



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Mycophenolate sodium

Proprietary Product Name: Myfortic

Sponsor: Novartis Pharmaceuticals Australia Pty
Limited

May 2013

TGA Health Safety
Regulation

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- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
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I. Introduction to product submission

Submission details

<i>Type of Submission:</i>	Major variation – extension of indications
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	7 September 2012
<i>Active ingredient:</i>	Mycophenolate sodium
<i>Product Name:</i>	Myfortic
<i>Sponsor's Name and Address:</i>	Novartis Pharmaceuticals Australia Pty Limited 54 Waterloo Road, North Ryde NSW 2113
<i>Dose form:</i>	Enteric coated tablet
<i>Strengths:</i>	180 mg and 360 mg
<i>Container:</i>	Blister pack
<i>Pack sizes:</i>	50 and 120 tablets
<i>Approved Therapeutic use:</i>	Myfortic is indicated for induction and maintenance treatment of adult patients with WHO Class III, IV or V lupus nephritis. This indication is based on the evidence in literature reports of studies of treatment in patients with lupus nephritis, the majority of whom were ISN/RPS (2003) Class IV. The evidence for efficacy was based on surrogate endpoints. ¹
<i>Route of administration:</i>	Oral
<i>Dosage (abbreviated):</i>	Lupus nephritis patients: Adequate dose finding studies have not been performed. The prescriber should adjust the dose based on clinical response. Induction treatment with Myfortic is usually administered in combination with corticosteroids. The recommended dose is 720 mg administered twice daily (1440 mg daily dose). A daily dose greater than 1440 mg/day has been used for induction therapy in some studies (see 'Clinical Trials' section). This dose may be tapered for maintenance purposes following a complete or partial response.
<i>ARTG Numbers:</i>	91939, 91940

¹ See Weening JJ, D'Agati VD, Schwartz MM, *et al.* The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004;15(2):241-250 for a description of the World Health Organization (WHO) and the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis.

Product background

Mycophenolate sodium (MPS), the active ingredient in Myfortic enteric coated (EC) tablets, is the sodium salt of mycophenolic acid (MPA), an anti-proliferative immunosuppressant belonging to the anti-metabolite class of immunosuppressants. Mycophenolic acid is a non-nucleoside, non-competitive, reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), which is the rate limiting enzyme in the de novo synthesis pathway of guanosine triphosphate (GTP). Both T and B lymphocytes are highly dependent on this pathway for the generation of guanosine nucleotides, whereas non-lymphoid cells can utilise a salvage pathway for generation of GTP. Mycophenolic acid selectively decreases the lymphocyte nucleotide pool and is considered to have potential to decrease recruitment of lymphocytes and monocytes into sites of chronic inflammation.

Myfortic was first registered on the Australian Register of Therapeutic Goods (ARTG) in March 2003 for *the prophylaxis of acute transplant rejection in adult patients receiving allogeneic renal transplants*.

This AusPAR describes the application by Novartis Pharmaceuticals Australia Pty Limited (the sponsor) to extend the approved indications for Myfortic to include the treatment of lupus nephritis (LN).

The current application is a literature based submission. It is specific to Australia and has been submitted in response to a request from the Chair of the Expert Advisory Panel (EAP) on Aboriginal and Torres Strait Islander (ATSI) Medicines to address the current lack of specific LN treatments on the Australian Pharmaceutical Benefits Scheme (PBS), which subsidise the cost of medicines to the consumer.

The extension of indication for Myfortic EC tablets requested initially was:

Myfortic is indicated for induction and maintenance treatment of lupus nephritis.

Following receipt of the initial (first round) clinical evaluation report (CER), the sponsor proposed to amend the requested indication to the following:

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

Myfortic was designated as an orphan drug for induction and maintenance treatment of LN on 11 January 2010.

Published references referred to in this AusPAR have been listed at the end of the document (see References).

Regulatory status

The product received initial ARTG Registration on 26 March 2003. At the time of this approval, no application for Myfortic for induction and maintenance treatment of LN was submitted elsewhere in the world.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Background and rationale

Approximately 60% of patients with systemic lupus erythematosus (SLE) have been documented to develop clinically relevant LN characterised by deposition of immune complexes in the glomeruli and subsequent tissue injury. Using estimates of prevalence of LN, the estimated maximum number of Australians with LN is 1362 for non-indigenous persons and 286 for indigenous individuals.

This application is a literature-based submission. A pre-submission meeting with the TGA was held on 2 February 2010 at which time the literature search strategy was provided by the sponsor. The TGA assessment concluded that the search strategies provided a good coverage of the clinical trials and studies for Myfortic. Updated searches from September 2009 to May 2010 were recommended.

The evidence submitted in support of registration of Myfortic in LN was presented in a total of 45 publications in four main groups:

- Efficacy and safety of Myfortic in treatment of patients with LN
- Equivalency of Myfortic and mycophenolate mofetil (MMF)²
- Efficacy of MMF in patients with LN
- Other references.

The sponsor did not indicate which of the study reports were considered pivotal or supportive. This failure considerably slowed and complicated the process of evaluation.

In direct support of the proposed indication, three articles were submitted, each reporting results of EC tablets containing MPS (EC-MPS) treatment of selected Asian patients, predominantly female, aged 14 to 50 years with World Health Organization (WHO) Class III, IV and V LN (see Table 1, below, for WHO classification definitions). Included were two cohort studies and one prospective study with historical controls treated with monthly intravenous (IV) cyclophosphamide.

A total of 45 patients were treated in these non-randomised, non blinded trials. One patient was maintained in remission following change in treatment from MMF to EC-MPS. Of the remainder, 16/44 achieved complete remission and 17/44 achieved partial remission.

It is conceded that in the process of evaluation of an orphan drug, concessions may have to be made in standards of evidence presented.

² Mycophenolate mofetil (MMF) is the 2-morpholinoethyl ester of MPA and is converted to MPA in the body. It has been registered in Australia since the late 1990s for prophylaxis of organ transplant rejection.

Table 1. World Health Organization morphologic classification of lupus nephritis (modified in 1982)

Class	Characteristics
Class I	Normal glomeruli a. Nil (by all techniques) b. Normal by light microscopy, but deposits by electron or immunofluorescence microscopy
Class II	Pure mesangial alterations (mesangiopathy) a. Mesangial widening and/or mild hypercellularity (+) b. Moderate hypercellularity (++)
Class III	Focal segmental glomerulonephritis (associated with mild or moderate mesangial alterations) a. With “active” necrotizing lesions c. With “active” and sclerosing lesions d. With sclerosing lesions
Class IV	Diffuse glomerulonephritis (severe mesangial, endocapillary or mesangiocapillary proliferation and/or extensive subendothelial deposits) a. Without segmental lesions b. With “active” necrotizing lesions c. With “active” and sclerosing lesions d. d. With sclerosing lesions
Class V	Diffuse membranous glomerulonephritis a. a. Pure membranous glomerulonephritis b. b. Associated with lesions of class II c. c. Associated with lesions of class III d. d. Associated with lesions of class IV
Class VI	Advanced sclerosing glomerulonephritis

No Risk Management Plan (RMP) was included in the initial dossier. Exemption from this requirement was granted by the TGA. As part of the company’s local post-marketing surveillance activities, Novartis Pharmaceuticals Australia plans to establish a patient registry to monitor the safety of Myfortic when used in patients with LN. At the time of submission, the specifics of the registry design were still under development but were to include the capture of key demographic and outcome information.

Pharmacokinetics

Pharmacokinetic equivalence of Myfortic and MMF

Eight pharmacokinetic (PK) studies comparing MMF with EC-MPS were evaluated and five were chosen as illustrative of different points. One single dose study, two multiple dose studies and one pre-dose study were undertaken in stable, adult renal transplant patients also treated with cyclosporine. There were no studies including patients with LN. One study included patients with nephritis (immunoglobulin A (IgA)) also treated with low dose prednisolone.

All studies reported longer time to the MPA maximum plasma concentration (T_{max}) for the EC formulation, as would be expected. All studies reported considerable inter-individual and intra-individual variation. The single dose study of Arns *et al.*, 2005 and the multiple dose study of Budde *et al.*, 2007a reported bioequivalent MPA exposure for MMF 1000 mg and EC-MPS 720 mg and lower MPA maximum plasma concentration (C_{max}) for both EC-MPS doses; for the single and the multiple dose studies, respectively: 90% confidence interval (CI) 57, 140 and 70, 113.

The single dose study of Arns *et al.*, 2005 also reported bioequivalent MPA glucuronide (MPAG) C_{max} and area under the plasma concentration-time curve (AUC), while the multiple dose study of Budde *et al.*, 2007a reported IMPDH AUC 14% lower for EC-MPS than for MMF.

Budde *et al.*, 2007b systematic review of results of three multiple dose studies found that mean pre-dose MPA plasma concentration (C_0) values were consistently higher for EC-MPS than for MMF. This report also documented a number of outliers with relatively high values.

The multiple dose study of Tedesco-Silva *et al.*, 2005 reported results for acyl-MPAG (AcMPAG), thought to be an active metabolite. The MPA AUC and C_{max} results in this study differed from those of Budde *et al.*, 2007b and are summarised thus:

- The ratio of MPA AUCs and C_{max} was outside the bioequivalence range: 125% (90% CI 108, 129), and 116% (90% CI 94, 142), respectively.
- The MPA minimum plasma concentration (C_{min}) results were similar between groups.
- Inactive metabolite MPAG AUC and C_{max} were estimated to be 22% higher for EC-MPS than for MMF with 90% CI outside the bioequivalence range.
- For the potentially active metabolite AcMPAG, both AUC and C_{max} were within bioequivalence range.

The results of the study were stated to be influenced by values for 4 of the 40 patients with relatively high C_0 levels.

In addition, the study of Tedesco-Silva *et al.*, 2005 reported that the metabolite AcMPAG had slower clearance than MPA. This is of interest because it has been shown to have some IMPDH-II inhibitory activity, although not as potent as MPA, and because it may undergo hydrolysis, molecular rearrangement and covalent binding to proteins and nucleic acids. The formation of such stable adducts has been suggested to play a role in the manifestation of drug toxicities, either through direct disruption of the function of critical proteins or through antigen formation with subsequent hyper-sensitivity and other immune reactions.

A further consideration was identified in a paper by Joy *et al.*, 2009³ in which a summary of a study of the PK of MPA were examined in LN. Both creatinine clearance and serum

³ This paper was not submitted for evaluation, but was located in the Periodic Safety Update Report 7.

albumin level were identified as primary contributors to MPA exposure and should be considered when evaluating dosages. The author concluded: *Clinicians need to be mindful of clinical changes that occur throughout the course of LN in order to maintain efficacy and reduce toxicity from MPA therapy.*

Finally it is noted that at present the *Dosage and Administration* section of the proposed PI states: *A dose of 1440 mg/day of mycophenolate sodium has been shown to be equivalent to 2 g/day of mycophenolate mofetil. Myfortic and CellCept (mycophenolate mofetil) should not be indiscriminately interchanged or substituted because of their different PK profiles.* This statement is clearly at odds with the sponsor's current attempt to show equivalence of PK profiles.

Pharmacodynamics

No specific studies were provided.

Efficacy and safety

Equivalence of efficacy and safety of Myfortic and mycophenolate mofetil

Five reports were included: two were considered pivotal, one for efficacy and one for safety. Each of these included renal transplant patients co-administered cyclosporine with or without corticosteroid.

