

SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of CellCept. This scientific discussion has been updated until 01 August 2003. For information on changes after 01 August 2003 please refer to module 8B.

1. Introduction

CellCept contains the active substance mycophenolate mofetil (MMF) produced by chemical synthesis from mycophenolic acid (MPA). MPA is a chemical substance produced by fermentation using a strain of *Penicillium stoloniferum*. MPA, the active metabolite, is a selective, non-competitive, reversible inhibitor of inosine monophosphate dehydrogenase. This inhibition leads to a nucleotide deficiency within cells that slows proliferative rate. In lymphocytes, a slow proliferation rate and changes to the surface glycosylation of adhesion molecules render the lymphocytes less effective in recognising and eliminating allografts in animal models.

Renal transplant

The Marketing Authorisation for CellCept in renal transplant patients was granted on 14 February 1996. At this time, approximately 9,000 renal transplants were performed each year in Europe. Acute rejection is the clinical manifestation of the immunologic disparity of donor and recipient and, if not prevented or treated, will result in graft loss. In 1996, therapies with cyclosporin, corticosteroids, and azathioprine in various combinations were the most common regimens. With these immunosuppressive regimens 1-year allogeneic graft survival was 80-90%. Long term graft survival was lower, with a 3-year graft survival of about 60-70%. Reducing the incidence of acute rejection may potentially translate into significant improvement in the long term outcome of renal transplantation.

Paediatric renal transplants

In the late 1990's approximately 650 paediatric renal transplants were performed annually in the EU and approximately 550 in the USA. Prior to the approval of CellCept for paediatric use on 16 July 2001, the immunosuppressive regimens used in children were similar to those for adults (with the exception of CellCept), *i.e.*, azathioprine (AZA) in addition to cyclosporin and corticosteroids, with lymphocyte antibody induction therapy (ATG, ALG or OKT3) often added immediately post-transplant. Younger children often need higher doses of cyclosporin to maintain adequate blood levels. Following renal transplantation, one-year graft survival rates in Europe from the late 1980's to the late 1990's were 61-81% in children (*versus* 75-83% in adults). Acute rejection has been reported to develop in 40-70% of children treated with cyclosporine-AZA containing regimens with most occurring in the first 3 months post-transplant. As with adults, acute rejection is the most important predictor of subsequent chronic rejection in children.

The causes of end-stage renal failure differ between adults and children, however the only aetiologies that are considered to impact on graft survival are focal glomerulosclerosis, which occurs more frequently in children than adults (8% vs 3%), congenital nephrotic syndrome, and, above all, acute allograft rejection. Several factors not directly related to the pathogenesis of renal failure also affect graft loss. Graft survival is poorer in very young children (< 3 years) and as this often results from vascular thrombosis, it may be due to mechanical factors resulting from placing a relatively large organ in a small child. Children under 6 years of age have a higher incidence of non-specific cellular immune responsiveness which is likely to be the reason they are reported to experience more episodes of acute rejection than adults and consequently are often treated with more intense immunosuppression.

Cardiac transplant

Cardiac transplant is the treatment of choice in selected patients for end-stage cardiac failure. Transplant programmes are limited by the availability of donor organs. The American Heart Association has developed guidelines identifying patients whose survival ought to be increased by cardiac transplant, *e.g.* NYHA class IV patients with less than 12-month life expectancy and class III patients with poor exercise tolerance. Therefore, patients receiving cardiac transplant are a very ill group of patients.

The posttransplant requirement for immunosuppressive therapy develops over time. Normally 3 different phases can be recognised: the peri-operative phase, the acute phase, and the maintenance phase. Doses of immunosuppressants are adjusted according to these phases and the acute rejection status of the patient. The long-term results of cardiac transplantation are negatively influenced by the development of coronary artery vasculopathy, infection and malignancies. Graft failure occurs in approximately 3% of patients in the first year but the total mortality rate at one year is 21%. The main cause of death in the first year is infection.

Hepatic transplant

In the late 1990's, approximately 3,500 hepatic transplants were carried out in Europe annually with surgical and post-operative immunosuppression resulting in 50–70% acute rejection episodes in the first 6 months post-transplant but with a 1 year survival of 70–80%. At this time there was no standard immunosuppressant regimen but usually either cyclosporin or tacrolimus both with corticosteroids were used. Azathioprine (AZA) was often added to the cyclosporin plus steroid to reduce the dose of cyclosporin and reduce the rate of chronic (ductopenic) rejection. As tacrolimus is considered to be a better immunosuppressant than cyclosporin, AZA is not often added to tacrolimus containing regimens.

The prevention of acute rejection is the main focus of immunosuppressant therapy. However acute rejection *per se* rarely leads directly to death or graft loss but chronic rejection of the grafted liver results in an occlusive arteriopathy and loss of bile ducts that can have a fatal outcome. This chronic rejection is the main cause of irreversible hepatic graft failure.

2. Part II: Chemical, pharmaceutical, and biological aspects

Composition

The first pharmaceutical forms of CellCept to be authorised were the capsules and tablets. A number of other pharmaceutical forms of CellCept have been authorised subsequently - see Steps taken after authorisation - all containing the same active substance, mycophenolate mofetil (MMF):-

CellCept 250mg capsules - the formulation of the finished product consists of MMF granules filled into hard gelatine capsules in PVC blisters with push-through foil lidding. Excipients and pack sizes are defined in the SPC, sections 6.1 and 6.5 respectively.

CellCept 500mg tablets - are presented in white opaque PVC blisters with push-through foil lidding. Excipients and pack sizes are defined in the SPC, sections 6.1 and 6.5 respectively.

CellCept 1g/5ml powder for oral suspension – each bottle contains 35g MMF in 110g powder. 5ml of the reconstituted suspension contains 1g of MMF. Excipients and pack sizes are defined in the SPC, sections 6.1 and 6.5 respectively. An oral dosing dispenser (syringe) is included in the pack.

CellCept 500mg powder for concentrate for solution for infusion – each vial contains 500mg MMF as the hydrochloride salt. The powder must be reconstituted and then further diluted with glucose intravenous infusion 5% before use. Excipients and pack sizes are defined in the SPC, sections 6.1 and 6.5 respectively.

Active substance

The active substance in CellCept is mycophenolate mofetil (MMF) produced by chemical modification (esterification) of the free acid, MPA, itself produced by fermentation using a strain of *Penicillium stoloniferum*. MPA is separated from the mycelium and further purified by crystallisation, and the esterification of MPA with 2-morpholinoethanol produces mycophenolate mofetil. The product is purified by crystallisation and is then dried and sieved. Full details of the manufacture and quality control of the drug substance were submitted in the first centralised application for CellCept Capsules 250 mg, supplemented with additional information when relevant to the particular pharmaceutical form in question.

The proof of structure of MPA and MMF has been established using the usual spectroscopic techniques.

Since the first authorisation, a modification has been made to the strain of the producer organism in order to increase the yield of MPA. The new strain (PF18-21) is said to be a mutant of the existing

strain produced by classical mutation manipulations, and is not the result of genetic engineering. A new specification has been provided for the organism, this consists of a morphological description, a potency assessment and absence of contamination. To support this change, four batches of crude MPA were manufactured using the new strain. All batches met the specification and no new impurities were detected. Therefore, whilst this was a major change, it was considered to be without impact on the safety and efficacy of the product as previously established. Some acceptable minor modifications have also been made to the fermentation process and synthetic process for converting MPA into MMF

The active substance specification includes tests for identity, loss on drying, clarity of solution, assay (titration 98-102%), chromatographic purity (HPLC 98-102%), related substances (HPLC), residue on ignition, heavy metals, residual solvents, etc.

