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: November 2011

1. Purpose of Application

To extend the current Section 100 (Highly Specialised Drugs Program) and Section 85 Authority Required listing to include treatment, initiated by a nephrologist, of a patient 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 drug had not previously been considered by the PBAC for this indication.

3. Registration Status

The submission was considered for registration and PBS listing under the TGA/PBAC parallel process. At the time of PBAC consideration, only the Clinical Evaluation Report was available and 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 of a patient with biopsy-proven WHO Class III, IV or V lupus nephritis.

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 receive induction therapy with intravenous cyclophosphamide for 6 months then maintenance therapy with azathioprine. Patients may also be treated with mycophenolate, but this is not currently PBS-subsidised for LN.

The submission proposed that the place in therapy of mycophenolate sodium (MPS) is as an alternative therapy to IV cyclophosphamide for induction and to 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, both were considered appropriate by the PBAC.

7. Clinical Trials

The submission provided no direct comparative evidence of mycophenolate sodium (MPS) versus the nominated comparators (IVCP in the induction and AZA in the maintenance phases of treatment for LN).

The evidence presented for MPS were mostly non-randomised single arm studies:

- Flanc (2004): retrospective case series conducted in Thailand;
- Mak (2008): retrospective case series conducted in Hong Kong;
- Traitanon (2008): prospective cohort study conducted in Thailand. Includes a historical control group treated with IVCP; and
- Vazquez (2006): prospective cohort study conducted in Argentina.
- Trial 2420: a randomised trial which compared MPS + standard dose oral corticosteroids (SDO) versus MPS + low dose oral corticosteroids (LDO).

The 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:

- four direct randomised comparative trials of MMF and IVCP in induction therapy: Appel (2009), El-Shafey (2010), Ginzler (2005) and Ong (2005); and
- four direct randomised comparative trials of MMF and AZA in maintenance therapy: Chan (2005), Contreras (2004), Houssiau (2010) and Wofsy (2010). Wofsy (2010) reports the result of the maintenance phase of the ALMS trial, induction phase results were

reported by Appel (2009).

The submission assumed that the accepted dose relativity in renal transplantation (1440 mg/day MPS is equivalent to 2 g/day MMF) would also apply to LN.

The following trials had been published at the time of submission:

Trial ID	Protocol title / Publication title	Publication
Non randomised studies of MPS in LN		
Kitiyakara et al	Treatment of lupus nephritis and primary glomerulonephritis with enteric-coated mycophenolate sodium.	Clinical Nephrology 2008;69(2):90-101.
Mak S et al	Efficacy of enteric-coated mycophenolate sodium in patients with active lupus nephritis.	Nephrology 2008;13:331-6.
Traitanon O et al	Efficacy of enteric-coated mycophenolate sodium in patients with resistant-type lupus nephritis: a prospective study.	Lupus 2008 Aug 1;17(8):744-51.
Avihingsanon Y et al	Enteric-Coated Mycophenolate Sodium (EC-MPS, Myfortic ®) for the Treatment of Resistant Lupus Nephritis.	Abstract presented at the American Society of Nephrology meeting 2006.
Jayne D et al	Enteric-Coated Mycophenolate Sodium (EC-MPS) for the Treatment of Lupus Nephritis - MyLupus Study.	J Am Soc Nephrol 2010;21 (Abstract 2253):626A.
Vazquez V et al	Preliminary results in Lupus Nephritis patients treated with enteric coated mycophenolate sodium.	Abstract presented at the American Society of Nephrology meeting 2006.
Trials of MMF in LN		
Induction therapy of MMF versus IVCP		
Appel GB et al	Mycophenolate Mofetil versus Cyclophosphamide for Induction Treatment of Lupus Nephritis.	J Am Soc Nephrol 2009; 20(5):1103-12.
El-Shafey E et al	Is mycophenolate mofetil superior to pulse intravenous cyclophosphamide for induction therapy of proliferate lupus nephritis in Egyptian patients.	Clinical Expertimential Nephrology 2010;14:214-21.
Ginzler EM et al	Mycophenolate Mofetil or Intravenous Cyclophosphamide for Lupus Nephritis.	New England Journal of Medicine 2005;353(21):2219-28.
Ong LM et al	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 therapy of MMF vs AZA		
Chan TM et al	Long-Term Study of Mycophenolate Mofetil as Continuous Induction and Maintenance Treatment for Diffuse Proliferative Lupus Nephritis.	J Am Soc Nephrol 2005;16 (4):1076-84.
Contreras G et al	Sequential Therapies for Proliferative Lupus Nephritis.	New England Journal of Medicine 2004;350(10):971-80.
Houssiau FA et al	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.
Wofsy D 2010	Asprev Lupus management study maintenance results. (Abstract CS12.6 /PO2.E.23).	9th International Congress on Lupus 2010.
Otto A.	MMF bests azathioprine for preventing lupus nephritis relapse: Trial finds no new safety signals.	Media Release: Elsevier Global Medical News. 23-7-2010.