The study of Salvadori *et al.*, 2004 was rated National Health and Medical Research Council (NHMRC) level II according to NHMRC evidence hierarchy⁴, and Jadad⁵ score 5. The study was designed to evaluate statistical equivalence of treatment with EC-MPS compared to MMF. The primary outcome was efficacy failure based on the incidence of biopsy-proven acute rejection (BPAR), graft loss, death or loss to follow-up at 6 months. There were 213 patients in the EC-MPS group and 210 in the MMF group. The patient population was predominantly Caucasian.

Within the first 6 months post-transplant, on the basis of intention to treat (ITT) analysis, the incidence of efficacy failure, defined as the incidence of BPAR, graft loss, death or loss to follow up, was similar for EC-MPS and MMF (25.8% and 26.2%, respectively). The 95% CI for efficacy failure was -8.7, +8.0, indicating clinical equivalence between the two study treatments.

The study of Budde *et al.*, 2004 was also rated NHMRC level II, Jadad score 5. The aim was to investigate whether renal transplant patients could be safely converted from treatment with MMF to EC-MPS. The primary objective was to assess safety with respect to gastrointestinal adverse events and neutropenia at three months. Efficacy was a secondary objective and was assessed as for the study of Salvadori *et al.*, 2004, above. There were

⁴ National Health and Medical Research Council (NHMRC). *National Health. A guide to the development, implementation and evaluation of clinical practice guidelines*. Endorsed 16 November 1998. [Designation of levels of evidence: I: evidence obtained from a systematic review of all relevant randomised controlled trials; II: evidence obtained from at least one properly designed randomised controlled trial; III-1: evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method); III-2: evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted time series with a control group; III-3: evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group; IV: evidence obtained from case series, either post-test or pre-test and post-test.]

⁵ Jadad AR, Moore R.A., Carroll D. *et al.* Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Controlled Clinical Trials* 1996 17 (1): 1-12. [The Jadad scoring system is a procedure to independently assess the methodological quality of a clinical trial. A paper reporting a clinical trial can receive a Jadad score between 0 and 5.]

159 patients in the EC-MPS group and 163 patients in the MMF group. The patient population was predominantly Caucasian.

There was no statistically significant difference detected between the two groups with respect to nausea, dyspepsia, upper abdominal pain, gastro-oesophageal reflux, gastritis, anorexia or diarrhoea, nor for neutropenia or for efficacy failure. There was no sample size calculation and the study numbers may have been too small to detect statistically significant differences.

Mycophenolate mofetil in patients with LN

Three articles reporting meta-analyses were included, one of which was considered pivotal. Reasons for not regarding the other two as pivotal are provided in the attached extract from the CER (Attachment 2).

The meta-analysis of Zhu *et al.*, 2007 was considered to have a satisfactory search strategy; the authors stated the absence of competing interests and financial supports. The issue of heterogeneity was addressed.

In this analysis, three induction trials compared MMF with cyclophosphamide: Ginzler *et al.*, 2005, and Ong *et al.*, 2005 used IV cyclophosphamide (IVC); Chan *et al.*, 2000 used oral cyclophosphamide. Two trials (Contreras *et al.*, 2004, and Chan *et al.*, 2005) documented results of maintenance therapies including MMF, cyclophosphamide and azathioprine.

For analysis purposes the authors accepted the individual investigator's definition of complete remission. For induction therapy the calculated risk ratio (RR) for complete remission was 1.81 in favour of MMF (95% CI 0.70, 4.68). For partial remission the RR was 1.06 (95% CI 0.71, 1.59). In both instances the RR included 1. For safety findings, the RR for infection was 0.65 (95% CI 0.51, 0.82). For amenorrhoea, leucopenia and gastrointestinal symptoms the 95% CI included 1.

The authors undertook a sensitivity analysis including only the two studies with IVC treatment arms. The RR for complete remission then becomes significant in favour of MMF: 3.10 (95% CI 1.38, 7.01). Other results were said not to have been altered by the removal of results from the study of Chan *et al.*, 2000. On the basis of this analysis, the authors claimed efficacy superiority for MMF compared to IVC.

For maintenance therapy, the RR of results for MMF compared with azathioprine included 1 for the following: incidence of death, end stage renal disease (ESRD), relapse and doubling of serum creatinine. For safety results, there was no statistical difference shown for amenorrhoea and herpes zoster. Results for other adverse events were not included in the submission.

Although this was considered the best of the three submitted meta-analyses, there were concerns. The following problems were identified by the authors:

- None of the studies were double blind.
- There were small numbers of participants in all studies.
- Inclusion of patients with WHO Class III and V LN with better prognosis.
- Maintenance treatment given to patients not in remission.
- The distribution of races.

The following additional problems were identified by the clinical evaluator:

- The method of assigning weight to the various studies was not specified.

- The conclusion of “superiority” is considered to require a well designed study with superiority as the pre-defined objective.
- There were significant problems detected in the individual studies included in this analysis as described in the extract from the CER (Attachment 2).
- The considerable heterogeneity detected by Zhu *et al.*, 2007 relates to primary objectives, statistical approaches and length of time of treatment before analysis.

Eight articles reporting individual studies were evaluated; five were considered pivotal or supportive, four of which were chosen because of their inclusion in the meta-analysis of Zhu *et al.*, 2007. The fifth study report (Appel *et al.*, 2009) was relatively recent. All studies were open-label.

Three induction studies compared MMF to IVC: Appel *et al.*, 2009, Ginzler *et al.*, 2005, and Ong *et al.*, 2005. One induction study compared MMF to oral cyclophosphamide (Chan *et al.*, 2000). The WHO Classes enrolled included: Appel *et al.* 2009 and Ginzler *et al.* 2005: Classes III, IV and V; Ong *et al.* 2005: Classes III and IV; and Chan *et al.* 2000: Class IV.

The planned doses of MMF and IVC were similar. IVC was administered in monthly pulses. Oral cyclophosphamide was administered daily. Each study included use of corticosteroid.

No common primary endpoint or statistical approach was employed. The result of the primary analysis of Appel *et al.*, 2009, Ong *et al.*, 2005 and Chan *et al.* 2000 demonstrated no significant difference between groups. However, lack of finding of significant difference is not the same as proving non-inferiority or equivalence, and does not exclude the possibility that a statistically significant difference may be present. The study of Ginzler *et al.* 2005 reported that having met the criteria for non-inferiority, the results were sufficient to allow the conclusion of superiority of MMF compared to IVC.

The main concerns with each of the studies were:

- Ginzler *et al.* 2009: Assessment of progress at 12 weeks with treatment cross-over for some, but not all of the patients who met the criteria for cross-over. The IVC group’s response rate was exceptionally low.
- Ong *et al.* 2005: Exclusion after randomisation of over 27% of patients in the MMF treatment arm, based on reassessment of renal biopsies.
- Chan *et al.* 2000: randomisation and allocation concealment not discussed. The wide CI reflect the small study numbers and made the result difficult to interpret.

The two maintenance studies (Chan *et al.*, 2005 and Contreras *et al.*, 2004), compared MMF with azathioprine; the Contreras study also included an IVC group. Both used survival statistics. There was no statistical difference in primary objective results of serial serum creatinine documented in the study of Chan *et al.*, 2005. Compared to the IVC group the event free survival was statistically higher in the azathioprine ($p = 0.009$) and MMF groups ($p = 0.05$).

The main concerns with each of the studies were:

- Chan *et al.*, 2005: the extension component of the study was considered observational.
- Contreras *et al.*, 2004: the timing of statistical analysis was not stated. The numbers at risk dropped rapidly and to very low numbers, and information on disposition and censoring was lacking.

In conclusion, with regard to direct evidence in support of use of Myfortic in the treatment of LN, the level of evidence presented is not considered sufficiently free from potential bias to be wholeheartedly endorsed. However, it would seem that EC-MPS has some efficacy in treatment of this condition.

With regard to PK equivalence of Myfortic and MMF, it is accepted that MPA exposure is generally similar for EC-MPS and MMF in the study population including stable renal transplant patients, however, two small studies documented higher exposure following exposure to EC-MPS. There appears to be considerable inter-individual variation in results and the results of studies with small sample size are readily influenced by outliers. It appears that there may be a sub-population of patients who metabolise EC-MPS more slowly than the majority of patients. In stable renal transplant patients, it appears that C_{max} is lower for EC-MPS and that C_0 is likely to be higher, and possibly considerably higher. The results of these studies done on renal transplant patients are likely to have been influenced by co-medication with cyclosporine which is said to potentiate enterohepatic recirculation of MPA. Cyclosporine is used by some medical practitioners in treatment of LN, but not commonly it would appear. The results of the study of Czock *et al.*, 2007, including small numbers of patients with IgA nephritis, indicate that confounding by indication is a possibility.

Therapeutic equivalence of MMF and Myfortic was shown according to the pre-determined criteria in renal transplant patients. However, the result reported was based on the ITT population, whereas the per-protocol population is generally preferred for equivalence studies; the ITT analysis has the capacity to be biased towards equivalence. In addition, as with all studies included in the submission, the endpoint is composite with the potential to add variance which is an undesirable property in equivalence testing.⁶

In the safety study undertaken in renal transplant patients, there was no statistically significant difference detected between the MMF and EC-MPS groups with respect to nausea, dyspepsia, upper abdominal pain, gastro-oesophageal reflux, gastritis, anorexia or diarrhoea, nor for neutropenia or for efficacy failure.

The studies submitted in support of equivalence of efficacy and safety of EC-MPS and MMF were undertaken in transplant patients co-medicated with cyclosporine, predominantly including Caucasians and males. While equivalence of efficacy and similarity of safety profiles were reported, there appears no clear cut reason for preferring one formulation over the other. Furthermore, external validity is considered a problem.

With respect to the efficacy of MMF in treatment of LN, lack of consistency of individual study designs, and some serious problems with the conduct of studies, made assessment difficult, and contributed to weakness in the meta-analysis. The studies included patients who were designated "Black, Hispanic, Asian and White". Efficacy and safety in the Australian Aboriginal population have not been studied.

Efficacy beyond 10 years of treatment has been demonstrated only for cyclophosphamide based regimens. And *'it remains to be proved whether MMF will ultimately be as effective as cyclophosphamide in pre-empting ESRD. The two most common choices for maintenance therapy are MMF and azathioprine... [however] premature declaration of superiority or rushing into discrediting old treatments that have served patients well need to be avoided'* in the editorial opinion of Boumpas *et al.*, 2010.

With regard to safety, no collation of data was presented in the sponsor's summaries and overviews and the evaluator did not attempt such an assemblage. In general, the adverse events reported were in keeping with the known safety profile of each product. No new safety issues were identified, and each study independently was not powered to assess significance of differences or to identify uncommon or rare drug related adverse events.

Two Novartis funded, non-randomised, open label studies (Chan *et al.*, 2007; Bolin *et al.*, 2007) were included in the submission, with the aim to show that gastrointestinal

⁶ Committee for Proprietary Medicinal Products Guideline CPMP/EWP/908/99. Points to consider on multiplicity issues in clinical trials. September 2002

symptoms attributed to use of MMF were improved by switching to EC-MPS. Not only was the potential for bias considered significant, the low level of initial symptoms, and the relatively small improvement were considered of borderline clinical significance.

The renal transplant safety study did not show difference between MMF and EC-MPS in gastrointestinal symptoms. Considering that the underlying mechanism of gastrointestinal damage is thought likely to be apoptosis caused by MPA (Nguyen *et al.*, 2009), it seems possible that enteric coating may delay the onset, rather than ameliorate the problem.

Safety

See *Efficacy and safety*, above.

List of questions

The TGA provided the sponsor a copy of the CER, along with an invitation to provide a response to matters raised therein.

