Multiple Technology Appraisal

Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85)

Full submission document for enteric-coated mycophenolate sodium (Myfortic®) and everolimus (Certican®)

Novartis

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EXECUTIVE SUMMARY

This is an evidence submission from Novartis for two interventions – enteric-coated mycophenolate sodium (EC-MPS; Myfortic®) and everolimus (Certican®) – for the Multiple Technology Appraisal: Immunosuppressive therapies for kidney transplantation in adults (review of technology appraisal guidance 85).[1]

For maintenance therapy, NICE TA85 recommends calcineurin inhibitors (CNIs), such as ciclosporin or tacrolimus, and antiproliferative agents, such as azathioprine, sirolimus or mycophenolic acid (MPA), used in combination regimens with or without corticosteroids for immunosuppression in adults receiving kidney transplants.[1] As several major trials have been published since 2004, notably B301 and B302 for EC-MPS and A2309, B201 and B251 for everolimus, this evidence submission has been compiled to inform the review of TA85.

The focus of the submission is in line with the NICE scope for initial and long-term maintenance therapy. The interventions considered are:

- EC-MPS, in combination with ciclosporin and corticosteroids, for the prophylaxis of acute transplant rejection in adult patients receiving allogeneic renal transplants
- Everolimus, in combination with reduced-dose ciclosporin microemulsion and corticosteroids for prophylaxis of acute transplant rejection in adult patients at low to moderate immunological risk receiving allogeneic renal transplants. Please note that everolimus will not yet have a licence for this indication at the time this submission is made.

Epidemiology and background

Renal transplantation is the treatment of choice for end-stage renal failure (ESRF) because, if successful, the subsequent quality and duration of life are better than with long-term dialysis. Approximately 2,142 renal transplants from deceased donors are performed in the UK each year.[2] The current cost of treating people with ESRF has been estimated at 1–2% of the total NHS budget.[3] Consistent evidence shows that renal transplant recipients are more likely than the general population to have comorbidities such as cardiovascular disease, specific types of cancers, gastrointestinal (GI) complications, as well as suffer from poorer psychosocial functioning and higher anxiety and depression rates.[3] Because graft rejection remains a central issue in organ transplantation, successful transplantation is reliant on the use of immunosuppressive agents. A variety of immunosuppressive drugs are currently used in the management of renal transplantation in the UK; an overview of the interventions used for induction and maintenance therapy is provided in the submission.

Evidence for clinical effectiveness and safety

A comprehensive systematic review of evidence for clinical effectiveness and safety of EC-MPS and everolimus was recently carried out in accordance with NICE guidelines but is as yet unpublished. This submission includes data from 27 efficacy and safety studies (13 for EC-MPS

and 14 for everolimus), including 15 randomised clinical trials (RCT) (seven trials for EC-MPS and eight for everolimus). Each intervention is considered separately.

Summary of key findings on clinical efficacy and safety for EC-MPS

Clinical evidence for EC-MPS is available for the combination with ciclosporin (licensed regimen), as well as in unlicensed combinations. Seven RCTs, three open-label extension studies of RCTs, as well as three non-RCTs are included as evidence for efficacy and safety of EC-MPS for initial and long-term maintenance therapy.

Data shows EC-MPS to have equivalent efficacy to MMF with comparable safety profile, whilst resulting in fewer GI side effects, and subsequent potential improved patient functioning and patient well-being.

- Renal transplant patients on maintenance therapy can be converted from MMF to EC-MPS without compromising on the safety and efficacy associated with MMF
- EC-MPS-treated patients were maintained on full-dose MPA more frequently than MMF-treated patients with concomitant calcineurin inhibitor (CNI) exposure with potential beneficial effects on immunosuppressive efficacy

Summary of key findings on clinical efficacy and safety for everolimus

Everolimus is considered in combination with reduced-dose ciclosporin (with or without corticosteroids) for prophylaxis of acute transplant rejection in adult patients receiving allogeneic renal transplants. Some of these combinations are not in line with the anticipated licenced combination. Eight RCTs, five prospective studies and one observational study are included as evidence for efficacy and safety of everolimus for initial and long-term maintenance therapy.