The original submission for the capsules provided the impurity profiles and general specification for the active substance used in stability, toxicology and clinical studies, and the specification applicable to the oral pharmaceutical forms has been justified with reference to these studies. A separate specification for the active substance to be used in the parenteral product has also been justified from a toxicological perspective and the batch data show good consistency.

The stability of the active substance has been demonstrated arising from a large amount of accumulated data under ICH conditions. An acceptable retest period has been established.

Other ingredients

The excipients in each pharmaceutical form are listed in the relevant SPC section 6.1. Each one has been justified with reference to its established use and special function, and is of PhEur quality where applicable. Other in-house specifications where no PhEur monographs exist have been justified.

There is no significant risk of transmission of TSE arising from the use of these excipients.

Capsules and Tablets:

Product Development and Finished Product

These oral dosage forms are of standard formulation and have been developed to release the active substance rapidly prior to absorption. The manufacturing process is also standard and generates a suitably uniform product which routinely complies with the specification.

The product specifications for these simple oral dosage forms include relevant tests for identity, assay, dissolution etc. which should indicate reliable performance in the clinic.

Stability of the Products

The physicochemical stability of the capsules and tablets has been established by 'early' studies, some of them initiated before the ICH stability guideline was finalised, and supplemented later with ICH studies. The results indicate no significant changes in the products during the shelf-life and storage conditions as recommended in the SPC.

Powder for oral Suspension:

Product Development and Finished Product

In general the low aqueous solubility of MMF has facilitated the development of the oral suspension. The main development objectives have been to provide a formulation of powder, which, when reconstituted with water will give a stable suspension resistant to adventitious microbial contamination, and capable of producing a uniform dose. Attention has therefore been paid to the uniform particle size of the active substance, the use of a standard preservative (methyl parahydroxybenzoate) and the employment of buffering agents and viscosity-modifying agents (xanthan gum). Aspartame has been added as a sweetening agent to improve palatability. During manufacture, particular attention has been paid to homogeneity of the powder blend during filling, in order to ensure uniformity of dose of the finished product.

The specification includes relevant tests for identification, assay, loss on drying, fill weight and appearance, etc. All tests are carried out on the suspension reconstituted according to the standard instructions but using double distilled water. The lower shelf life limits for methylparaben content have been justified by preservative efficacy testing.

Stability of the Product

Stability data were provided for three batches manufactured at full-scale at the intended commercial site and stored under various ICH conditions including light exposure. All results remained within specification limits. At 25°C/60%RH there was no significant loss of potency but under accelerated conditions the MMF content fell by up to 6% with a corresponding increase in MPA content. The sorbitol ester of MPA was also detected on storage but no other degradation product peaks above 0.05%. There was an increase in moisture content both at 25°C/60%RH and at 40°C/75%RH. Dissolution profiles did not change under normal storage conditions but there is a slowing of dissolution rate for samples stored at higher temperatures. Exposure to intense light had no apparent effect and the Z-isomer (produced by light exposure of drug substance) did not appear in these samples.

Based on these results, a shelf life of 24 months is proposed when the product is stored below 30°C.

Stability of the reconstituted suspension has also been investigated for the same batches as above. Samples were stored inverted at 25°C/60%RH, 30°C/60%RH and 5°C, or stored horizontal to light exposure, for up to 12 weeks. A shelf life of 60 days is proposed when the product is stored below 30°C in the reconstituted form.

In addition, simulated in-use studies have confirmed that a uniform dose of MMF can be repeatedly obtained from the reconstituted suspension using the oral doser provided in the pack, and uniformity of dosage is not a problem.

Powder for concentrate for solution for infusion:

Product Development and Finished Product

The low aqueous solubility of MMF has been overcome by using MMF hydrochloride in this case. Critical processing parameters have been studied and are adequately controlled. Standard containers and closures for a lyophilised product are used, and container/closure integrity has been validated. The manufacturing process includes compounding, sterile filtration/vial filling and lyophilization, and process validation studies have established the critical control parameters. A standard steam sterilisation cycle is used for equipment, and the freeze dryers are sterilised according to well established and validated procedures.

Validation of the aseptic manufacturing steps was carried out with media fill runs, and an acceptable failure rate has been defined. Batch analysis data for the production scale batches shows consistent compliance with the proposed release specifications.

Separate release and shelf life specifications are defined. These are satisfactory for a sterile injectable product and include tests for assay, identity, degradation products, particulate matter, endotoxins, sterility, etc.

Stability of the Product

Long term stability data at 30°C and at 25°C/60%RH were presented for 36 months storage of upright and inverted vials. Accelerated stability data extends to 6 months at 40°C/75%RH or 12 months at 40°C/ambient RH. Stability was also been assessed at 5°C and under light stress by validated methods. The results support the shelf life of the product as defined in the SPC.

In addition, compatibility studies have been carried out on a range of i.v. fluids. Only glucose intravenous infusion 5% was found suitable as a reconstitution and dilution vehicle; other infusion solutions produced an immediate cloudiness and visible particulates. Compatibility was demonstrated with both glass and PVC containers and with the administration sets used.

Vials were reconstituted as recommended with 14 ml of glucose intravenous infusion 5% to give a solution with a concentration of 35 mg MMF per ml. The vials were stored upright or inverted at approximately 23°C for up to 24 hours in normal room light. Vials were also stored inverted at

40°C/75%RH and in a -15°C to 25°C freeze-thaw 12 hour cycle. Reconstituted solutions further diluted in i.v. bags to a concentration of 6 mg MMF per ml were stored at approximately 23°C or at 30°C for up to 24 hours in normal room light. The recommended maximum storage period for infusion solutions to maintain chemical and physical quality is 12 hours after preparation.

However, because the product contains no antimicrobial preservative, it is recommended in the SPC that the reconstituted product and any further dilutions should be used immediately, or within 3 hours.

Relative Bioavailability of the pharmaceutical forms

Compared to CellCept capsules, the tablets provide a concentration-time profile characterised by a bioequivalent AUC and a slightly reduced C_{max} .

A comparative study between the intended commercial formulation of suspension and the existing capsule product showed that the two formulations were bioequivalent (within 90% confidence intervals for the ratios).

In healthy volunteers, the MPA AUC after a 1.5 g single intravenous and oral dose were bioequivalent. In renal transplant patients, the mean MPA AUC was similar following oral or intravenous administration and it was unaffected by rate of intravenous infusion of MMF.

Discussion on chemical, pharmaceutical and biological aspects.

The active substance has been manufactured, characterised and controlled in an acceptable way.

The individual pharmaceutical forms have all been developed in a rational way and are also manufactured and controlled by validated methods relevant to their final use in patients.

3. Part III: Toxicopharmacological aspects

Pharmacodynamics/Pharmacokinetics

Mycophenolate mofetil, as a prodrug, is converted rapidly to MPA after oral administration in all mammalian species examined. MPA, the active metabolite, is a selective, non-competitive, reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH). This inhibition leads to a nucleotide deficiency within cells that slows proliferative rate, in particular in lymphocytes which have a more susceptible Type II IMPDH; the slow proliferation rate and changes to the surface glycosylation of adhesion molecules render the lymphocytes much less effective in recognising and eliminating allografts in animal models.