Initial clinical summary and conclusions

Benefit risk assessment

Benefits

Lupus nephritis is a condition with potential to cause significant morbidity and mortality. There is no argument that proliferative LN requires affordable, safe, effective treatment.

Myfortic has been demonstrated to have short term (6–12 months) efficacy in the treatment of LN in observational studies undertaken in small numbers of Asian patients and utilising surrogate endpoints. In support of the findings there is evidence of equivalence of MMF and EC-MPS MPA exposure, safety and efficacy, *albeit* in post transplant patients. In addition, efficacy of MMF in the treatment of LN has been documented.

Oral medication is likely to be better tolerated than IV medication and orally administered medication does not require skilled staff with sterile conditions and equipment for administration.

Risks

The evidence submitted for efficacy and safety of EC-MPS in the treatment of LN is considered tortuous and indirect. Much of the data was collected in renal transplant patients rather than LN patients; in patients with differing racial characteristic from those common in the Australian setting; in male patients; and in compliant patients. This chain of evidence is considered the basis of hypothesis rather than proof of concept. The treatment would potentially be required for protracted periods of time as LN is chronic and subject to flares of increased activity, thus solid evidence of efficacy and safety is considered a basic requirement.

The superiority of EC-MPS over MMF with regard to gastrointestinal symptoms is not considered proven, and neither is superiority of MMF over cyclophosphamide and azathioprine with regard to overall safety and efficacy in treatment of LN. In addition, long-term efficacy of MMF, or EC-MPS, in preventing ESRD has not been proven beyond doubt.

The known safety profile of EC-MPS includes the following concerns

- Myfortic is contraindicated in pregnancy; use of MMF has been associated with increase rate of congenital malformation and pregnancy loss. The LN patient population is predominantly female, of child bearing age.
- EC-MPS is not recommended for use in lactation.
- Increased risk of malignancy including skin cancer. The advice to avoid exposure to sunlight and UV light to limit potential for skin cancer would be problematic for patients living in Australia.
- Susceptibility to infection. There is a disproportionate disease burden in remote Aboriginal communities compared with the general Australian population. Communicable diseases of particular importance to Indigenous people include: tuberculosis; hepatitis (A, B, and C); sexually transmitted infections; HIV/AIDS; Haemophilus influenzae type b (Hib); pneumococcal disease, and meningococcal disease.⁷ Australian Aboriginals have been reported to have incidence of blood stream infection amongst the highest in the world.⁸
- Reduced effectiveness of vaccination.
- Gastrointestinal toxicity including ulceration, haemorrhage and perforation.
- Blood dyscrasias – weekly, progressing to monthly blood counts are advised for the first year.
- Increased blood creatinine.
- Progressive multifocal leukoencephalopathy.

In considering the risks, it is acknowledged that LN affects more non-Aboriginal Australians than Aboriginal Australians. However, the request for registration with a view to inclusion of Myfortic on the PBS, was made on behalf of the EAP on ATSI Medicines. Thus special consideration is given to the risks in the Aboriginal population.

Aboriginal health workers have reported occurrence of inappropriate use of medication and non-compliance. In addition, Consumer medicine information (CMI) is often considered difficult to understand, culturally inappropriate and unlikely to be used.⁹ Sharing of medication has been reported to occur.¹⁰ Storage difficulties are also prevalent in rural Aboriginal communities; storage is often inadequate and unsafe.¹¹ Myfortic needs to be stored below 30°C, protected from light and moisture.

Balance

In pragmatic terms, it is accepted that the medications used in the treatment of LN would share many of the risks outlined above. It is accepted that affordable treatment is a priority. It is also accepted that despite the lack of clinical trial evidence, EC-MPS is being used off-label to treat patients with LN. However, the balance at this point in time would seem to be heavily weighted to risk.

⁷ Information obtained at

<http://archive.healthinfolnet.ecu.edu.au/html/html_overviews/overviews_our_communicable.htm>

⁸ Einsiedel LJ and Woodman RJ. Two nations: racial disparities in bloodstream infections recorded at Alice Springs Hospital, central Australia, 2001–2005. *Med J Aust* 2010;192(10):567-571 [obtained at <http://www.mja.com.au/public/issues/192_10_170510/ein10732_fm.html>]

⁹ Hamrosi K, Taylor SJ, Aslani P. Issues with prescribed medications in Aboriginal communities: Aboriginal Health Workers' perspectives. *Rural and Remote Health* 6: 557. (Online) 2006. [obtained at <<http://www.rrh.org.au/articles/subviewnew.asp?ArticleID=557>>

¹⁰ Information obtained at <http://caepr.anu.edu.au/>

¹¹ Larkin C and Murray R. Assisting Aboriginal patients with medication management. *Aust Prescr* 2005;28:123-5 [obtained at <<http://www.australianprescriber.com/magazine/28/5/123/5/>>]

Initial recommendation

Registration of Myfortic for the proposed indication is not recommended.

If this recommendation is rejected following expert consultation and negotiation, the following conditions based on the perceived need to conscientiously manage all components of risk outlined above are recommended.

- Detail of the register to which the sponsor has committed should be submitted to the TGA for evaluation prior to registration.
- It is recommended that a RMP is formulated, with particular considered attention given to prevention of each of the risk factors detailed above.

In the event of registration, it is recommended that the draft PI and CMI documents should be revised. The issues relating to the Product Information are:

Clinical trials: the proposed wording is considered to imply that small randomised trials may have been done.

Indication: The studies submitted for evaluation were undertaken in predominantly adult patient populations, with predominantly WHO Class IV nephritis. It is considered that the indication should reflect this.

Dosage and Administration: The support for the indication is based heavily on the assumption that MMF and EC-MPS are equivalent. It is recommended that the existing advice that the two formulations are not interchangeable should be removed.

The issue relating to the CMI is that it is considered likely to be culturally inappropriate for the remote community Australian ATSI. It is recommended that this issue is addressed in the RMP.

Details of additional recommended revisions to the PI and CMI are beyond the scope of this AusPAR.

Sponsor's response to the clinical evaluation report

The sponsor's response to matters that had been raised in the CER (see *List of Questions*, above) include a proposal to amend the *Indication* requested originally (*Myfortic is indicated for induction and maintenance treatment of lupus nephritis*) to:

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

The sponsor's response included several additional publications (supplementary clinical data), a RMP, and comments on the following:

- The clinical need of patients with LN;
- Evidence in support of Myfortic;
- Risk assessment of Myfortic;
- Special considerations for Aboriginal Australians.

Additionally, comments were provided on the limitations of current treatment options for patients with LN. The sponsor also addressed the evaluator's recommendations regarding the need for a RMP and changes to the PI.

TGA evaluations of the sponsor's comments and supplementary data are shown under *Supplementary Clinical Evaluation and Pharmacovigilance Findings*, below.

Supplementary clinical evaluation report

A supplementary CER was prepared to take into account the sponsor's comments on the initial CER and to evaluate the supplementary clinical data provided, which included:

- Protocol for the patient registry, and Australian RMP (see Pharmacovigilance Findings, below);
- Revised PI and CMI documents;
- Details of an updated literature search;
- Clinical Summary and Overview of supplementary data;
- Clinical study report of a Novartis sponsored Study A2420 (a randomised, multicenter, parallel group open-label, 6-month study of efficacy and safety of Myfortic in combination with two corticosteroid regimens for the treatment of LN flare);
- Literature references identified in an updated literature search;
- Copies of other references cited in Novartis' response to the CER.

Novartis submitted 45 publications in the initial application. A further 43 articles have been submitted in the supplementary data, seventeen of which were identified for evaluation. The evidence is summarised and discussed below.

Evaluator's comments on Novartis' response to the CER

The sponsor has not included evidence regarding the off-label use of Myfortic in Australia including documentation of the safety of off-label use.

The risks associated with cyclophosphamide are accepted. However, the application is to register Myfortic and therefore primarily the risks of Myfortic are relevant to the evaluation.

It is agreed that the ATSI and non-ASTI populations are similarly at risk of the known safety concerns of Myfortic. The extent to which they are susceptible to the risks has not been studied. A major concern with regard to Myfortic is the teratogenic potential. If use of Myfortic results in birth of infants with congenital abnormalities such as congenital diaphragmatic hernia, anomalies of the distal limbs and heart, oesophagus and kidney, then the parents and the community will not be considered well served.

The sponsor has been advised to provide adequate, culturally appropriate educational material but has not yet done so. In Study A2420, participants were required to use two effective methods of contraception once it became clear from post-market surveillance that significant birth defects were occurring in women using MMF in pregnancy. The FDA considers the risk sufficiently worrying to have mandated the following boxed warning unlike either cyclophosphamide or azathioprine.

WARNING: Female users of childbearing potential must use contraception. Use of Myfortic® during pregnancy is associated with increased risks of pregnancy loss and congenital malformations.

With respect to contraception the revised A2420 protocol specified: *'The two methods can be a double barrier method or a barrier method plus a hormonal method. Adequate barrier methods of contraception include: diaphragm, condom (by the partner), intrauterine device (copper or hormonal), sponge or spermicide. Hormonal contraceptives include any marketed contraceptive agent that includes an estrogens and/or a progestational agent. Patients should be aware that Myfortic reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness. Reliable contraception should start 4 weeks prior to beginning Myfortic.'*

It is considered that if this was a requirement for the study, it should be a requirement for each treated woman of child bearing potential and that patients should be adequately informed of the risk and the requirements for prevention.

The Lupus Nephritis Australian Registry

In the initial letter of application Novartis stated the intention to develop a registry. Instead, a Phase IV observational study, the Lupus Nephritis Australian Registry (LUNAR), is now proposed. The clinical evaluator considers the proposal to call the study a registry semantically incorrect and the effect in practical terms is to undermine active surveillance. This matter is to be evaluated by the TGA's Office of Product Review (OPR).

Direct evidence for EC-MPS

In direct support of the proposed *Indication*, three articles were submitted in the initial application dossier, each reporting results of EC-MPS treatment of selected Asian patients, predominantly female, aged 14 to 50 years with WHO Class III, IV and V LN (Kityyakara *et al.*, 2008, Mak *et al.*, 2008, Traitanon *et al.*, 2008). Included were two cohort studies and one prospective study in which patients treated with MMF were compared with historical controls treated with monthly IVC. The studies were considered observational.

A total of 45 patients were treated in these non-randomised, non blinded trials. One patient was maintained in remission following change in treatment from MMF to EC-MPS. Of the remainder, 16/44 achieved complete remission and 17/44 achieved partial remission.

Each of these exploratory studies, presented as direct evidence for efficacy and safety of EC-MPS in treatment of LN, is considered to have significant methodological inadequacies for regulatory purposes.

Included in the supplementary data was a summary of observational Study A2420, a randomised, multicenter, open-label, 6-month non-inferiority study of efficacy and safety of either standard dose or low dose corticosteroid regimens co-administered with EC-MPS for treatment of Class III or IV LN flares. The primary objective was to assess efficacy of the low dose corticosteroid regimen compared to the standard dose in terms of the proportion of patients in complete remission after 24 weeks of treatment. A total of 81 patients were randomised to treatment: 42 patients in the standard dose group, 39 patients in the low dose group.

Complete remission was achieved by 19.0% of the patients of the standard steroid dose group and 20.5% of the low dose group. Non-inferiority was not shown in the ITT population; the study was underpowered. The proportion of patients with partial remission at week 24 was 20/42 (47.6%) in the standard dose group and 14/39 (35.9%) in the low dose group.

Pharmacokinetic equivalence of EC-MPS and MMF

In the initial application dossier one single dose study, two multiple dose studies and one pre-dose study undertaken in stable, adult renal transplant patients examined the PK of EC-MPS compared to MMF. All studies reported longer time to T_{max} for the EC formulation as would be expected. All studies reported considerable inter-individual and intra-individual variation.