Current practise is to use CNI based regimens (tacrolimus or ciclosporin) in combination with antiproliferative agents (such as azathioprine, sirolimus or MPA) in the prophylaxis of renal allograft rejection. However, CNIs are known to have nephrotoxic effects on the body and exacerbate CV risk. Adding everolimus to a ciclosporin based regimen allows for reduction in ciclosporin dose whilst demonstrating:

- Non-inferior efficacy and safety parameters versus a regimen of CNI combined with MPA
- Month 12 renal function was shown to be numerically in favour of everolimus with reduced dose ciclosporin compared with MPA and standard dose ciclosporin in one trial (A2309)
- A lower risk of developing cytomegalovirus (CMV) infection compared with MMF and standard dose ciclosporin, with no significant differences in efficacy and other safety parameters. The activity of everolimus against CMV is noteworthy because CMV disease is associated with inferior long-term patient and graft survival
- Conversion from a CNI to everolimus or reduced-dose CNI therapy can improve left ventricular hypertrophy
- Fewer neoplasms compared with standard CNI exposure in kidney transplant recipients.

Summary of cost-effectiveness findings

A patient-level simulation model was developed to assess the cost-effectiveness of everolimus with reduced dose ciclosporin compared with both tacrolimus and ciclosporin based regimens in patients who have undergone renal transplantation. As part of this assessment, EC-MPS was also compared with MMF (both in combination with ciclosporin). No subgroup analyses were undertaken.

The key findings of the comparison of everolimus and reduced dose ciclosporin with tacrolimus and standard dose ciclosporin were as follows:

- Everolimus is a cost-effective option for the NHS compared with tacrolimus.
- In the base case analysis, everolimus produced more quality-adjusted life-years (QALYs), at a lower cost, resulting in a dominant incremental cost-effectiveness ratio (ICER) and a net monetary benefit (NMB) value of £35,498.
- Results were verified by sensitivity analysis.
- Probabilistic sensitivity analysis (PSA) indicated that everolimus had a probability of being cost-effective of 100% at all willingness-to-pay thresholds analysed.
- Everolimus remained cost-effective within all ranges tested for each parameter examined during the deterministic sensitivity analysis. The only scenario of everolimus not being cost-effective was when the drug discontinuation rate for tacrolimus was increased to 25% or 50% while that for everolimus remained at 0%.

The key findings of the comparison of everolimus and reduced dose ciclosporin with MMF and standard dose ciclosporin were as follows:

- In the base case analysis, everolimus resulted in a gain of 0.99 QALYs at an incremental cost of £59,354 compared with MMF, resulting in an ICER of £59,696.
- These results were verified by sensitivity analyses:
- Deterministic sensitivity analysis showed that MMF remained the cost-effective option for all parameter ranges assessed
- PSA indicated that at a willingness-to-pay threshold of £20,000, the probability of everolimus being cost-effective is 0%; this remains at 0% until the threshold value is increased to approximately £87,000
- During the scenario analysis, in which the annual reduction in drug usage for everolimus was increased from 0% to 25% or 50%, everolimus became the more cost-effective option, even when the rate was also increased for MMF; for example, when the rate was increased to 25% for everolimus and 50% for MMF, the NMB for everolimus was £21,547. This indicates everolimus will be cost-effective if there is an annual reduction in its usage post-transplant, which is a highly plausible scenario.

The key findings of the comparison of EC-MPS with MMF (both in combination with ciclosporin) were as follows:

- The base case analysis indicated that EC-MPS is more cost-effective than MMF, estimating that patients on EC-MPS gain 0.80 QALYs at an incremental cost of £10,588, resulting in an ICER of £13,209 and NMB value of £5,444.
- Sensitivity analysis, however, showed a degree of uncertainty with these results. While EC-MPS remained cost-effective for all iterations tested during the deterministic sensitivity analysis, with the exception of the utility of CKD stage 3 patients, the PSA estimated that at a willingness-to-pay threshold of £20,000, EC-MPS only had a small probability of being cost-effective. This suggests the model results for EC-MPS are vulnerable to variations in underlying model parameters. It should also be noted that the probability of cost-effectiveness increased significantly, to approximately 60%, when the threshold value was changed to £30,000.