The action of MPA is not totally specific to desired targets and above a certain level of systemic exposure, all species used in safety testing show changes in haematopoiesis and lymphoid tissue atrophy. It is to be expected that, in patients, the plasma concentration associated with the recommended dose regimen will also produce adverse effects in cells other than lymphocytes.

One objection related to the omission of a solid dose formulation in preclinical kinetic study was raised during the procedure. The company justified this point stating that the suspension formulation used was considered the best absorbed oral formulation to use.

Toxicology

The toxicology programme included acute, subchronic, and chronic oral studies as well as reproductive, mutagenicity and carcinogenicity studies. As the clinical use will be mainly oral, the primary route of exposure in the toxicology studies was oral (gavage). Additional studies were conducted by the intravenous and subcutaneous routes to further characterise the toxicological profile.

The principal target organs in mice, rats, dogs and monkeys were the haematopoietic, gastrointestinal and lymphoid systems. No unusual histopathology or other toxicity was observed in the carcinogenicity studies. No mutagenic potential was found for MMF or MPA in the studies performed. There was no effect on male fertility in rats for the doses used. In the female fertility and reproduction study in rats the highest doses used caused malformations. MMF is teratogenic in rats and rabbits.

An extensive toxicology programme was conducted in support of the clinical use of MMF using the oral and intravenous routes. Acute, subchronic, special toxicity studies and *in vitro* compatibility studies were conducted in support of the intravenous formulation development, previously submitted and reviewed during the approval of the oral product. These data also enabled conduct of the intravenous clinical development programme, various parts of which were submitted and reviewed with the oral application.

The toxicity profile of MMF obtained following intravenous administration is comparable with that following oral administration. Thus, the completed toxicology data with the intravenous route, together with the comprehensive package generated to support oral administration, are adequate to support approval of this dosage form. The existing toxicology data are sufficient to support intravenous dosing in humans at 1 g bid for up to 14 days.

No additional toxicology studies have been conducted since the initial review of CellCept capsule and tablet formulations, as the assessment of the studies reviewed at that time is considered of equal relevance to the intravenous administration

During the assessment procedure, concerns were raised about the safety margin. Based on plasma levels of MPA achieved in toxicology studies and the extent of binding to plasma proteins, the monkey data show a small but demonstrable margin of safety for MPA/MMF. Monkeys were most likely exposed to several fold more MPA than expected exposure in man. However, at the maximum recommended doses for humans the systemic exposure resembles that linked to toxic reactions in test animals. The therapy cannot be said to have a safety margin. But to achieve optimum benefit, a predictable degree of risk has to be accepted and in this case outweighs the potential for toxicity indicated by the preclinical animal data. Intensified surveillance and a post-marketing surveillance study were requested as a specific obligation to the Marketing Authorisation Holder.

Mutagenic potential

A variation was submitted to update the preclinical safety data section of the SmPC (Section 5.3) to include advice on the mutagenic potential of MMF observed with repeated administration, arising from tests suggested by the FDA.

Data from one *in vitro* (No 104 M 00) and one *in vivo* (No 169 M 00) study were provided.

The mouse lymphoma/ thymidine kinase model was used to test for mutagenicity *in vitro*. Cell survival was assessed together with changes in the number of mutant clones induced in the presence of MMF. The presence of enhanced numbers of small colonies was considered indicative of clastogenic activity. The authors of the study conclude that MMF has weak mutagenic and clastogenic activity. Further, that the clastogenic activity observed has no carcinogenic consequences since in a previous study (Syntex study AT 6703, not resubmitted) no tumorigenic effects in mice were observed after 2 years of treatment with 180mg/kg/day. In her report, the assessor concurs with this conclusion.

The mouse bone marrow micronucleus test was used to test for mutagenicity *in vivo*. Cytotoxicity was measured by the ratio of polychromatic cells to normochromatic cells (PCE/NCE) per animal. Mutagenicity was estimated by the occurrence of micronuclei. Male and female mice received 30, 100 or 300mg/kg MMF by oral gavage for 1 to 10 days in the initial dose range finder assay and for 1 or 8 days in the main study. Bone marrow cells were harvested 24 hours after the last administered dose of MMF or 24 to 72 hours after the single MMF dose. Cytotoxicity was measured by the ratio of PCE/NCE per animal. Mutagenicity was estimated by the occurrence of micronuclei per NCE and /or micronuclei per sample of at least 4000 PCE per animal. The data show that a clear mutagenic effect is observed when mice are repeatedly treated with high doses of oral MMF for several days (300mg/kg/day for 2-8 days, *cf* normal dose ~30-40mg/kg/day in humans).

The validity of the study was questioned since % of polychromatic erythrocytes relative to normochromatic erythrocytes (% PCE), appears to vary by more than the designated 40% in several groups in both the dose range finder study and the main study and between males and females of the same treatment groups. However, it is accepted that the validity criteria should apply primarily to the control groups.

In addition, the reason for choosing 8 days treatment in the main study was not provided. The main study could under- or overestimate MMF mutagenic effects due to the selection of an

inappropriate time point. The MAH selected a treatment period of 8 days after performing an extensive range finder assay with 2,4,6,8,10 days treatment. It may be that MMF is less mutagenic than the data suggest but, since clastogenicity has only been assessed at one time point, this is difficult to establish. Also, there was an implicit assumption that mutagenicity is correlated with cytotoxicity, but this has not been demonstrated for the *in vivo* study. Statistically significant clastogenicity/mutagenicity is present when cytotoxicity is not marked, hence “at cytotoxic dose levels” was removed from the SPC. Also, justification for the proposed wording is based on *only* the highest dose giving a positive mutagenic effect. The mutagenicity test was considered positive by the MAH if 3 pre-set conditions were met. Although the highest dose tested passed these conditions, no statistical analysis was provided to ascertain if the middle dose was significantly mutagenic. The assessor concluded that the SPC wording should be revised to reflect the mutagenic activity at 100 mg/kg/day.

In the light of the positive mutagenic studies, at relatively low doses, submitted with this variation, the data in the original toxicology dossier were re-analysed. This analysis showed that the original carcinogenicity studies were positive. It is however concluded that although statistically significant carcinogenicity is present in the animal studies, the magnitude of this effect is unlikely to have any clinical relevance. Moreover, it would seem that there is little to distinguish between the genotoxic / carcinogenic potential of all the immunosuppressants cited, especially when the increased risk of cancer due to immunosuppression *per se* is taken into account.

The Safety Working Party (SWP) concluded that the genotoxic potential of MMF was related to its mechanism of action. As such, this raised no new safety issues and the benefit to risk remained favourable for MMF treatment.

In terms of the genotoxic risks of using MMF in children, the SWP assessed them to be less than those for other immunosuppressants such as azathioprine.