The single dose study of Arns *et al.*, 2005 reported that doses of EC-MPS 640 and 720 mg to be bioequivalent to 1000 mg MMF for MPA AUC_(0-∞). T_{max} was delayed for EC-MPS compared to MMF, and C_{max} was lower for EC-MPS than for MMF, and was lower for the 720 mg dose than for the 640 mg dose, with 90% CIs outside the accepted bioequivalence

levels; well outside those limits for the 720 mg dose. Based on the result of this study the two formulations cannot be considered truly bioequivalent.

The multiple dose study of Budde *et al.*, 2007a reported the finding of bioequivalence with regard to AUC in general agreement with the findings of the single dose study reported by Arns *et al.*, 2005. The MPA C_{max} result for 720 mg EC-MPS was less than that of MMF 1000 mg; the EC-MPS MPA t_{max} was delayed as it was in the single dose study and in keeping with the enteric coating of the EC-MPS formulation. With repeated doses, the EC-MPS MPA C_{min} averaged approximately twice that of MMF. Again, overall, the two formulations could not be considered bioequivalent.

The single dose study of Arns *et al.*, 2005 reported bioequivalent MPAG C_{max} and AUC while the multiple dose study of Budde *et al.*, 2007a reported IMPDH AUC 14% lower for EC-MPS than for MMF.

In a further report, Budde *et al.*, 2007b undertook a systematic review of results of three multiple dose studies and found that MPA C₀ values were consistently higher for EC-MPS than for MMF. This report also documented a number of outliers with relatively high values.

The multiple dose study of Tedesco-Silva *et al.*, 2005 reported results for acyl-MPAG (AcMPAG), thought to be an active metabolite. The MPA AUC and C_{max} results in this study differed from those of Budde *et al.*, 2007b and are summarised thus:

- The ratio of MPA AUCs and C_{max} was outside the bioequivalence range: 125% (90% CI 108, 129), and 116% (90% CI 94, 142), respectively.
- The MPA C_{min} results were similar between groups.
- Inactive metabolite MPAG AUC and C_{max} were estimated to be 22% higher for EC-MPS than for MMF with 90% CI outside the bioequivalence range.
- For the potentially active metabolite AcMPAG, both AUC and C_{max} were within bioequivalence range.

The study of Tedesco-Silva *et al.*, 2005 reported that the AcMPAG had slower clearance than MPA. This is of interest because this metabolite has been shown to have some IMPDH-II inhibitory activity, although not as potent as MPA, and because it may undergo hydrolysis, molecular rearrangement and covalent binding to proteins and nucleic acids. The formation of such stable products has been suggested to play a role in the manifestation of drug toxicities, either through direct disruption of the function of critical proteins or through antigen formation with subsequent hyper-sensitivity and other immune reactions.

The PSUR (provided in the original dossier) included summary of a study by Joy *et al.*, 2009 in which the PK of MPA was examined in LN. Both creatinine clearance and serum albumin level were identified as primary contributors to MPA exposure and should be considered when evaluating dosages. The author concluded: *Clinicians need to be mindful of clinical changes that occur throughout the course of LN in order to maintain efficacy and reduce toxicity from MPA therapy.*

The conclusion drawn following evaluation of these study reports was that MPA AUC is generally similar for EC-MPS and MMF in stable renal transplant patients, however, two small studies documented higher AUC exposure for EC-MPS compared to MMF. There appeared to be considerable inter-individual variation in results and the results of studies with small sample size are readily influenced by outliers. It appeared that there may be a sub-population of patients who metabolise EC-MPS more slowly than the majority of patients. In stable renal transplant patients, it appears that C_{max} is lower for EC-MPS and that C₀ is likely to be higher, and possibly considerably higher. The results of these studies

done on renal transplant patients are likely to have been influenced by co-medication with cyclosporine which potentiates enterohepatic recirculation of MPA.

In the supplementary data, two further PK studies were submitted. The study of Rupprecht *et al.*, 2009 compared the influence of pantoprazole 40 mg twice daily on the bioavailability of a single dose of MMF 1000 mg or EC-MPS 720 mg and demonstrated little effect on PK parameters of EC-MPS in comparison to marked reduction in PK results for MMF.

The Novartis-sponsored study of Tedesco-Silva *et al.*, 2010, a multiple-dose, crossover study, compared the inter- and intra-subject variability of MPA pre-dose levels from EC-MPS and MMF, each with cyclosporine in clinically stable renal transplant patients, two thirds of whom were male. The results indicated that intra-subject variability for C_0 , C_{max} and $AUC_{(0-3 h)}$ was significantly greater for EC-MPS than for MMF. Inter-individual variability was numerically higher for the EC-MPS than for MMF.

The authors of this article use the results to state in the abstract that '*In conclusion, pre dose MPA trough level monitoring appears of limited value during EC-MPS and MMF therapy given the large intra-subject variability in MPA C_0 h levels with both treatments*', whereas in the discussion the authors state that the findings raised questions about the value of therapeutic drug monitoring.

Tedesco-Silva *et al.*, 2010 also state it was suggested that outside clinical studies, variability might be even higher because of a more unreliable drug intake. While in *de novo* patients, time dependent changes of MPA PK is a main contributor to the high intra-subject variability in pre dose levels, this does not apply to the maintenance transplant population. In this setting, day-to-day fluctuations in the enterohepatic recirculation of MPA may explain a significant portion of the observed intra-subject variability; genetic factors have been reported as possible determinants for the high between-subject variability.

The evaluator agrees that genetic determinants could well play a part in inter-individual variation. The authors of this Novartis study have not theorised that problems with the formulation may play a part in intra-subject variability. Rather than being an argument against therapeutic drug monitoring, the variability could well be the basis of an argument for therapeutic drug monitoring. Furthermore the greater variability reported for EC-MPS compared to MMF is considered a potential problem relating to reliance on the product for therapeutic safety and efficacy.

Houssiau *et al.*, 2010, in the discussion of their study testing superiority of MMF versus azathioprine in maintenance therapy, discuss the possibility that patients who failed on one or the other drug may actually have been under dosed or non-adherent to the medication. They state that this hypothesis might not be too farfetched based on the recent finding that patients who have undergone kidney transplant had a lower rejection rate if MMF doses were titrated according to serum MPA titres instead of fixed (dose). They state that individualised MMF dosing based on drug exposure has been shown to significantly improves patient outcomes after renal transplantation.

Efficacy and safety of EC-MPS versus MMF in renal transplantation

Two study reports included in the initial dossier were considered pivotal, one for efficacy and one for safety. Each of these included renal transplant patients co-administered cyclosporine with or without corticosteroid.

The study of Salvadori *et al.*, 2004 was rated NHMRC level II and Jadad score 5. The study evaluated statistical equivalence of treatment with EC-MPS compared to MMF. The primary outcome was efficacy failure based on the incidence of biopsy-proven acute rejection, graft loss, death or loss to follow-up at 6 months. There were 213 patients in the

EC-MPS group and 210 in the MMF group. The patient population was predominantly Caucasian and male.

Within the first 6 months post-transplant, on the basis of ITT analysis, the incidence of efficacy failure, defined as the incidence of BPAR, graft loss, death or loss to follow up, was similar for EC-MPS and MMF (25.8% and 26.2%, respectively). The 95% CI for efficacy failure was -8.7, +8.0, indicating equivalence according to pre-specified criteria.

The study of Budde *et al.*, 2004 was also rated NHMRC level II, Jadad score 5. The aim was to investigate whether renal transplant patients could be safely converted from treatment with MMF to EC-MPS. The primary objective was to assess safety with respect to gastrointestinal adverse events and neutropenia at 3 months. Efficacy was a secondary objective and was assessed as for the study of Salvadori *et al.*, 2004, above. There were 159 patients in the EC-MPS group and 163 patients in the MMF group. The patient population was predominantly Caucasian and approximately two thirds of patients were male.

There was no statistically significant difference detected between the two groups with respect to nausea, dyspepsia, upper abdominal pain, gastro-oesophageal reflux, gastritis, anorexia or diarrhoea, nor for neutropenia or for efficacy failure. There was no sample size calculation and the study numbers may have been too small to detect statistically significant differences.

While accepting the findings of these two studies, the evaluator considers that it is not sound logic to accept non-inferiority of efficacy in treatment of one condition as proof of non-inferiority of efficacy in another unrelated condition.

MMF treatment of LN

Reports of single studies

In the initial evaluation, five study reports were considered pivotal or supportive. All studies were open-label.

Three induction studies compared MMF to IVC: Appel *et al.*, 2009, Ginzler *et al.*, 2005, Ong *et al.*, 2005. One induction study compared MMF to oral cyclophosphamide (Chan *et al.*, 2000). The WHO Classes enrolled included: Appel *et al.* and Ginzler *et al.*: Classes III, IV and V; Ong *et al.*: Classes III and IV; and Chan *et al.*: Class IV.

The planned doses of MMF and IVC were similar. IVC was administered in monthly pulses. Oral cyclophosphamide was administered daily. Each study included use of corticosteroid.

No common primary endpoint or statistical approach was employed. The result of the primary analysis of Appel *et al.*, Ong *et al.* and Chan *et al.* demonstrated no significant difference between groups. However, lack of finding of significant difference is not the same as proving non-inferiority or equivalence, and does not exclude the possibility that a statistically significant difference may be present. The Study of Ginzler *et al.* reported that having met the criteria for non-inferiority, the results were sufficient to allow the conclusion of superiority of MMF compared to IVC.

The main concerns with each of the studies were:

- Ginzler *et al.* 2005: Assessment of progress at 12 weeks with treatment cross-over for some, but not all of the patients who met the criteria for cross-over. The IVC group's response rate was exceptionally low.
- Ong *et al.* 2005: Exclusion after randomisation of over 27% of patients in the MMF treatment arm, based on reassessment of renal biopsies.
- Chan *et al.* 2000: randomisation and allocation concealment not discussed. Wide CI reflect the small study numbers and made the result difficult to interpret.

The two maintenance studies (Chan *et al.*, 2005 and Contreras *et al.*, 2004) compared MMF with azathioprine; the Contreras *et al.* study also included an IVC group. Both used survival statistics. There was no statistical difference in primary objective results of serial serum creatinine documented in the study of Chan *et al.*, 2005. Compared to the IVC group the event free survival was statistically higher in the azathioprine ($p = 0.009$) and MMF groups ($p = 0.05$).

The main concerns with each of the studies were:

- Chan *et al.*, 2005: the extension component of the study was considered observational.
- Contreras *et al.*, 2004: the timing of statistical analysis was not stated. The numbers at risk dropped rapidly and to very low numbers, and information on disposition and censoring was lacking.

The supplementary data included two reports of small studies of induction therapy limited to 6 months, one from Egypt (El-Shafey *et al.*, 2010) and one from China (Li *et al.*, 2011). These studies had different definitions of complete remission, which was the primary outcome in each. Both reported similar response rates for MMF versus IVC, and in the study of Li *et al.*, 2011, similar response to tacrolimus.

Two studies of maintenance therapy were included. The study of Dooley *et al.*, 2011 was considered a stand out in design and reporting and was rated a Jadad score of 5. This 36 month, randomised 1:1, double-blind, double dummy, Phase III study compared oral MMF 2 g per day and oral azathioprine 2 mg/kg per day plus placebo in each group, in patients who met the response criteria during a 6 month induction trial with either MMF or cyclophosphamide. The primary efficacy end point was the time to treatment failure, measured as the time until the first event and defined as death, ESRD, sustained doubling of the serum creatinine level, renal flare, or the need for rescue therapy. The hazard ratio (HR) for treatment failure, 0.44 (95% CI 0.25, 0.77; $p = 0.003$) favouring MMF. Overall observed rates of treatment failure were 16.4% (19 of 116 patients) in the MMF group and 32.4% (36 of 111) in the azathioprine group. The finding was consistent, for sub-analysis of results based on induction treatment with IVC, but the HR for MMF induction included 1, as did sub-analyses based on race, and geographic region.