8. Results of Trials

Non-randomised studies of MPS:

The number and proportion of patients experiencing a partial or complete response in the MPS trials were presented in the 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 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 number of patients assessed in each trial as having a partial or complete response to induction therapy from the MMF versus IVCP induction trials was presented. The submission also presented results of a meta-analysis.

When the trials were combined in a meta-analysis, the results of comparisons of partial response (PR) and complete response (CR) were not statistically significant between MMF and IVCP, however the result for partial or complete response demonstrated that patients treated with MMF had a higher response rate compared to patients treated with IVCP using risk difference (RD) comparisons, however this result was no longer statistically significant when the analysis was re-conducted using relative risk (RR) comparisons.

Although the PBAC agreed that combining the MMF induction trials in a meta-analysis may not be appropriate due to significant heterogeneity resulting from differences in baseline patient characteristics, study designs and differences in the definitions for each outcome between trials, the results of the analysis were considered helpful in assessing the clinical effectiveness claims.

Maintenance Phase: MMF versus AZA
The number of patients assessed in each trial as having renal relapse was presented. As with the MMF induction trial results the submission also presented results of meta-analyses.

Three of the four trials detected fewer renal relapses in patients treated with MMF compared to AZA. In Wofsy 2010, the difference was also statistically significant.

In the meta-analysis a statistically significant reduction in relapse with MMF versus AZA was demonstrated in the risk difference. However, as with induction therapy, the difference was not statistically significant when relative risk was used. Again, the PBAC agreed that combining the trials in a meta-analysis may not be appropriate due to differences in baseline patient characteristics, study designs and differences in the definitions for each outcome between trials.

The submission claimed the results reported by Wofsy 2010 were the most relevant. Wofsy 2010 trial (which was the maintenance phase of the Appel 2009 induction trial) was the largest trial and the only trial to (a) re-randomise patients at the start of the maintenance phase, and (b) only included patients who had a partial or complete response to induction therapy. However, patients in Contreras 2004 also appeared to have been responders to induction therapy.

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

Based on the trials, 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.

There was 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. The submission argued that after 24 weeks of follow up increased malignancy risk or gonadal toxicity with IVCP was not expected. As the results of the maintenance phase had only been presented in abstract form (Wofsy 2010; Otto 2010), the effect of IVCP therapy on malignancy risk or gonadal toxicity from this trial had not yet been reported.

The submission provided additional data on potential safety concerns beyond those identified in the clinical trials (for MPS, IVCP and AZA).

Safety data from the seventh Post Marketing Safety Update Report (PSUR 7) for MPS were consistent with the known AEs associated with MPS in the renal transplant setting which are documented in the PI. In 2008 a Dear Doctor Letter was issued to advise physicians that cases of progressive multifocal leukoencephalopathy (PML) had occurred in patients taking MMF. The submission stated that thus far no cases of PML have been identified in patients on MPS.

9. Clinical Claim

The submission described MPS:

- For induction therapy: as non-inferior in terms of comparative effectiveness compared with IVCP, but with better safety; and
- For maintenance therapy: as superior in terms of comparative effectiveness over AZA, but with similar safety.

The PBAC considered that for induction therapy MMF (and thus MPS) is probably non-inferior to IVCP and has superior safety, mainly due to avoidance of longer term adverse events of IVCP such as impaired fertility rather than any short term adverse events.

The PBAC accepted that MMF (and thus MPS) is non-inferior to AZA in terms of safety. However, there is still some uncertainty regarding the sponsor's claim of superior efficacy as it is based on one trial reported by Wofsy 2010. Other trials of MMF versus AZA did not detect a statistically significant reduction in rate of renal flares even though the results generally favoured MMF.

10. Economic Analysis

The submission presented a trial based cost effectiveness (CE) analysis comparing the current treatment algorithm, where IVCP is used first-line and MPS used second-line should patients fail to achieve a response to IVCP, with the proposed algorithm, where MPS would be used as first-line therapy followed by IVCP in the event of not achieving a response to MPS. Maintenance phase treatments included AZA or MPS.

The time horizon of the trial based economic evaluation was 42 months (6 months induction and 36 months maintenance).

The costs included were the drug costs, the cost of administering IVCP, and the cost of prophylaxis for potential gonadal toxicity with IVCP.