In conclusion, from the data submitted, MMF is associated with statistically significant clastogenicity and carcinogenicity in animal studies. The MAH argued that the latter is due to immuno-suppression *per se*, rather than due to the clastogenicity observed. The clinical data comparing MMF with azathioprine would suggest that this may be so. Furthermore, the magnitude of the genotoxic effects seen with MMF may suggest that they are not of clinical relevance, and that they do not change the positive benefit to risk of MMF as an immunosuppressant. However section 5.3 of the SPC addresses pre-clinical safety data and, as such, should clearly reflect the positive nature of the genotoxicity studies in animals. The SPC wording was revised as to reflect the positive nature of these mutagenicity and carcinogenicity studies in animals. Considering that statistically significant clastogenicity/mutagenicity is also present at 100mg/kg/day MMF for 8 days, when cytotoxicity is not marked, “at cytotoxic dose levels” was removed: two genotoxicity assays (in vitro mouse lymphoma assay and in vivo mouse bone marrow micronucleus test) showed a potential of MMF to cause chromosomal aberrations. These effects can be related to the pharmacodynamic mode of action, i.e. inhibition of nucleotide synthesis in sensitive cells. Other *in vitro* tests for detection of gene mutation did not demonstrate genotoxic activity.”

4. Part IV: Clinical aspects

The assessment of clinical aspects of the dossier is reported according to the different main stages of development separately, namely for the renal and cardiac transplant programme, the line extensions for powder for solution for infusion and powder for oral suspension, the hepatic transplant programme and paediatric renal transplant programme.

Renal and Cardiac transplantation programme

Clinical pharmacology (Capsules, tablets)

Following oral administration, MMF undergoes first pass metabolism to MPA with MMF not detectable in the systemic circulation.

MPA is metabolised principally by glucuronyl transferase to form the phenolic glucuronide mycophenolic acid glucuronide (MPAG) which is pharmacologically inactive.

MMF is almost completely absorbed following oral administration and the mean bioavailability, based on MPA AUC, is about 94% in healthy volunteers. MPA at clinically relevant concentrations is 97% bound to plasma albumin. The main route of elimination of MPA is excretion in urine as MPAG.

In the main efficacy study in cardiac transplanted patients, plasma samples were obtained in a sub-set of patients. MPA, C_{max} and AUC increased with time between the first few days after treatment and after 6 months but these findings were not statistically significant. Similar findings occur when MMF is used in renal transplant patients.

Mean plasma concentrations of the phenolic glucuronide of MPA (MPAG) were 2-3 times greater after 5 days treatment compared with day 1 post-transplant, but reached a plateau with long-term use.

In general MPA and MPAG plasma concentrations increase with dose and MPA steady state was achieved in 3-5 days of multiple dosing.

Bioequivalence

In comparison with CellCept capsules, tablets provide a concentration-time profile that is characterised by a bioequivalent AUC and a slightly reduced C_{max} . However there is no evidence to suggest that the lower C_{max} of the tablet can affect the efficacy. Therefore, the tablet formulation was considered to be an acceptable alternative pharmaceutical form.

Clinical Efficacy

The clinical indication (capsules and tablets) related to the prophylaxis of acute organ rejection in renal and cardiac transplantation is supported by three large double blind studies in renal transplant patients, one against placebo and two against azathioprine (AZA) and one large double blind study against AZA in cardiac transplant patients.

Renal transplant studies

The MMF clinical programme for the indication of prevention of renal allograft rejection involved 3 randomised, double-blind, multicentre trials with 1493 patients who received concomitant cyclosporin A (CsA) and corticosteroids (see Table 1). Two of these trials had a 3 arm parallel group design (AZA, MMF 2 g, MMF 3 g) in which regimens for the prevention of allograft rejection were compared. The primary efficacy endpoint was biopsy proven acute rejection or treatment failure in the first 6 months after transplantation. Secondary efficacy endpoints were presumptive acute rejection, treatment of rejection, cumulative doses of immunosuppressants, renal function and graft/patient survival.

Although no formal dose-ranging study has been performed, the choice of daily doses 2 g and 3 g for the pivotal clinical trials was justified based upon the relationship between the pharmacokinetics of MMF and its clinical effects, as confirmed in a Randomised Concentration Control Trial of MMF, when combined with CsA and corticosteroids..

Table 1. Summary of pivotal efficacy studies graft rejection rates

Design of the study	No. of Patients	Outcome/Comment
double blind placebo controlled	491	Prevention of acute rejection. Graft rejection rates were significantly higher in the placebo group than in the groups treated with MMF
double blind azathioprine controlled	499	Prevention of acute rejection. Graft rejection rates were significantly higher in the azathioprine group than in the groups treated with MMF
double blind azathioprine controlled	503	Prevention of acute rejection. Graft rejection rates were significantly higher in the azathioprine group than in the groups treated with MMF

Abbreviations: MMF: mycophenolate mofetil.

These studies showed that MMF 1 or 1,5 g administered orally twice a day is more effective as an adjunctive immunosuppressant to a standard immunosuppressive regimen of cyclosporin and corticosteroids than either azathioprine or placebo in reducing the incidence of biopsy-proven

rejection or treatment failure during the first 6 months after renal transplantation. The best benefit-risk ratio was in favour of MMF 2 g daily and this dose was chosen to be recommended for the prevention of rejection.

All patients from the 3 controlled prevention trials were followed for graft and patient survival at 1 year post-transplant. The data obtained were supportive of the efficacy and safety observed in the analyses performed when all patients had completed 6 months.

Cardiac transplant studies

The clinical programme for the indication of prevention of cardiac allograft rejection involved one randomised, double-blind parallel group comparison study of MMF and AZA, both in conjunction with cyclosporin and corticosteroids.

Azathioprine is an immunosuppressant, which is approved to enhance the survival of organ transplants including cardiac transplants in conjunction with cyclosporin and steroids.

The dose of CellCept used for the clinical study was 3 g/day (1.5 g bid) starting as soon as possible after transplant. The choice of the dose was according to the study investigators' views and it was based on clinical considerations (not to risk using a potential under-immunosuppressive dose of CellCept) and on statistical considerations (limited numbers of cardiac transplants performed).

Table 2 shows the efficacy results and the long-term data are also presented (study MYCS 1864).

Table 2. Results of pivotal efficacy study and long term data

	Randomised		Treated	
	AZA	MMF	AZA	MMF
Rejection with haemodynamic Compromise + re-transplant + death in first 6 months	121/323 38%	120/327 37% p=0.75	100/289 35%	92/289 32% p=0.34
(Re-transplant +) ¹ death in first 12 months	49/323 15%	42/327 13% $\delta=2\%$ LCL=-2.5%	33/289 11%	18/289 6% $\delta=5.2\%$ LCL=0.9% (p=0.026)
Re-transplant + death in first 24 months	65/323 20.1%	54/327 16.5% $\delta=3.8\%$ LCL=-1.8%	49/289 17%	27/289 9.3% $\delta=7.6\%$ LCL=2.5%
Mortality to date (from safety data)	66/323 20%	52/327 16%	50/289 17%	28/289 10%
Rejection with <u>severe</u> haemodynamic compromise + re-transplant + death in first 6 months	65/323 20%	59/327 18% (p=0.49)	50/289 17%	33/289 11% (p=0.045)

Abbreviations: see Table 1; AZA: azathioprine; LCL: Lower limit of 95% confidence interval (Non-inferiority limit is -10%); δ : AZA-MMF (difference in incidence)

¹ Only 1 re-transplant occurred and the patient died 1 month later

As far as the long-term efficacy data are concerned, the 2-year data confirm the non inferiority of MMF compared to AZA for graft loss (re-transplant + death), with a difference between treatments of 7.6% with lower limit of the 95% confidence interval of 2.5%.

Clinical Safety

Renal transplant studies

At the time of authorisation adverse event data were available from 3155 patients treated with doses up to 5g MMF daily. One year data on those patients in trials with MMF were provided at a later stage.