The study of Houssiau *et al.*, 2010 was a multicentre, randomised, controlled, unblinded 48 week trial testing superiority of MMF versus azathioprine as maintenance treatment. Included were 105 patients aged ≥ 14 years with WHO class III, IV, Vc or Vd LN. There were some discrepancies in baseline characteristics. The Kaplan-Meier probability of renal flare HR was 0.75 (CI 0.33, 1.71) $p = 0.486$. Superiority was not demonstrated.

Systematic reviews and meta-analyses

One meta-analysis was evaluated in the original CER (Zhu *et al.*, 2007) and a further six systematic reviews/meta-analyses addressing efficacy and safety of induction therapy with MMF versus cyclophosphamide were evaluated for the supplementary clinical report. The study reports included in the meta-analyses were rated Jadad scores between 0 and 3. The studies of Ginzler *et al.*, 2005, Ong *et al.*, 2005, and Chan *et al.*, 2000 were included in all meta-analysis. The Aspreva Lupus Management Study (ALMS) reported by Appel *et al.*, 2009 was included in all except the meta-analysis of Mak *et al.*, 2009; however, results of the ALMS study were included in abstract form in the meta-analysis of Mak *et al.* 2009. The analysis by Lee *et al.*, 2010 also assessed maintenance therapy comparing MMF with azathioprine. A review by Swan *et al.*, 2011 compared response of Class V membranous LN with steroid therapy alone in comparison to treatment with a variety of non steroid immunosuppressant therapies.

With respect to induction therapy, complete remission, partial remission and overall remission RRs included 1 for each of the meta-analysis reports. The risk of amenorrhea

following treatment with cyclophosphamide was found to be greater than with MMF by Touma *et al.*, 2011, Kamanamool *et al.*, 2010, and Mak *et al.*, 2009. Leucopenia risk from treatment with cyclophosphamide was determined to be greater by Kamanamool *et al.*, 2010 and Mak *et al.*, 2009. Alopecia was less likely to occur with the use of MMF than with IVC according to Touma *et al.*, 2011. There appeared to be no difference in rates of infection, death or ESRD.

Regarding maintenance therapy, the RR included 1 for response and development of ESRD in the analysis of Lee *et al.*, 2010. The report of Dooley *et al.*, 2011, of a randomised, double-blind, double-dummy study comparing MMF with azathioprine in maintenance treatment of patients who had previously responded to induction therapy, concluded that MMF is more effective than azathioprine in maintenance therapy for preventing relapse. The single trial report of Houssiau *et al.*, 2010 tested but failed to show superiority of MMF versus azathioprine; however, the numbers included in the study were small.

The meta-analysis of Mohan *et al.*, 2011 concluded that complete remission with MMF was more likely in patients outside Asia, while Isenberg *et al.*, 2010 in their report of sub-analysis of a single trial, concluded that response for Asian and White patients was similar, while Black and Hispanic patients were less responsive to IVC than to MMF.

The review of Swan *et al.*, 2011 comparing non steroid immunosuppressant therapy with steroid only therapy for Class V LN concluded with the recommendation that non steroid immunosuppressants in combination with steroids are to be recommended in view of their finding of better overall response to combined therapy. The report of Radhakrishnan *et al.*, 2010 of post-hoc analysis of results of a single trial suggested that MMF is as effective as IVC in treatment of Class V LN, but that neither treatment is very effective.

The consistency in results of the meta-analyses of induction therapy is in part due to inclusion of much the same data in each analysis. It is considered that observational, non-randomised studies and studies with a retrospective component are of questionable value in a meta-analysis and may serve to bias the result. In addition, while well conducted meta-analyses examining results of high quality studies are considered high level evidence, meta-analyses are all considered observational.

Studies with differing primary objectives and with differing definitions of response add confusion. In general the authors of meta-analyses must accept the definitions included in the primary reports. Studies which are not blinded increase the possibility of bias, though with objective outcomes based on laboratory findings it may be argued that risk of bias is reduced. However, non-blinded studies with composite endpoints, even if the individual elements of the endpoint are objective, may be subject to bias when some components are consistent with response and others are borderline or inconsistent with response. In addition, all studies relied on surrogate endpoints.

With respect to safety, reliability of results depends on which adverse events are reported, how they are recorded during the study and the manner in which they are interpreted by the original investigators. Safety was not the primary outcome of any of the studies included in the meta-analysis. The original articles of Appel *et al.*, 2009, Ginzler *et al.*, 2005, Chan *et al.*, 2005, and Ong *et al.*, 2005 did not discuss the method of reporting or recording of adverse events, nor the completeness of the data reported. Other original texts were not revisited for this information. It was also not apparent in the meta-analyses whether the adverse events reported were required to have been determined to be treatment related or otherwise.

Benefit risk assessment

Benefits

- There is a clear need for effective, safe and affordable treatment for LN, a condition with potential to cause significant morbidity or mortality.
- Treatment with oral medication has advantages of being non painful, oral treatment does not require specialised medical assistance or sterile equipment.
- Induction treatment with MMF has been shown in randomised, controlled, unblinded trials and meta-analyses to have similar efficacy to IVC. Maintenance treatment for 36 weeks with MMF has been shown in a randomised, controlled, double blind, double dummy study (Dooley *et al.*, 2011) to have significantly better results than azathioprine in patients who have responded to induction therapy.
- Observational studies have documented response in patients treated with EC-MPS.
- Registration of Myfortic may be followed by inclusion of Myfortic on the PBS resulting in more affordable treatment for patients with LN. Presently there is no medication registered for this indication and thus no other treatment eligible for subsidisation.
- The PK of EC-MPS are not substantially altered by co-administration of the proton pump inhibitor pantoprazole.

Risks

- Systemic lupus erythematosus predominantly affects women of child bearing age. MPA has been demonstrated to be teratogenic and to increase the probability of spontaneous abortion. The congenital abnormalities reported in relation to MMF use have potential to cause death or significant disability and this adverse event would impact most on a person other than the one requiring treatment. The registration of a teratogenic drug for use in this population is considered of great concern.
- Direct evidence for efficacy of Myfortic in treatment of LN is limited to observational studies.
- Evidence presented in the report of observational Study A2420 demonstrated that the primary outcome, complete remission, was only recorded for approximately 20% of patients after 6 months of treatment.
- There is no long term evidence to support Myfortic use.
- The bulk of evidence submitted in support of the application was based on literature reports of studies using MMF. In addition, there are problems with many of the study designs and literature reports of efficacy and safety of MMF in treatment of LN, as discussed comprehensively in the evaluation reports.
- Therapeutic bioequivalence of MMF and EC-MPS has not been studied in treatment of LN.
- For regulatory purposes, therapeutic equivalence of MMF and EC-MPS in renal transplantation is not considered sufficient evidence for therapeutic equivalence in LN.
- EC-MPS has demonstrated considerable inter-individual and intra-individual PK variation, which may impact both safety and efficacy.
- Neither Myforic nor CellCept are registered for the requested indication anywhere else in the world.

Final recommendation

Subject to the Delegate's approval of the RMP, the recommendation is for approval of the use of Myfortic for patients with LN. This recommendation has been found very difficult to determine despite the acknowledged need.

Recommended conditions for registration and Product Information

Prior to registration it is required that the sponsor justifies the proposed dosage of 1440 mg daily which differs from that used in Study A2420 in which it was stated that all patients were treated with Myfortic at a daily dose of 2160 mg daily after an initial 2 weeks treatment with 1440 mg per day.

Should the extension of indication be registered, it is recommended that further changes to the PI are made, including the following:

- Strengthened warnings relating to the use of Myfortic in pregnancy, including a "black box warning"¹² is recommended for both the PI and the CMI.
- *Indication:* It is recommended that the following statement or similar is included. *Evidence for this indication is based on literature reports of studies of treatment with mycophenolate mofetil in patients with LN, the majority of whom were in ISN/RPS (2003) Class IV. The evidence for efficacy was based on surrogate endpoints.*
- *Contraindications:* It is recommended that the reason Myfortic is contraindicated in pregnancy is included under this heading, that is, the use of Myfortic during pregnancy is associated with increased risks of pregnancy loss and congenital malformations.
- *Precautions:* It is recommended that the order of headings in this section is revised and that precautions relating to use in pregnancy are strengthened. In addition it is recommended that two types of reliable contraception are specified in line with the requirements of Study A2420.
- *Dosage and Administration:* Justification for the proposed dosage is required before a recommendation can be finalised.

Details of other recommended revisions to the PI are beyond the scope of this AusPAR.

V. Pharmacovigilance findings

Risk management plan

The Australian-specific RMP (version 1.0 dated 24 January 2012) was submitted as supplementary data to the current application on specific request by the TGA. It is noted that the sponsor has not undertaken a formal clinical development programme to support this application, therefore some sections of the RMP were unable to be provided. The sections that have been provided were based on mutual agreement between the sponsor and the TGA's OPR.

Safety specification

The summary of the Ongoing Safety Concerns as specified by the sponsor is as follows:

¹² A boxed warning is a succinct warning statement printed at the start of the approved PI, designed to alert prescribers to an important safety issue with a medicine. The warning is highlighted by a bold black surround or "box".

Important identified risks	<ul style="list-style-type: none"> • Malignancy • Infections • Blood dyscrasias • Vaccination • Gastrointestinal disorder • Reproductive toxicity
Important potential risks	<ul style="list-style-type: none"> • Progressive multifocal leukoencephalopathy
Important identified interactions	<ul style="list-style-type: none"> • Antacids with magnesium and aluminium hydroxide • Azathioprine • Cholestyramine and drugs that interfere with enterohepatic circulation • Tacrolimus • Live vaccines

OPR reviewer comment:

Myfortic is proposed as a long-term therapy for LN. The RMP states “(Myfortic) *has a well-established safety profile in renal transplant patients*”. However, to the evaluator’s knowledge there are no long-term safety data for patients treated with Myfortic for LN. It is not unreasonable to consider that long-term safety issues might differ in the LN population compared to transplant patient cohorts. Therefore it is recommended that “*Long-term safety in patients with LN*” be added to the ongoing safety concerns as “Important missing/limited information”. Furthermore, consideration should be made by the sponsor to address the proposed concern of “Long-term safety in patients with LN” with appropriate pharmacovigilance and risk minimisation measures.

Otherwise the above summary of the Ongoing Safety Concerns is considered acceptable.

Pharmacovigilance plan

The pharmacovigilance plan comprises targeted questionnaires as well as a “patient registry”.

Targeted follow-up of serious adverse events (SAEs)

For the safety concerns of malignancy, blood dyscrasias, and reproductive toxicity the sponsor proposes targeted follow-up of serious spontaneous reports, serious post-marketing surveillance study reports, serious reports from other programs where data is being handled as solicited and all clinical trial SAE reports. The follow-up questionnaires have been provided with the submission.

The sponsor commits to providing updates of new and ongoing safety information *via* PSURs (provided as per TGA requirements) and to updating the RMP as necessary.

LUNAR

A key aspect of the pharmacovigilance plan is Study CERL080AAU06 otherwise referred to as LUNAR. This registry is multi-centred and non-interventional in design in order to collect outcome data on patients treated with immunosuppressant therapy for LN. According to the RMP this registry is designed to act as additional pharmacovigilance for all ongoing safety concerns.

