a partial or complete response in the MPS trials were presented in the re-submission.

The pooled partial or complete response ranged from 56.3% of patients on MPS in Traitanon et al (2008) to 100% of MPS patients in Mak et al (2008). The re-submission claimed that this was comparable with the rates reported for the MMF arms of the MMF vs IVCP for induction phase trials.

INDUCTION PHASE: MMF VERSUS IVCP

The MMF induction trials in the meta-analysis show considerable differences between baseline patient characteristics, study design and differences in the definitions for each outcome (complete response (CR) and partial response (PR)) between trials. For the outcome of PR, none of the trials detected a statistically significant difference between the MMF and

IVCP treatment arms. For CR and any response (i.e. CR or PR) the risk difference (RD) reported by Ginzler 2005 demonstrated that statistically significantly more patients treated with MMF had achieved a CR and any response versus IVCP, however this difference was no longer statistically significant for the relative risk (RR).

The patients enrolled in Ginzler (2005) were largely similar to those enrolled in the other induction trials, with the exception that more patients enrolled in Ginzler (2005) had Stage V kidney histology and a higher mean 24 hour urine protein level. It is not known whether these differences in baseline characteristics lead to the differences in the results reported.

The meta-analysis results of the PR, CR and any response comparisons were not statistically significant between MMF and IVCP. The results are generally similar to those presented in the previous submission; however while the RD of the meta-analysis of PR/CR excluding Li (2009) and Mulic-Bacic (2008) is just significant, the RR is not.

MAINTENANCE PHASE: MMF VERSUS AZA

The MMF maintenance trials in the meta-analysis show considerable differences in baseline patient characteristics, study design and differences in the definitions for each outcome. All three maintenance trials detected fewer renal relapses in patients treated with MMF compared to AZA. In Dooley (2011), the difference was also statistically significant, with 16.4% and 32.4% of patients experiencing a renal relapse whilst on maintenance therapy with MMF and AZA, respectively. Dooley (2011) enrolled patients who may have had a better prognosis than the other trials (lower baseline serum creatinine and shorter duration of LN), thus the results should be interpreted cautiously as it is not known how these characteristics compare with the likely PBS population.

In the meta-analysis (whose result is largely driven by the results of Dooley 2011), there is a statistically significant reduction in relapse rates for MMF versus AZA. Compared with the previous submission, the appropriate removal of Chan (2005), which showed fewer renal relapses with AZA, has improved the RD and RR statistics in favour of MMF and switched the significance of the RR statistic from non-significant to significant.

For PBAC's view on these results, see Recommendation and Reasons.

The re-submission presented new toxicity data, which was consistent with data presented in the previous submission. Diarrhoea was more frequently reported in the MMF treatment arms. This is a known adverse event (AE) of MMF and hence consistent with the PI. There were more frequent reports of alopecia and lymphopenia in the IVCP treatment arms in the induction phase trials and a higher incidence of leucopenia in the AZA treatment arms in the maintenance phase trials. Incidences of all infections were comparable amongst all of the trials. No new data informing an extended assessment of comparative harms was presented in the re-submission.

9. Clinical Claim

The re-submission described MMF (MPS):

- For induction therapy: as non-inferior in terms of comparative effectiveness and superior in terms of comparative safety over IVCP; and
- For maintenance therapy: as superior in terms of comparative effectiveness and non-

inferior in terms of comparative safety over AZA.

The PBAC accepted that mycophenolate is equivalent to IV cyclophosphamide for response to induction therapy and as effective as azathioprine in the maintenance phase. The Committee noted that the re-submission had not made a cost-effectiveness claim over azathioprine.

In regard to safety, the PBAC noted that mycophenolate is a less toxic drug in the induction phase of LN compared to IVCP and had similar toxicity compared to azathioprine.

10. Economic Analysis

The re-submission presented an updated economic evaluation using a cost-consequence approach, compared with a cost-effectiveness analysis estimating an ICER for "additional cost per responder at 42 months" in the previous submission.

The cost analysis compared:

(i) the costs of the current induction treatment algorithm of using IVCP versus the proposed regiment of using MPS, and

(ii) the costs of the current maintenance treatment algorithm of using AZA versus the proposed regimen of using MPS.

The analysis assumed 6 months of induction and 36 months of maintenance treatment. A 'cost-minimised' price was derived from the cost analysis by calculating the MPS price which gave a zero cost difference across the current and proposed algorithms.

The re-submission calculated the weighted average price based on the proportion of milligrams of MPS used in the induction and maintenance settings rather than the proportion of patients assumed to be in each stage of therapy.

Should maintenance therapy exceed 36 months, there will be additional use in this stage of therapy which would consequently result in a decreased overall price for MPS.