The most frequent adverse events occurred in the gastrointestinal and haematological systems. Additional data provided reassurance in relation to malignant lymphoma/lymphoproliferative disorders. Results obtained were in accordance with the known highest risk period for development of lymphoma/lymphoproliferative diseases in transplant patients receiving standard therapy, which is the first year post-transplantation. One year data on opportunistic infections showed no impact on the increase of their incidence. The number of patients treated with MMF and the duration of their treatment at the recommended dose of 2g/daily were sufficient for the determination of the safety of MMF.

Cardiac transplant studies

Safety was considered for up to 2.5 years. Seventy percent (201/289) of the cardiac patients who took at least one dose of MMF and 60%(173/289) of the AZA patients had been followed up for over 1 year.

In cardiac patients, the most common adverse events over/up to 2.5 year exposure were gastrointestinal symptoms (e.g. nausea, diarrhoea, vomiting), leucopenia, abnormal liver function tests, and infections. Adverse events, which were more common with MMF compared to AZA in study MYCS 1864, are diarrhoea, vomiting, opportunistic infections, namely *herpes simplex* and *Zoster*. The incidence of haemoptysis was also higher in MMF treated patients (13/289, 4.5%) than in AZA treated patients (2/289, 0.7%). According to the additional comments that were provided by the Marketing Authorisation Holder, the severity was mild, many cases appeared to be blood staining in the sputum rather than blood loss from the lung and the platelets levels and other clotting factors did not appear to show any clinically relevant difference between AZA and MMF. Leucopenia was less common (4.5% with AZA and 3.5% with MMF).

Since the original data stated that the 3 g dose may have a worse safety profile than 2 g daily and, therefore, it was difficult to determine the degree and the consequences on the benefit/risk ratio, a comparison of the safety profile of MMF at 2 and 3 g per day in renal transplant patients with that of 3 g per day in cardiac transplant was done. A comparison of deaths, malignancies, opportunistic infections, serious adverse events and premature discontinuations from the study was done:

Differences of 5% or greater in the parameters are commented here below.

In the cardiac study (MYCS 1864) the death rate at any time post-operatively regardless whether the patient was on study medication was 14.5% on AZA and 8% on MMF (3 g per day). In the renal studies the relative percentages ranged between 5.1% and 6.4%. This difference is likely to relate to a greater peri-operative morbidity in patients having cardiac transplants.

Opportunistic infections occurred in 53.3% of cardiac patients on 3 g per day of MMF and for the other regimens this ranged from 43.6% to 47.6%. The difference may be explained by a greater degree of peri-operative morbidity and more extensive surgery in cardiac transplant patients. No clear-cut pattern emerges which relates the severity of the infection with the higher doses, however, the incidence of CMV tissue invasion and *Aspergillus* infections with MMF (3 g per day) was significantly lower than with the use of AZA (6 versus 14). The revised SPC now has a statement pointing out the increased, dose dependent, incidence of opportunistic infections with CellCept as opposed to AZA and the issue of fatal infections/sepsis is also covered.

Severe hepatitis occurred at 1.2% or less in the renal transplant patients but was 4.2 and 5.5% for AZA and MMF (3 g per day), respectively, in the cardiac transplant study (MYCS 1864). This again is an indicator that patients having cardiac transplants have more peri-operative morbidity, particularly heart failure, than those having renal transplant. In addition, surgery is more extensive with cardiopulmonary by-pass, transfusions, more extensive anaesthesia. These factors would increase the risk of post-operative hepatic events. However, the Marketing Authorisation Holder committed to closely monitor the post-marketing experience for hepatic reactions and specifically address the issue in the subsequent PSURs.

Severe neutropenia (neutrophil count of less than 500 per ml) was observed more frequently in both cardiac and renal transplant patients treated with MMF 3 g per day than in patients treated with AZA. The reaction is dose-dependent since its frequency was lower in patients treated with MMF 2 g per day. Therefore, this was clearly documented in the SPC.

With regard to all the other parameters (including withdrawal from study) it was considered that the reporting frequencies were within the 5% of one another and were therefore probably of no major clinical relevance.

Overall Conclusions and benefit/risk assessment (Renal and Cardiac transplant)

Quality

The active substance is well-defined, and the products are formulated, manufactured and controlled in a way that is characteristic of this pharmaceutical form. The specifications guarantee a consistent product with uniform bioavailability from batch to batch and the safety of the impurities has been demonstrated with reference to toxicology studies. Therefore, there are no outstanding major quality issues which may have a negative impact on the benefit/risk balance.

Pre-clinical pharmacology and toxicology

The CPMP considered that the applicant provided a satisfactory answer to each question/ objection that arose during the examination of the toxicological and pharmacological documentation. To reflect those data and to address minor comments by CPMP Members amendments to the SPC were implemented.

Clinical Efficacy

Renal transplantation has become the preferred treatment option for patients in end-stage renal disease. Immunosuppressant therapy is necessary to avoid renal allograft rejection.

The trials provided convincing evidence of the efficacy of MMF as adjunctive therapy to cyclosporine and prednisolone in preventing rejection after renal or cardiac transplant.

Clinical Safety

The number of patients treated with MMF and the duration of their treatment at the recommended dose of 2g/daily for renal transplant patients and 3g/daily for cardiac transplant patients were sufficient for the determination of the safety of MMF.

Benefit/risk assessment

During the review process for both the renal and the cardiac indications for CellCept, the CPMP Members raised questions regarding quality, safety and efficacy which resulted in the supply of additional data, especially data from 1 and 2- year patient follow-up and graft survival. Significant modifications of the Summary of Product Characteristics and Package Leaflet were made by the Members to reflect those data and to address minor comments.

Recommendation

In the light of all clarifications and additional data provided by the company the CPMP issued the corresponding positive opinions for renal and cardiac indications leading to the granting of a Marketing Authorisation for CellCept in the following indication:

“CellCept is indicated in combination with cyclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal or cardiac transplants”.

Line extension: Powder for Concentrate for Solution for Infusion

Clinical pharmacology (Powder for Concentrate Solution for Infusion)

The clinical pharmacology studies with the powder for concentrate for solution for infusion formulation have been conducted in healthy volunteers, in renal and hepatic transplant patients and in patients with renal or hepatic impairment. These studies were aimed at identifying the optimal dose-

schedule in different subject samples and at demonstrating the bioequivalence between oral and intravenous formulations, through the comparison of the relative pharmacokinetic parameters (Table 3).