Registry data is intended to be collected over a 5 year period for approximately 200 patients. Individual patient data will be collected from treating physicians *via* an online case report form (CRF) at a 6 monthly maximum interval.

The protocol describes interim analyses to be performed once a year for the duration of the registry with an overall analysis performed at its conclusion.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones***Targeted follow-up of SAEs***

The use of follow-up questionnaires for SAEs relating to the safety concerns of malignancy, blood dyscrasias and reproductive toxicity is considered appropriate. Additionally the questionnaires provided with the submission appear satisfactory for this purpose.

However, the sponsor has not provided rationale for why SAEs relating to the other safety concerns will not be further investigated with follow-up questionnaires. It is the evaluator's view that any SAE in the proposed target population should be considered important enough to follow-up.

The sponsor's commitment to submitting PSURs and updating the RMP as necessary is satisfactory.

LUNAR

Given the current safety profile of Myfortic, and its new proposed indication, active safety surveillance is warranted. This is proposed by the sponsor in the form of a patient registry (LUNAR). Upon consideration of the provided protocol however, it is the evaluator's view that LUNAR is actually a phase IV observational study rather than a registry. Patients on other medications for LN are also to be included, giving the impression that this study will instead aim to compare efficacy, safety or both rather than act strictly as a registry. In particular the proposed use of exclusion criteria will negatively impact upon the "real-world" approximation that a registry should aim to achieve.

Of particular concern is the proposed exclusion of women of child-bearing potential unless "effective" contraception is used. This implies that patients who are non-compliant with contraceptive advice would be excluded from the registry. There cannot be any absolute guarantee that a woman of child-bearing potential will not become pregnant on therapy (due to non-compliance with contraception or other reasons) and all pregnancy events would be critical to learning more about the safety of the drug for this indication. This is particularly important as the proposed patient population is predominantly females of reproductive age.

It is recommended to the Delegate that the sponsor should be directed to clarify exactly how they plan to handle reports of pregnancy related adverse events, as these would adversely impact the risk-benefit balance.

Overall a patient registry is an appropriate and probably essential post-marketing activity should this application be successful. However it is recommended to the Delegate that the sponsor be directed to reconsider its approach to the patient registry to better achieve safety surveillance in a "real-world" setting. The registry should ideally aim to include all patients treated with Myfortic for the indication of LN. The protocol should be re-designed to better represent a registry rather than an observational study and exclusion criteria should be removed.

The online CRF is the key information gathering tool for the registry. As this has not been provided with the submission, it is unclear exactly what information will be collected and therefore unclear how the registry will appropriately address each safety concern and achieve its stated outcomes. The accuracy and usefulness of any safety information gathered very much relates to specific questions in the CRF that act as prompts to clinicians to report particular adverse events. It is recommended that the sponsor be directed to provide the proposed CRF for evaluation by the TGA to ensure that it appropriately addresses the safety objectives stated.

Patient recruitment to the registry also remains unclear. The study protocol states that *"each centre should register all consecutive eligible patients who present during enrolment"*

from the starting date of the study, until the achievement of the study recruitment target". This does not describe the actual mechanism of how patients will be enrolled. Without a robust recruitment process it would appear that actually achieving the target of 200 patients in an estimated potential projected cohort of less than 2000 patients Australia-wide is likely to be unfeasible. Ideally, registry recruitment should be automatically linked to prescription or supply to ensure that all potential subjects are captured. It is recommended that the sponsor clarify exactly how patient recruitment will occur so there is more of an assurance that as many eligible patients as possible are included.

Risk minimisation activities

The sponsor plans to implement a comprehensive educational programme for the use of Myfortic in LN. The key features of this programme are outlined in the following table.

Educational Material	Objective	Safety concerns addressed
Dear Healthcare Professional Educational Letter	To inform healthcare professionals of: <ul style="list-style-type: none"> • approved indication • dosage for LN • key safety information 	<ul style="list-style-type: none"> • Malignancy • Infections • Haematological toxicity • Vaccination • Gastrointestinal toxicity • Reproductive toxicity • Progressive multifocal leukoencephalopathy • Interactions
Professional Association Letter	To inform the Associations of: <ul style="list-style-type: none"> • approved indication • key safety information • availability of healthcare professional, patient and indigenous patient educational material 	
Healthcare Professional Education Brochure	To inform healthcare professionals of: <ul style="list-style-type: none"> • approved indication • dosage for LN • detailed safety information 	
Patient Brochure	To inform patients of: <ul style="list-style-type: none"> • What is Lupus Nephritis? • What is Myfortic? • How to take Myfortic • What precautions should be taken • When to seek help 	
Patient Brochure for the Aboriginal and Torres Strait Islander (ATSI) community	To present the abovementioned patient information in a meaningful way for the Aboriginal and Torres Strait Islander community	

In general the stated objectives for the risk minimisation plan are appropriate. The rationale for use of patient group-specific as well as healthcare professional educational materials also seems to be appropriate. Unfortunately, as the actual materials that comprise the proposed educational programme have not been supplied with the

submission the evaluator is unable to determine or comment on the perceived suitability or effectiveness of the risk minimisation strategy. It is recommended to the Delegate that sponsor provide drafts of the proposed education materials for evaluation by the TGA prior to marketing, as these are key to the risk minimisation plan.

A survey is planned to assess the effectiveness of the proposed risk minimisation activities amongst physicians but a similar assessment does not appear to be planned for the patient population. As the risk minimisation plan consists of measures specific to patients as well as healthcare professionals, it is recommended to the Delegate that the sponsor consider implementing a way of measuring the effectiveness of the risk minimisation strategy amongst the patient population.

In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft PI document be revised as suggested in the CER, including as follows:

The Myfortic US product label (approved by the FDA on 27/10/2010) carries a black box warning that states: *Female users of childbearing potential must use contraception. Use of Myfortic during pregnancy is associated with increased risks of pregnancy loss and congenital malformations.*

It is noted that the proposed Australian PI does not carry a similar black box warning. It is considered that approval of the current submission would substantially increase the population of women of child-bearing potential taking Myfortic thus increasing the risk of a fetus being inadvertently exposed to the drug. The clinical evaluator suggested the inclusion of a black box warning informing of the risk of pregnancy related complications and the need for contraception whilst on therapy. It is agreed that a black box warning is probably warranted as additional risk minimisation and it is recommended to the Delegate that this be considered as a condition of registration.

Other comments on the proposed PI and CMI are beyond the scope of this AusPAR.

Sponsor's response to the RMP evaluation report

The sponsor's response document addressed the issues raised above as follows:

Long term safety data in patients with LN

The sponsor agreed to the addition of *Long term safety data in patients with LN* to the list of ongoing safety concerns as "important missing information".

All SAEs relating to the safety concerns should be followed up

The sponsor clarified that all SAEs relating to the safety concerns would be followed up; additional questionnaires for this purpose were provided to the TGA.¹³

LUNAR

The sponsor confirmed that LUNAR is a Phase IV observational study and not a Myfortic patient registry, although it was originally conceived as a registry. The sponsor provided clarification of exclusion criteria, methods used to address pregnancy related adverse, and patient recruitment methods.

Draft educational material

The sponsor provided material for review by TGA.¹⁴

¹³ The evaluator deemed these to be acceptable.

¹⁴ The evaluator considered the material provided was acceptable, and recommended that any further educational material should be provided for evaluation to the TGA prior to use.

Measuring effectiveness of patient education program

The sponsor proposed to conduct a survey of patients being treated for Myfortic for LN. The survey would be conducted no less than 1 year after Myfortic was launched and assistance to identify these patients would be sought from nephrologists.¹⁵

Boxed pregnancy warning

The sponsor did not agree to the inclusion of a boxed warning in the Australian PI for Myfortic. Differences in the use and interpretation of boxed warnings between the US and PI documents were noted, and procedures to communicate risks with Myfortic, including strengthened warnings in the Australian Myfortic PI, were described.

Summary of recommendations

The following is a summary of specific recommendations to the Delegate regarding the Myfortic RMP.¹⁶ The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted RMP is applicable without modification in Australia unless so qualified:

- The evaluator maintains the opinion that LUNAR does not satisfy the usual requirements that would be expected of a patient registry as a pharmacovigilance activity. As such all references in the RMP to the 'patient registry' should be amended to make it clear that LUNAR is actually an observational study.
- There is merit in LUNAR in its current form as a pharmacovigilance activity particularly with regards to collecting long-term safety data. However the Delegate should consider if this study alone is sufficient as active surveillance in the absence of a true patient registry.
- Given the relatively small number of proposed patients, the evaluator does not agree with the sponsor that conducting a mandatory registry would be necessarily unfeasible.
- The evaluator also notes that a suitable patient registry should not aim to include all patients with LN but rather all patients with LN and who are treated with Myfortic.
- The evaluator agrees that pregnant patients should not participate in LUNAR (as an observational study) or indeed be treated with Myfortic. Good clinical practice notwithstanding there cannot be any absolute guarantee that a patient will not become pregnant on Myfortic regardless of the risk minimisation strategy. The evaluator wishes to re-emphasise that events of pregnancy and pregnancy outcomes should be followed-up with some detail and reported to the TGA accordingly.
- As well as the Novartis standard follow-up procedures for reported pregnancies, which appear reasonable, occurrences of any pregnancy and follow-up as part of LUNAR should be included and reported as part of the Study.
- As the proposed CRF is not yet available the evaluator cannot provide comment on whether or not the primary information gathering tool for LUNAR is appropriately constructed to address the safety concerns/objectives as stated in the RMP. It is recommended that the sponsor be directed to provide the proposed CRF for evaluation by the TGA to ensure that it appropriately addresses the safety objectives stated.

¹⁵ The evaluator considered this proposal was acceptable.

¹⁶ This list of recommendations takes into account matters that were resolved in the sponsor's response to the RMP evaluation report.

- Regarding patient recruitment for LUNAR, the evaluator recommends that all patients treated with Myfortic for LN should be considered for recruitment. Given the reasonably small cohort of patients in Australia the recruitment strategy outlined by the sponsor seems appropriate. The safety profile of Myfortic used in Indigenous patients with LN should be considered an important objective.
- As LUNAR is the only additional pharmacovigilance activity, and participation is voluntary, the sponsor should develop a contingency or provide an assurance for alternative pharmacovigilance activities to be explored in the event that recruitment targets are not met.
- The sponsor has not provided evidence to support their claim that a black box warning is interpreted differently in Australia or a deterrent to prescribing in general terms. However the evaluator considers that the strengthened wording in the proposed PI and CMI adequately conveys the pregnancy related risks without the need for a black box warning. The educational material will also act as an additional safeguard.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

In support of this application, Novartis provided 45 published articles in the initial submission and a further 43 published articles in the supplementary submission following the initial (first round) clinical evaluation. Relevant publications were identified by the evaluators for detailed assessment.

Myfortic (EC-MPS) in the treatment of LN

The initial submission: for direct support of EC-MPS for the treatment of LN, three relevant articles were provided, including two retrospective case series and one prospective cohort study. These studies were conducted in selected Asian patients, mostly female, aged 14 to 50 years with WHO Class III, IV and V LN. A total of 45 patients were treated in these non-randomised, non blinded trials. The doses of EC-MPS were different in each study, and ranged from 540 mg twice daily to 720 mg twice daily. In the cohort study, the treatments with EC-MPS were compared with historical controls treated with monthly IVC. One patient was maintained in remission following the change in treatment from MMF to EC-MPS. Of the remainder, 16/44 achieved complete remission and 17/44 achieved partial remission. The studies were considered observational.