The analysis estimated the incremental cost per additional responder (drug cost only) to be less than $15,000. When the costs of prophylaxis for toxicity were included, the CE analysis showed that treatment with MPS for lupus nephritis was both more efficacious and less costly.

A comparison of patients treated with MPS in the induction and maintenance phases versus IVCP in the induction and AZA in the maintenance phases (ie, no consideration of second or third line for non-responders) was conducted during the evaluation. The cost per additional responder who did not relapse at 42 months was estimated to be less than $15,000 (assumed 100% of patients who responded to induction received 36 months of maintenance treatment, and no treatment costs for adverse events).

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients was estimated by the submission to be less than 10,000 in year 5 for induction and maintenance treatment. The estimate was considered uncertain.

The net financial cost to the PBS was estimated by the submission to be less than $10 million in year 5. The estimate was considered uncertain.

12. Recommendation and Reasons

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 considered that there is a high clinical need for mycophenolate in both the ATSI population and other patients with lupus nephritis as the oral formulation is more convenient to administer, particularly for patients in rural and remote locations. The PBAC considered that prescribers other than nephrologists might need to be included in the initiation criteria, as patients with lupus nephritis are also treated by other specialists.

The PBAC accepted that intravenous cyclophosphamide (IVCP) is the appropriate comparator for the induction phase and that azathioprine (AZA) is the comparator for the maintenance phase. The PBAC also accepted that mycophenolate sodium was likely to be similarly effective to mycophenolate mofetil and agreed that it reasonable to accept that equi-effectiveness demonstrated in the prevention of transplant rejection would translate to equi-effectiveness in the treatment of LN.

The PBAC noted that the submission provided no direct comparative evidence of MPS versus the nominated comparators and that the evidence presented for MPS is mostly non-randomised single arm studies. The main evidence presented was comparative trials of MMF versus IVCP in induction therapy and MMF versus AZA in maintenance therapy.

For the outcome of partial response for induction therapy, none of the trials detected a statistically significant difference between the MMF and IVCP treatment arms. For CR and any response (ie, CR or PR), the trial reported by Ginzler 2005 demonstrated that significantly more patients treated with MMF had achieved CR and any response versus IVCP (22.5% versus 5.8% for CR, and 52.1% versus 30.4% for any response). However, this difference between proportions of patients with any response was no longer significant when RR was used.

Despite this uncertainty, the PBAC considered that for induction therapy MMF (and thus MPS) is probably non-inferior to IVCP and has superior safety (mainly due to avoidance of longer term adverse events of IVCP (eg. potential to impair fertility) rather than any short term adverse events).

For the comparison of MMF versus azathioprine for maintenance therapy, three of the four trials (Chan 2005, Contreras 2004 and Houssiau 2010 and Wofsy 2010) found fewer renal relapses in patients treated with MMF compared to AZA. In Wofsy 2010, the difference was also statistically significant. The PBAC noted that the meta-analysis demonstrated a statistically significant reduction in relapse with MMF versus AZA for risk difference statistic but as with induction therapy, the difference was not statistically significant using relative risk.

The PBAC accepted that MMF (and thus MPS) is non-inferior to AZA in terms of safety. Notwithstanding that there is some uncertainty as it is based on one trial reported by Wofsy 2010. Other trials of MMF versus AZA did not detect a statistically significant reduction in rate of renal flares even though the results generally favoured MMF.

The PBAC noted that the economic evaluation was a trial based cost effectiveness analysis comparing the current and proposed treatment algorithms, where IVCP is currently used first-line and MPS used second-line should patients fail to achieve a response to IVCP. The proposed algorithm suggested that should MPS be PBS-listed, it would become the therapy of choice as first-line therapy, followed by IVCP in the event of not achieving a response to MPS. The PBAC noted that the model did not include an incremental cost/QALY, therefore, it was difficult to interpret the value of an incremental cost/extra responder over 42 months.

The PBAC considered that a cost-minimisation analysis of MPS versus cyclophosphamide in the induction phase and azathioprine in the maintenance phase may be more appropriate, noting that the evidence regarding the sponsor's claim of superior efficacy of MPS over azathioprine was not as convincing as the evidence for non-inferiority with cyclophosphamide.

The PBAC deferred its decision on the submission for MPS until there is further discussion with the sponsor regarding the approach to the economic modelling as well as further clarification regarding the status of the TGA consideration of MPS for the treatment of lupus nephritis.

The PBAC also acknowledged and noted the consumer comments on this item.

Recommendation:
Defer

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 looks forward to addressing the PBAC's concerns in a re-submission.