Table 3. Clinical pharmacology studies (Powder for Solution for Infusion)

Study	Description	No	Population	Study design
ICM 1900	Pharmacokinetics and safety of IV formulation	6	Healthy subjects	Dose-escalation, single dose (1.5 to 22.5 mg/kg over 1 h vs placebo)
CP 2294	Comparative bioavailability (IV vs oral)	12	Healthy subjects	Open, randomised, single dose, CO over vs oral (1.5 g oral vs 1.5 g IV)
II D 2176	Dose finding, pharmacokinetics in the proposed regimen	30	Renal transpl.	Open, dose finding (2 g IV bid over 40 min for 7 days; 3 g IV bid over 60 min for 7 days followed by 1.5 g bid orally for 7 days)
MYC 061	To identify an IV regimen which provides a plasma MPA concentration profile similar to that obtained following MMF orally	62	Renal transpl.	Open, randomised, PG (1.5 g IV bid over 1 hour for 7 days, 1.5 g iv bid over 3 hours for 7 days and 3 g IV bid over 24 hours for 7 days followed by 1.5 g bid orally for up to 12 weeks)
MYC S 2734	Bioavailability when switching from IV infusion to oral administration	31	First or second renal transpl.	Open, in the immediate post-operative period (1 g IV bid over 2 hours for 4 days followed by 1 g bid orally for 7 days)
II D 2190	Pharmacokinetics in paediatric patients	2	Renal transpl. (paediatric)	Case records
II D 2104	Dose finding in prevention of rejection	24	Hepatic transpl.	Open, dose finding (1.75 g IV over 1 hour followed by 1.75 or 2.00 or 2.25 or 2.5 g bid oral for up to 90 days)
MYC S 2378	Pharmacokinetics and safety	45	Hepatic transpl.	Open, randomised (2 g bid IV over 80 min, 2 g bid IV over 3 hours or 4 g/day continuously for 7 days followed by 2 g bid orally for up to 3 years)
CPP 2118	Pharmacokinetics	25	Renal impairment	Open, single oral dose (1 g <i>per os</i> then 1 g IV 40 min infusion in 4 patients)
CPP 030	Pharmacokinetics	6	Hepatic impairment	Open, single dose (1 g IV over 40 min)

CO = cross over; PG = parallel group; bid = twice daily; IV=intravenous

Healthy volunteers (Powder for Concentrate Solution for Infusion)

One study carried out in healthy volunteers proved that the kinetic parameters (C max and AUC) relative to the product itself (MMF), the active metabolite (MPA) and the glucuronide (MPAG) increase proportionally with the administered dose and that, following intravenous administration, MMF is rapidly metabolised to MPA (table 4).

Table 4. Study ICM 1900 – Healthy Volunteers (n=6) MPA Parameters - Mean (SD)

IV Dose(mg/kg)	AUC₀₋₄₈ (µg.h/ml)	AUC(µg.h/ml)	C_{max} (µg/ml)
1.5	4.21 (0.80)	N/C	2.51 (0.41)
7.5	30.8 (5.28)	34.1 (5.37)	15.8 (1.82)
15	67.3 (7.31)	70.8 (7.13)	35.3 (4.79)
22.5	116 (14.8)	121 (14.0)	60.2 (7.20)

In healthy volunteers, the MPA AUC after 1.5 g single intravenous and oral dose was 108±26.0 µg.h/ml and 101±23.4 µg.h/ml, respectively, proving the two different formulations are bioequivalent.

Renal transplant studies (Powder for Concentrate Solution for Infusion)

As far as the studies in renal transplant patients are concerned, MPA AUC is comparable following oral or intravenous administration and it is unaffected by rate of intravenous infusion of MMF.

The shifting from a 1.5 g bid intravenous to the same oral dose does not affect the MPA AUC₀₋₁₂ (39.1±9.86 µg.h/ml after 7-day intravenous administration versus 30.3±13.9 µg.h/ml after 1 day oral administration), although C_{max} was lower after oral administration (7.95±4.91 versus 20.9±6.35 µg.h/ml).

MPA AUC following intravenous and oral doses were lower in renal transplant patients, in the immediate post-transplant period, than those found in healthy volunteers. This was consistent with previous oral administration. The reasons for this remain unclear.

Based on the above studies a dosage schedule of MMF of 1 g bid infused over 2 hours was identified. This provides an MPA AUC equal to or greater than that provided by MMF 1 g bid *per os*. From the pharmacokinetic:pharmacodynamic (PK/PD) relationship this is predicted to provide comparable efficacy to the same dose given orally in patients following renal transplantation.

Hepatic transplant studies (Powder for Concentrate Solution for Infusion)

In patients with hepatic transplants, MPA AUC values following powder for sterile concentrate were similar to (dose adjusted) those found following renal transplantation.

Oral MMF administration produced lower mean MPA AUCs than those observed in renal transplant patients. However, this was a transient phenomenon with a 2-3 fold increase in AUC with the same dose of MMF maintained for up to 12 months. By months 9/12 MPA AUC₀₋₁₂ was comparable to (appropriately dose-adjusted) MPA AUC₀₋₁₂ in renal transplant patients and single dose AUC₀₋₁₂ in healthy subjects.

The lower MPA concentrations following oral MMF in hepatic transplant patients, in the period immediately following transplantation, may be attributable to diminished enterohepatic circulation or reduced absorption of drug material in this patient population.

Renal or hepatic impairment

Renal impairment does not appear to produce major differences in intravenous: *per os* pharmacokinetics and MMF clearance and biotransformation to MPA were not greatly affected by hepatic impairment.

Bioavailability and bioequivalence

A 6-day open label multi-dose pharmacokinetic study was carried out comparing intravenous administration of this product (1 g over 2 hours, twice daily) with orally administered CellCept Capsules 250 mg (1 g, twice daily). Plasma MPA was measured. The mean AUC₀₋₁₂ during intravenous treatment was approximately 24% greater, and the mean C_{max} 12% greater than that measured during oral treatment. The company concludes that the intravenous treatment regimen provides a satisfactory alternative to oral treatment in the immediate post-transplant period. This study is fully assessed in the assessment report on Part IV.

Dissolution rate data provided for the batch of capsules used in this study showed that the product is well within the product specification limit.

Clinical safety (Powder for Concentrate Solution for Infusion)

Three hundred and sixty nine subjects and patients (367 adults and 2 children) received at least one dose of MMF powder for solution for infusion. The safety data base provides information following MMF intravenous administration to patients following renal, hepatic, combined renal and pancreatic transplantation and subjects receiving single doses of MMF in pharmacokinetic studies. Most data from transplant patients was obtained during a period of intravenous administration in the early post transplant period which was then followed by oral administration.

In this assessment study MYC 2172 is important in that it provides controlled data permitting a comparison of the safety of intravenously and orally administered MMF in renal transplant patients during the immediate post transplant period and a comparison between intravenous active and intravenous placebo.

Minor differences in the unwanted effect profile related to site of infusion with a low incidence of phlebitis and thrombosis peripherally following active medication. Administration via a central venous catheter presents an acceptable alternative with similar safety.

In this critical post operative stage following renal transplantation there were no features of the powder for concentrate for solution for infusion safety profile which would detract from its use, given adherence to the recommendation that MMF must not be administered by rapid or bolus intravenous infusion. The SPC recommends that the 1 g dose is diluted to 6 mg/ml and administered slowly over 2 hours.

Gastrointestinal events were reported with a comparable frequency following intravenous and oral administration.

The relatively high adverse event rates reported are features of the patient populations and the immediate post transplant period when multiple concomitant medication is being administered.

The SPC states that the product should be used only in units specialised in the care of renal/hepatic transplant patients. This will ensure adequate and appropriate haematological and biochemical monitoring and treatment of eventual untoward effects of the immunosuppression. It will also ensure strict attention to the intravenous infusion site to minimise local effects and any longer term effects.

Conclusions concerning the relationship between dose and safety (as mentioned above) were confounded by the relatively small numbers of patients who received MMF 1.5 mg bid powder for sterile concentrate, the uncontrolled nature of this information and that different reporting practices in Europe compared to North America could have been responsible for the apparent better profile of MMF 1.5 mg bid powder for sterile concentrate compared to MMF 1.0 g bid powder for sterile concentrate.