As pointed out by the evaluator, these studies are exploratory in nature and are considered to have significant methodological inadequacies for regulatory purposes.

Supplementary data: A summary of Study A2420 was provided. Study A2420 was an open label, randomised, multicenter, 24 weeks non-inferiority study. The study assessed the

efficacy and safety of either standard dose or low dose corticosteroid regimens co-administered with EC-MPS for treatment of Class III or IV LN flares. The primary outcome was the proportion of patients who achieved complete remission after 24 weeks of treatment. A total of 81 patients were randomised with 42 in the standard dose group and 39 in the low dose group. All patients were treated with Myfortic 2160 mg daily after an initial 2 weeks on 1440 mg daily. All patients had a bolus of 0.5 g IV methylprednisone for 3 days before oral corticosteroid therapy. Complete response was achieved in similar proportion of patients in the two groups (19.0% in the standard dose group and 20.5% in the low dose group). The partial response rate was numerically higher in the standard dose group (47.6% versus 35.9%). Clinically notable elevations in creatinine and a rise in urine protein/creatinine ratio ($\geq 50\%$ above baseline) were reported in a higher number of patients in the low dose group. Non-inferiority was not shown in the ITT population. The evaluator commented that the study was underpowered and the sample size was small.

Efficacy and safety of MMF for the treatment of LN

Individual studies

Initial submission: three studies with induction therapy and two studies with maintenance therapy were considered pivotal or supportive. All studies were open-label studies. The three induction studies (Appel *et al.*, 2009, Ginzler *et al.*, 2005, Ong *et al.*, 2005) compared MMF to IVC: One induction study compared MMF to oral cyclophosphamide (Chan *et al.*, 2000). The patients were mostly diagnosed with LN of WHO class III, IV or V. The doses of MMF were similar in each study (2 g/day). IVC was administered in monthly pulses while oral cyclophosphamide was administered daily. Each study included the use of corticosteroid. No common primary endpoint or statistical approach was employed. The results of the primary analyses of Appel *et al.*, Ong *et al.* and Chan *et al.* demonstrated no significant difference between the treatment groups.

For the two maintenance studies, Chan *et al.*, 2005 compared MMF (0.5-0.75 g twice daily) with azathioprine (1-1.5 mg/kg/day) and Contreras *et al.*, 2004 compared prednisone in combination with either IVC, MMF (0.5-3 g/day), or azathioprine (1-3 mg/kg/day). There was no statistical difference in the analysis of primary outcomes in terms of serial serum creatinine in the study by Chan *et al.*, 2005. In the study by Contreras *et al.*, 2004, the event free survival was statistically higher in the azathioprine ($p = 0.009$) and the MMF groups ($p = 0.05$) than that in the IVC group.

Supplementary data: A Further two studies of induction therapy and two studies of maintenance therapy were provided. Two small studies of induction therapy were limited to 6 months, one from Egypt (El-Shafey *et al.*, 2010) and one from China (Li *et al.*, 2011). The primary outcome was complete remission for the two studies but the definition of complete remission was different. Both studies reported similar rates of complete remission for MMF and IVC, and, in the study of Li *et al.*, 2011, a similar rate of response to tacrolimus.

The two maintenance studies were by Dooley *et al.*, 2011 and by Houssiau *et al.*, 2010. The study by Dooley *et al.* was well designed and was rated a Jadad score of 5. It was a 36 month, randomised (1:1), double-blind, double-dummy, Phase 3 study. MMF (2 g daily) plus placebo was compared with azathioprine (2 mg/kg daily) plus placebo in patient who met the response criteria during a 6 month induction trial with either MMF or cyclophosphamide. The primary endpoint was the time to treatment failure measured as the time until the first event which was defined as death, ESRD, sustained doubling of the serum creatinine level, renal flare, or the need for rescue therapy. The observed overall rates of treatment failure were 16.4% (19/116) in the MMF group and 32.4% (36/111) in the azathioprine group. The HR for treatment failure was 0.44 (95% CI 0.25, 0.77; $p = 0.003$), favouring MMF. The finding was consistent for sub-analysis based on induction

treatment with IVC, but the HR for MMF induction included 1, as did sub-analyses based on race, and geographic region.

The study of Houssiau *et al.* 2010 was a multicentre, randomised, controlled, unblinded 48 week trial testing superiority of MMF versus azathioprine as maintenance therapy. A total of 105 patients aged ≥ 14 years with WHO Class III, IV, Vc or Vd LN were included. There were some discrepancies in baseline characteristics. The Kaplan-Meier probability of renal flare showed that the HR was 0.75 (0.33, 1.71) with $p = 0.486$. Superiority was not demonstrated.

Systemic reviews and meta-analysis

Seven published articles were discussed in the CER, including one meta-analysis from original submission (Zhu *et al.*, 2007) and 6 systematic reviews/meta-analyses from the supplementary data.

The study reports included in these meta-analyses were rated Jadad scores between 0 and 3. The studies of Ginzler *et al.*, 2005, Ong *et al.*, 2005, and Chan *et al.*, 2000 were included in all meta-analysis. The ALMS study reported by Appel *et al.*, 2009 was included in all except the meta-analysis of Mak *et al.*, 2009; however, results of the ALMS study were included in abstract form in the meta-analysis of Mak *et al.* 2009. The analysis by Lee *et al.*, 2010 also assessed maintenance therapy comparing MMF with azathioprine. The review by Swan *et al.*, 2011 compared steroid therapy alone versus combination therapy with a variety of immunosuppressant in subjects with Class V membranous LN.

Induction therapy: for complete remission, partial remission, and overall remission, the Risk Ratios included 1 for each of the meta-analysis reports. The analysis by Touma *et al.*, 2011, Kamanamool *et al.*, 2010, and Mak *et al.*, 2009 showed that the risk of amenorrhea following cyclophosphamide therapy was greater than that following MMF therapy. There was a greater risk of leucopenia associated with cyclophosphamide therapy as analysed by Kamanamool *et al.*, and Mak *et al.* Alopecia was less likely to occur with MMF than with IVC according to Touma *et al.* There appeared to be no difference in rates of infection, death or ESRD.

Maintenance therapy: the RR included 1 for the development of ESRD in the analysis by Lee *et al.*, 2010. The report of Dooley *et al.*, 2011, of a randomised, double-blind, double-dummy study comparing MMF with azathioprine in maintenance treatment of patients who had previously responded to induction therapy, concluded that MMF is more effective than azathioprine in maintenance therapy for preventing relapse. The single trial report by Houssiau *et al.*, 2010 failed to show superiority of MMF over azathioprine; but the sample size was small in that report.

The meta-analysis by Mohan *et al.*, 2011 concluded that complete remission with MMF was more likely in patients outside Asia. In contrast, the sub-analysis of a single trial by Isenberg *et al.*, 2010 concluded that Asian and White patients have a similar response, while Black and Hispanic patients were less responsive to IVC than to MMF.

The review of Swan *et al.*, 2011 compared various immunosuppressant therapies with steroid only therapy for the treatment of Class V LN and concluded that immunosuppressant therapies in combination with steroids appear to be more effective than steroids alone for inducing partial or complete remission in patients with membranous LN who have nephrotic proteinuria at baseline. The post-hoc analysis by Radhakrishnan *et al.*, 2010 suggested that MMF is as effective as IVC for the treatment of Class V LN, but neither treatment was very effective.

Therapeutic equivalence of EC-MPS and MMF in renal transplant patients

Two study reports included in the initial dossier were considered pivotal, one for efficacy and one for safety. Each of these included renal transplant patients co-administered cyclosporine with or without corticosteroid.

The study of Salvadori *et al.*, 2004 was rated NHMRC level II and Jadad score 5. The study assessed the therapeutic equivalence between EC-MPS and MMF in stable renal transplant patients. There were 213 patients in the EC-MPS group and 210 in the MMF group. The patients were predominantly Caucasian and male. The primary outcome was treatment failure based on the incidence of BPAR, graft loss, death or loss to follow-up at 6 months. Within the first 6 months post-transplant, ITT analysis showed that the incidence of treatment failure was similar for EC-MPS and MMF (25.8% and 26.2%, respectively). The 95% CI for the difference was -8.7, +8.0, indicating equivalence according to pre-specified criteria.

The study of Budde *et al.*, 2004 was also rated NHMRC level II, Jadad score 5. The study assessed whether renal transplant patients could be safely converted from MMF to EC-MPS. The primary objective was to assess safety with respect to gastrointestinal adverse events and neutropenia at 3 months. Efficacy was a secondary objective. There were 159 patients in the EC-MPS group and 163 patients in the MMF group. The patients were predominantly Caucasian and about two thirds of them were male. No statistically significant difference between the two groups was detected with respect to nausea, dyspepsia, upper abdominal pain, gastro-oesophageal reflux, gastritis, anorexia, diarrhoea, or neutropenia. No difference was found in the incidence of treatment failure. There was no sample size calculation and the study numbers may have been too small to detect statistically significant differences.

Bioequivalence of EC-MPS and MMF in renal transplant patients

In the initial dossier; one single dose study, two multiple dose studies and one pre-dose study, all conducted in stable, adult renal transplant patients, examined the bioequivalence of EC-MPS compared to MMF.

The single dose study reported that EC-MPS 640 mg and 720 mg is bioequivalent to 1000 mg MMF for MPA $AUC_{(0-\infty)}$. T_{max} was delayed for EC-MPS. C_{max} for EC-MPS was lower than C_{max} for MMF, with 90% CIs outside the bioequivalence levels. Based on the result of this study, the two formulations cannot be considered truly bioequivalent.

The multiple dose study reported the bioequivalence of EC-MPS to MMF with regard to AUC. The MPA C_{max} for EC-MPS 720 mg was less than that of MMF 1000 mg; the MPA T_{max} was delayed with EC-MPS. With repeated doses, MPA C_{min} for EC-MPS averaged approximately twice the MPA C_{min} for MMF. Overall, the two formulations could not be considered truly bioequivalent.

The single dose study by Arns *et al.*, 2005 reported bioequivalent MPAG (an inactive metabolite) C_{max} and AUC, while the multiple dose study by Budde *et al.*, 2007a reported that the IMPDH AUC was 14% lower for EC-MPS than for MMF.

A systematic review by Budde *et al.*, 2007b based on three multiple doses studies found that MPA C_0 values were consistently higher for EC-MPS than for MMF. This report also documented a number of outliers with relatively high values.

The multiple dose study by Tedesco-Silva *et al.*, 2005 reported the PK results which were different from those of Budde *et al.*, 2007b: the C_{min} were similar between EC-MPS and MMF; AUCs and C_{max} was outside the bioequivalence range; the AUC and C_{max} for the inactive metabolite (MPAG) were 22% higher for EC-MPS than for MMF, the AUC and C_{max} were within bioequivalence range for AcMPAG, a potentially active metabolite.

The submitted PSUR included summary of a study by Joy *et al.*, 2009 in which the PK of MPA was examined in subjects with LN. Both creatinine clearance and serum albumin level were identified as primary contributors to MPA exposure. The authors commented that clinicians need to be mindful of clinical changes throughout the course of LN in order to maintain efficacy and reduce toxicity from MPA therapy.

Two more PK studies were submitted in the supplementary data. The study of Rupprecht *et al.*, 2009 compared the influence of pantoprazole 40 mg twice daily on the bioavailability of a single dose of MMF 1000 mg or EC-MPS 720 mg in 12 healthy volunteers. The study showed that pantoprazole had little effect on the exposure of EC-MPS while there was marked reduction in the exposure of MMF.