For PBAC's view see Recommendation and Reasons

11. Estimated PBS Usage and Financial Implications

The re-submission estimated the likely number of patients, in the induction and maintenance phase of therapy, to be less than 10,000 in Year 5.

The PBAC considered that the estimates of patients were very uncertain, and likely to be an overestimate.

The re-submission estimated the financial cost/year to the PBS (excluding co-payments), minus any savings in use of other drugs, to be less than $10 million in Year 5 of listing.

12. Recommendation and Reasons

The PBAC recommended extending the current General Schedule Authority Required listing to include maintenance treatment, following initiation and stabilisation, of patients with biopsy-proven WHO Class III, IV or V lupus nephritis, where therapy remains under the supervision and direction of a nephrologist reviewing the patient, and extending the Section 100 Highly Specialised Drugs Program Private Hospital Authority Required and Public Hospital Authority Required (Streamlined) listings to include management by or in

consultation with a nephrologist, of patients with biopsy-proven WHO Class III, IV or V lupus nephritis.

The PBAC noted that lupus nephritis is a rare illness with high clinical need.

The PBAC recommended mycophenolate sodium on a cost minimisation basis to IV cyclophosphamide in the induction phase and on a cost minimisation basis to azathioprine in the maintenance phase.

The PBAC reaffirmed that the appropriate comparators were IV cyclophosphamide for the induction phase and azathioprine for the maintenance phase.

The PBAC noted that no evidence against the appropriate comparators for mycophenolate sodium had been presented in the re-submission, but considered that it could be pragmatically substituted for mycophenolate mofetil.

The PBAC considered that based on the meta-analysis results presented in the re-submission of response to induction therapy, which included six head-to-head trials comparing mycophenolate mofetil to IV cyclophosphamide, there was reasonable evidence that mycophenolate is equivalent to IV cyclophosphamide for response to induction therapy.

For the comparison of mycophenolate to azathioprine in maintenance treatment, the PBAC noted the results of a meta-analysis including three trials (Contreras 2004; Houssiau 2010; and Dooley 2011) showing a statistically significantly greater reduction in renal relapse for mycophenolate compared to azathioprine. However, only the Dooley (2011) trial reported a statistically significant reduction in renal relapse, with the Contreras (2004) and Houssiau (2010) trials demonstrating a trend towards less relapse. The PBAC accepted that mycophenolate is as effective as azathioprine in the maintenance phase and the Committee noted that the re-submission had not made a cost-effectiveness claim over azathioprine.

The PBAC noted that mycophenolate is a less toxic drug in the induction phase of lupus nephritis compared to IV cyclophosphamide. The PBAC further considered that mycophenolate had a similar toxicity compared to azathioprine.

The PBAC noted that the cost-minimisation presented in the re-submission is based on a lower cost of mycophenolate in the induction phase when compared to IV cyclophosphamide, which also has additional costs associated with gonadal toxicity that increases its comparative cost against mycophenolate. However, the PBAC noted that there is a significantly higher drug cost for mycophenolate in the maintenance phase in comparison to azathioprine, which is offset by the lower cost of mycophenolate in the induction phase. The PBAC noted that there is extensive use of mycophenolate in the maintenance phase, and this could potentially be longer than the assumption of 36 months used in the cost analysis. The PBAC was therefore uncertain whether mycophenolate would remain cost equivalent with its comparators if the maintenance phase extends beyond 36 months.

Recommendation:
MYCOPHENOLATE SODIUM, tablet (enteric coated), 180 mg and 360 mg (mycophenolic acid)

Restriction:	Caution: Careful monitoring of patients in mandatory. Authority Required Maintenance therapy, following initiation treatment, of a patient with biopsy-proven WHO Class III, IV or V lupus nephritis where therapy remains under the supervision and direction of a nephrologist reviewing the patient. The name of the nephrologist reviewing treatment and the date of the latest review, which must be within the last 12 months, must be included in the authority application.
Max Qty: Rpts:	120 5
	Caution: Careful monitoring of patients in mandatory. Section 100 (Highly Specialised Drugs Program) Public Hospital Authority Required (STREAMLINED) Private Hospital Authority Required Management of a patient with biopsy-proven WHO Class III, IV or V lupus nephritis by or in consultation with a nephrologist. The name of the consulting nephrologist must be included in the patient medical records. Management includes initiation, stabilisation and review of therapy as required.
Max Qty: Rpts:	240 5

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

Novartis welcomes the PBAC's decision and is pleased to have been able to respond to the request from the Expert Advisory Panel to seek TGA registration and PBS listing for patients with lupus nephritis.