Safety data in other clinical settings provided support for the use of MMF powder for concentrate for solution for infusion.

MMF powder for concentrate for solution for infusion permits use in the immediate post transplant period, when it is recognised that the start of immunosuppressive therapy is important and when oral therapy may not be possible or appropriate. Further, the product can be used, in the proposed dose, regardless of renal function at the time. Overall the benefit: risk assessment would favour use in the immediate post renal transplant period.

Discussion and benefit/risk assessment (Powder for Concentrate Solution for Infusion)

The quality of CellCept 500 mg powder for concentrate for solution for infusion, as demonstrated in the chemical, pharmaceutical documentation, was considered acceptable.

The studies in healthy volunteers to assess bioavailability followed standard practice and were randomised with an appropriate washout.

The studies in patients following renal transplantation of necessity used one sequence intravenous to oral and had to be conducted within a limited time period and with continual administration. The design in the renal transplant patient studies (061, MYC 2734 and IID 2176) presented more as an

assessment of formulation switch rather than a formal investigation of bioavailability. However, the design was in line with the proposed clinical use.

Preliminary studies lead to an anticipation of a closer match of mean MPA AUC following intravenous and oral MMF than was found in study MYC 2734 which demonstrated higher AUC following intravenous than oral administration. Given that safety was not compromised following intravenous use and that the PK/PD relationship shows that MPA AUC is related to the probability of rejection, the values found following intravenous administration should provide comparable immunosuppressive activity to that following oral administration.

MPA AUC following intravenous and oral administration of MMF was lower in renal transplant patients in the immediate post transplant period compared to healthy volunteers. This is consistent with previous experience but the reasons remain unclear.

The safety of MMF powder for concentrate for solution for infusion did not show clinically meaningful differences when compared to oral administration apart from a low incidence of thrombosis and phlebitis associated with the infusion site.

The data provide support for the suitability of intravenous use as an alternative when oral administration is not feasible in the period immediately following renal transplantation for a maximum duration of 14 days.

In conclusion, the active substance is well-defined, and the products are formulated, manufactured and controlled in a way that is characteristic of this pharmaceutical form. The specifications guarantee a consistent product with uniform bioavailability from batch to batch and the safety of the impurities has been demonstrated with reference to toxicology studies. Therefore, there were no outstanding major quality issues which may have a negative impact on the benefit/risk balance.

CPMP Recommendation

The CPMP considered this Line Extension to be acceptable and agreed on the proposed wordings to be introduced into the Summary of Product Characteristics based on the observations and the appropriate conclusions.

Line extension: Powder for Oral Suspension

Bioavailability and Bioequivalence (Powder for Oral Suspension)

Following oral administration MMF is rapidly absorbed and then de-esterified to form the active MPA. This is further metabolised to the pharmacologically inactive glucuronide (MPAG). Bioavailability studies have determined both the MPA and MPAG plasma levels.

Pilot study MYCS 2644

This study investigated the comparative bioavailability of a single 1000mg dose of MMF from a 'fast-dissolving' and a 'slow-dissolving' suspension formulation (containing 0.08% and 0.24% xanthan gum respectively) and from 4 x 250mg capsules. The suspension and capsule formulations were bioequivalent in all respects other than Tmax which was shorter for the suspension formulations. The slow-dissolving suspension containing 0.24% xanthan gum gave pharmacokinetic parameters slightly closer to those from the capsule. However a level of 0.16% xanthan gum was chosen for further development of the product. Since the slow-dissolving suspension produced an in vivo Tmax of 0.525 hours (± 0.175) and the fast-dissolving suspension 0.536 hours (± 0.266) no particular conclusions can be drawn regarding the discriminatory power of the in vitro test method.

Bioequivalence Study MYCS 2684

This was the definitive comparative study between the intended commercial formulation of suspension and the existing capsule product. Single 1000 mg doses of MMF were administered in a randomised cross-over design study, using 5ml of suspension of four 250mg capsules. The two formulations were bioequivalent (within 90% confidence intervals for the ratios) with respect to AUC, AUC_{last} and C_{max} for both MPA and MPAG. The plasma MPA Tmax for suspension and capsule were 0.666 hours (± 0.426) and 0.825 (± 0.351) respectively but this is not a statistically significant difference. However, the plasma MPAG Tmax did show a significantly faster appearance of the glucuronide when the

suspension formulation was given. The conclusions are that the oral suspension is bioequivalent to the capsule.

Benefit/risk assessment (Powder for Oral Suspension)

The active substance is well-defined, and the products are formulated, manufactured and controlled in a way that is characteristic of this pharmaceutical form. The specifications guarantee a consistent product with uniform bioavailability from batch to batch and the safety of the impurities has been demonstrated with reference to toxicology studies. Therefore, there were no outstanding major quality issues which may have a negative impact on the benefit/risk balance.

CPMP Recommendation

The CPMP considered this Line Extension to be acceptable and agreed on the proposed wordings to be introduced into the Summary of Product Characteristics based on the observations and the appropriate conclusions.

Interaction with Oral Contraceptives

The MAH has submitted data from an open sequential design study (BP15543) of one menstrual cycle on oral contraceptives (OC), 3 cycles on OC plus MMF 1g bid and a final cycle on OC alone.

The primary objective was to determine if MMF influenced the ovulation suppressing action of OCs as measured by plasma levels of luteinising hormone (LH), follicle stimulating hormone (FSH), and progesterone. The relevant secondary objective was to assess the effects of MMF on the pharmacokinetics of OCs.

Subjects were women with severe plaque psoriasis (not a current indication) taking any commercially available OC (bi-phasic and tri-phasic formulations were permitted after a protocol revision). Nine (9) different OC formulations were used.

Clinical Efficacy

Pharmacodynamic results. One of the 19 patients was excluded from all results because of lack of compliance and two more were excluded from part of the pharmacokinetic evaluation. Seventeen (17) of 18 women showed no relevant rise in progesterone. In one patient (no 105), levels rose (from 2.09 nmol/l to 4.08 nmol/l) indicating ovulation in cycle 4 but she took her OC (Varnoline) late for both cycles 2 and 4 and also was noted to take the OC at varying times of the day. Serum LH and FSH levels remained suppressed and within the normal range for women on OCs, although there was a slight trend LH levels to rise from cycle 1 to cycle 5.

Pharmacokinetic results. The ethinyloestradiol AUC and C_{max} values with and without MMF were considered to be bioequivalent, however, for the two gestagens (3-keto-desogestel and levonorgestrel), the sample size was too small to draw conclusions at the 90%CI level.

Clinical Safety

In the 5 months of the study, 94% (17/18) patients reported 67 adverse events, but there were no serious adverse events and no study withdrawals due to adverse events. Sixteen (16) severe adverse events were considered to be probably or possibly related to study treatment (OC and/or MMF), with 14 reported when both OC and MMF were being taken concurrently. Of these, there were 4 reports of upper abdominal pain (in 3 subjects), 3 reports of headache (3 subjects) with none of the other 7 events occurring more than once.

Discussion on clinical aspects

The one study was performed in a small number of women with a relatively large number of different OCs, however, the balance of evidence is that MMF is unlikely to affect the efficacy of oral contraceptives and no gross interaction between OCs and MMF was detected

Because of the adverse effects of MMF on fetal development appropriate information has been included in the *Pregnancy and Lactation* section of the SPC on the lack of an interaction between CellCept and OCs.