The Novartis study by Tedesco-Silva *et al.*, 2010 is a multiple-dose (21 days) crossover study comparing the inter- and intra-subject variability of MPA pre-dose levels from EC-MPS (720 mg twice daily) and MMF(1000 mg twice daily), each in combination with cyclosporine, in stable renal transplant patients. The results indicated that intra-subject variability for C_0 , C_{max} and $AUC_{(0-3 h)}$ was significantly greater for EC-MPS than for MMF. Inter-individual variability was numerically higher for EC-MPS than for MMF. Tedesco-Silva *et al.*, 2010 also stated that the variability might be even higher outside the setting of a clinical trial due to unreliable drug intake.

Clinical evaluator's recommendation

The clinical evaluator recommends approval of Myfortic for the treatment of adult patients with WHO Class III, IV or V LN. This is subject to the satisfactory RMP. Recommended changes to the PI include:

- *Black box warning*: to include a black box warning for both the PI and CMI in order to strengthen the warning relating to the risk of Myfortic use in pregnancy.
- *Clinical trials*: Revision of the proposed summary of study A2420.
- *Indication*: to include the following or similar statement in the Indication:
 - *'Evidence for this indication is based on literature reports of studies of treatment with mycophenolate mofetil in patients with LN, the majority of whom were in ISN/RPS (2003) Class IV. The evidence for efficacy was based on surrogate endpoints.'*
- *Contraindications*: to include the reason that Myfortic is contraindicated in pregnancy,
 - *'Use of Myfortic during pregnancy is associated with increased risks of pregnancy loss and congenital malformations'*.
- *Precautions*: the order of headings in this section is to be revised and that precautions relating to use in pregnancy are strengthened. In addition, two types of reliable contraception are specified in line with the requirements of Study A2420.
- *Dosage and Administration*: Justification for the proposed dosage is required before a recommendation can be finalised.

Summary of Novartis's response to the CERs

Novartis agrees with some of the recommended amendments to the proposed PI but does not agree to include a black box warning relating to risk in pregnancy. One of the arguments is that there is no such black box warning included in the Australian PI for Cellcept (MMF which is converted to the same active substance as Myfortic, MPA); inclusion of the black box warning in Myfortic PI would be an inconsistent requirement of the TGA.

With respect to the additional statement recommended to be included in the *Indications* section, Novartis does not believe it is reasonable to request a statement referencing MMF be included in the Indication section. Rather, Novartis considers that it is more correct to refer to reports of studies of treatment with mycophenolate and to include this kind of statement in the *Clinical Trial* section.

With regards to the proposed dosage of 1440 mg daily, Novartis states that this dose is justified by the fact that many of the published studies used this dose or an equivalent dose of MMF (2000 mg daily), such as in the study by Dooley *et al.*, 2011, El-Shafey *et al.*, 2010, Houssiau *et al.*, 2010, Kitiyakara *et al.*, 2008, Mak *et al.*, 2008, Traitanon *et al.*, 2008, Chan *et al.*, 2000, Chan *et al.*, 2005, Ong *et al.*, 2005, and Bao *et al.*, 2008. The choice of 1440 mg daily is also supported by the existing pre-clinical toxicology data and many years of clinical safety experience in patients with kidney transplants. The dosage used in clinical practice is determined in conjunction with clinical and biophysical responses. The dose of Myfortic used in Study A2420 (up to 2160 mg daily) was chosen based on the study published by Ginzler *et al.*, 2005 where the initial dose of mycophenolate mofetil was 1000 mg daily and increased to a maximum of 3000 mg/day.

Risk management plan

The Australian-specific RMP (version 1.0 dated 24 January 2012) was submitted as supplementary data to the current application upon a specific request by TGA. The recommendations by the RMP evaluator are supported. The sponsor has provided an update of the RMP (version 1.1, dated 9 May 2012) in respond to the RMP evaluation report.

Of note, the RMP evaluator considers that the strengthened wordings in the proposed PI and CMI (provided as attachments to the sponsor's response to the RMP evaluation report and to the Delegate's overview) adequately convey the pregnancy related risks without the need for a black box warning. The educational material will also act as an additional safeguard. It is also noted that the sponsor is planning a post-marketing study in patients who will be treated with Myfortic.

Risk-benefit analysis

Delegate considerations

The direct evidence provided to support the efficacy of Myfortic (EC-MPS) for the treatment of LN is limited to a few observational studies. The clinical responses to EC-MPS therapy were documented in these studies. In Study A2420, the primary outcome of complete remission was recorded for approximately 20% of patients after 6 months of EC-MPS therapy.

The majority of the submitted published articles are related to the efficacy and safety of MMF for the treatment of LN. These articles include published reports of individual studies, review articles and meta-analyses. The problems with the design and conduct of these individual studies and the limitations of the meta-analyses have been discussed in the CER (see Attachment 2). MMF has been shown to have similar efficacy to IVC for LN induction therapy in randomised, controlled, unblinded trials and meta-analyses. Maintenance therapy with MMF was shown to have significantly better results than azathioprine in a randomised, controlled, double blind, double dummy, 36 weeks study in patients who have responded to induction therapy.

The therapeutic equivalence of MMF and EC-MPS has been demonstrated in renal transplantation patients in the submitted studies; however, it is not clear if the therapeutic

equivalence of MMF and EC-MPS in renal transplantation patients can be extrapolated to patients with LN.

The evaluation of bioequivalence studies revealed that MPA AUC is generally similar for EC-MPS and MMF in stable renal transplant patients, however, higher AUC exposure for EC-MPS compared to MMF was seen in two small studies. In stable renal transplant patients, it appears that C_{max} is lower and C_0 is likely to be higher for EC-MPS compared to MMF. There appeared to be greater inter-individual and intra-individual PK variability reported for EC-MPS compared to MMF; this is considered a potential problem which may impact on both safety and efficacy.

Safety data from published studies are usually limited. Myfortic has the risks that are common to all immune-suppressants. Of particular concern is that MPA has been demonstrated to be teratogenic and to increase the probability of spontaneous abortion. The congenital abnormalities reported in relation to MMF have potential to cause death or significant disability. Systemic lupus erythematosus predominantly affects women of child bearing age. The registration of a teratogenic drug for use in this population is of great concern.

In response to the initial (first round) CER, the sponsor emphasised the advantage of Myfortic therapy over the standard therapy with IVC. The study by Laskari *et al.*, 2010 was discussed, and in relation to therapy in women with LN, the prolonged course of cyclophosphamide for induction therapy had a 4-fold risk of amenorrhea and a 5-fold risk of sustained amenorrhea compared to a short course of cyclophosphamide followed by MMF ($p = 0.001$ and 0.009 , respectively). Evidence from the meta-analyses by Mak *et al.*, 2009 and Touma *et al.*, 2011 suggested that mycophenolate better preserves ovarian function in comparison to cyclophosphamide.

The justification for the proposed daily dosage is provided in the sponsor's response to the supplementary clinical evaluation, and is considered acceptable by the Delegate.

Based on the evidence provided and the arguments discussed above, the Delegate is of the view that the benefits and risks balance is considered as positive for Myfortic use in the induction and maintenance treatment of adult patients with WHO Class III, IV or V LN, provided that the currently agreed RMP be properly implemented and the RMP be updated in light of any new safety findings following the registration and marketing of the product.

Proposed action

Pending ACPM advice (see below), the Delegate recommends the registration approval of Myfortic EC tablets for the induction and maintenance treatment of adult patients with WHO Class III, IV or V LN.

The final approval is subject to the satisfactory negotiation of the PI following the ACPM resolution.

Implementing the currently agreed RMP (version 1.1, dated 9 May 2012) and any subsequent RMP updates should be a condition of registration.

The advice specifically requested from ACPM

- Does ACPM support the extension of indication to include '*the induction and maintenance treatment of adult patients with WHO Class III, IV or V lupus nephritis*' on the basis of the literature evidence as discussed in the evaluation report?
- What is the opinion of the ACPM with respect to the inclusion of a black box warning in the PI/CMI highlighting the pregnancy related risks?

- What is ACPM's opinion with respect to the inclusion of the following statement in the indication section?
 - *Evidence for this indication is based on literature reports of studies of treatment with mycophenolate mofetil in patients with LN, the majority of whom were in ISN/RPS (2003) Class IV. The evidence for efficacy was based on surrogate endpoints.*
- Does ACPM consider that the proposed dosage of 1440 mg daily is acceptable?

Response from sponsor

The sponsor provided comments on the matters addressed to ACPM by the Delegate and on several other matters raised in the Delegate's overview including the following:

- Extrapolation of the equivalence of MMF and EC-MPS in renal transplantation patients to patients with LN
- Inter- individual and intra-individual PK variability reported for EC-MPS compared to MMF
- Registration of a drug for use in a condition that predominantly affects women of child bearing age
- Proper implementation of the RMP

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered this product to have an overall positive benefit-risk profile for the following indication:

For the induction and maintenance treatment of adult patients with WHO Class III, IV or V LN.

(This indication is based on the evidence in literature reports of studies of treatment in patients with LN, the majority of whom were in ISN/RPS (2003) Class IV. The evidence for efficacy was based on surrogate endpoints)

In making this recommendation the ACPM noted that the evidence in the literature-based submission was generally inadequate in terms of interpretation of surrogate endpoints, poorly documented or no randomisation, short duration, and limited dosage studies. The ACPM was not satisfied that the optimum dosage has been established or that the available data support the sponsor's proposed dosing recommendations. The ACPM advised that in view of the absence of dosing information in adolescents, the indication be limited to the adult population.

However, the ACPM agreed the benefit-risk profile was appropriate for the proposed indication, advising that the PI and CMI must include more robust information about the status of the supporting clinical evidence.

In addition, the ACPM advised that the use of this product will be limited to prescribing by specialists who are expert in managing the safety risks associated with the contraindication for the use in pregnancy. A Black Box warning was not recommended.

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- a statement in the *Clinical Trials* section of the PI to more accurately reflect the available evidence and support suitable dosing.
- a statement in the *Dosage and Administration* section of the PI and CMI to more accurately reflect that adequate dosage studies have not been performed and in particular that the daily dose of greater than 1440 mg/day for induction therapy had been used in some studies (for example MMF 3 g dose with a median dose achieved of 2.6 g/day was used in the pivotal ALMS study).
- a statement in the *Contraindications* section of the PI and CMI to ensure awareness of significant pregnancy risks.

The ACPM advised that the conditions of registration should include commitment by the sponsor to conduct robust phase IV studies that enable the collation of long-term evidence to support safety profile, and dosage.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Myfortic mycophenolate sodium tablets (180 mg and 360 mg) for the following new indication:

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

This indication is based on the evidence in literature reports of studies of treatment in patients with lupus nephritis, the majority of whom were ISN/RPS (2003) Class IV. The evidence for efficacy was based on surrogate endpoints.

The full indications are now:

Myfortic is indicated for the prophylaxis of acute transplant rejection in adult patients receiving allogeneic renal transplants.

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

This indication is based on the evidence in literature reports of studies of treatment in patients with lupus nephritis, the majority of whom were ISN/RPS (2003) Class IV. The evidence for efficacy was based on surrogate endpoints.

This approval is based on the evaluation of the information and data provided with the original letter of application and with any subsequent correspondence and submissions relating to the application.

Specific conditions of registration applying to these goods

- The implementation in Australia of the Myfortic MPA tablet RMP version 1.1, 9 May 2012 included with the submission and any subsequent revisions, as agreed with the TGA and its Office of Product Review.
- A case report form for LUNAR that is acceptable to the TGA must be provided to the Office of Product Review.

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Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

Attachment 2. Extract from the Clinical Evaluation Report

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