CPMP Recommendation

The CPMP considered this Type II variation to be acceptable and agreed on the proposed wordings to be introduced into the Summary of Product Characteristics based on the observations and the appropriate conclusions.

Interaction with Cyclosporin

Variation to update Section 5.2 of the SmPC to include details of pharmacokinetic interaction with cyclosporin.

The MAH has submitted a Clinical Expert Report presenting an overview of 8 studies evaluating the pharmacokinetic profile of MMF both with and without cyclosporin

Pharmacokinetic properties

In vitro studies (n=2)

Two *in vitro* studies indicate that cyclosporin may inhibit the biliary excretion of the phenolic glucuronide of MPA (MPAG). MPA (the 2-(4-morpholino) ethyl ester of mycophenolic acid) is the active metabolite of inactive MMF. This inhibition would reduce the extent of entero-hepatic recycling of MPA and result in a reduction in plasma levels of MPA.

Studies comparing the pharmacokinetic profile of MMF with and without cyclosporin (n=2)

Two **renal** studies, both carried out by the same investigator (Smak Gregoor), have been submitted. The first was a parallel group study in 18 patients receiving MMF plus cyclosporin A plus prednisone and 11 on MMF plus prednisone. Patients had been on MMF 2g/day for at least 3 months. The trough MPA levels (micrograms/ml) were significantly lower ($p < 0.0001$) in the group on cyclosporin – 1.98 ± 0.12 vs 4.38 ± 0.40 in the non-cyclosporin group. The second study was in 52 patients who had received MMF (2g/day) plus cyclosporin plus prednisone for 6 months after renal transplant. Pharmacokinetic parameters were measured after 3 months. MPA levels during treatment with MMF plus cyclosporin plus prednisone were significantly lower ($p = 0.002$) than with MMF plus prednisone (1.87 micrograms/ml, 0.56-5.27 vs 3.16, 0.32-7.78). In contrast, between 6 and 9 months, the MPA-trough levels for patients continuing on triple therapy and those discontinuing prednisone did not change

Studies comparing the pharmacokinetic profile of MMF with cyclosporin or tacrolimus (n=4)

These 4 studies demonstrated that the pharmacokinetics of MMF were similar when administered with tacrolimus and when administered alone whereas plasma MPA levels in patients receiving cyclosporin were lower than in patients on MMF plus tacrolimus or MMF alone.

DISCUSSION

The data clearly show that cyclosporin reduces MPA levels. However, the pivotal clinical efficacy studies were carried out using a combination of CellCept plus cyclosporin and corticosteroids, with individual study centres often using doses of cyclosporin and prednisone they considered appropriate and adjusting doses to maintain the required blood levels and according to clinical need. The SmPC clearly states that CellCept plus cyclosporin and corticosteroids should be used in the currently authorised indications. Consequently, the interaction between CellCept and cyclosporin has no efficacy implications and the current dosing instructions are satisfactory.

Interaction with prodrug of aciclovir and ganciclovir

The MAH has submitted an Expert Report. Additional data from studies in paediatric and adult patients receiving organ transplants and data from a review of reports of overdose in patients being treated with MMF was also submitted. The interaction between CellCept and aciclovir and ganciclovir is mentioned in the currently approved SmPC. The current evidence suggest that the prodrugs of acyclovir and ganciclovir (valaciclovir and valganciclovir respectively), are subject to the same interactions and should therefore be subject to the same precautions regarding concomitant use with MMF and the active metabolite (MPA). Higher MPAG and acyclovir plasma concentrations have been observed when MMF was administered with either aciclovir or ganciclovir, than when the drugs have been administered alone. The plasma concentrations of MPAG, aciclovir and ganciclovir are increased in the presence of renal impairment. Therefore, the potential exists for MMF and aciclovir/ganciclovir to compete for tubular secretion, further increasing the concentrations of both drugs. The MAH has proposed to address these potential interactions by adding information about both prodrugs (valaciclovir and valganciclovir) to the SmPC.

Aciclovir: The changes in MPAG pharmacokinetics (MPAG increased by 8%) were minimal in the presence of renal impairment, as are aciclovir concentrations, the potential exists for mycophenolate mofetil and aciclovir, or its prodrugs, e.g. valaciclovir, to compete for tubular secretion and further increases in concentration of both drugs may occur.

Ganciclovir: No substantial alteration of MPA pharmacokinetics are anticipated and CellCept dose adjustment is not required. In patients with renal impairment in which CellCept and ganciclovir or its prodrugs, e.g. valganciclovir, are co-administered the dose recommendations for ganciclovir should be observed and patients monitored carefully.

Hepatic transplant programme

Clinical Pharmacology (Hepatic transplant)

Following oral administration, MMF is rapidly and completely absorbed. Both oral and IV MMF are completely metabolised to the active component MPA. MPA, which is subject to entero-hepatic circulation, is principally metabolised by glucuronyl transferase to the inactive phenol glucuronide, MPAG.

Study ICM 1812 and its extension, ICM 1813

This was an open-label 56-day study in 158 post-graft patients including 35 liver transplant recipients. Patients received oral MMF in doses ranging from 1.5 to 3.5g daily for treatment of refractory rejections. The mean treatment start date in these patients was 147 days post-transplant.

There was great variability in most pharmacokinetic parameters, however the MPA and MPAG C_{max} and AUC_{0-12} increased with dose (1g bd *versus* 1.5g bd) but there were insufficient patients to determine these parameters for higher doses. After the first dose of 1g of MMF, the MPA and MPAG C_{max} and AUC_{0-12} for hepatic patients were slightly lower than in the renal transplant patients with refractory rejection.

Study IID 2104

This was an open-label 3-month dose-escalation pharmacokinetic study in liver transplant patients receiving MMF plus ATG (antithymocyte globulin), cyclosporin and prednisone. Patients were randomised to receive 1.75, 2.0, 2.25 or 2.5g of oral MMF bid after an initial 4 days at 1.75g bid. Six patients received a single dose of 1.75g of MMF by infusion. In addition to plasma pharmacokinetic measures on days 11 and 15 the biliary excretion of MPA and MPAG was measured. It should be noted that the sub-groups were small ranging between 2 and 6 patients.

There was a considerable inter-patient variability in pharmacokinetic parameters but following 1.75g of MMF the mean MPA AUC₀₋₁₂s were comparable for oral dosing (for one day) and IV dosing (following a single infusion). Following oral doses, no direct relationship between MMF dose (at any particular time) and MPA AUC was noted, however, there was a tendency for MPA AUC to increase over the 3 months of the study. Approximately 20% of MPAG (inactive metabolite) and less than 1% of MPA (active metabolite) were excreted in the bile.

Study MYCS 2378

This open clinical study was designed to evaluate the pharmacokinetics of MPA and MPAG for 3 infusion schedules of IV MMF followed by oral dosing in 45 hepatic transplant recipients. Patients were randomised to receive one of three 24-hour infusion regimens: 2 g MMF bid as two 80 minute infusions, 1g MMF bid as two 3 hour infusions and 1g MMF qid as four 6 hour infusions.

Each IV regimen lasted for approximately 7 days and was followed by a switch to oral MMF, 2g bid, for up to 3 years post transplant. Pharmacokinetic parameters were evaluated in blood and urine in all patients on each day between 1 and 7 (whilst patients were on IV MMF), on days 8 and 14, month 3 and sometime between months 6 and 12.

MMF became unmeasurable in plasma within 10 minutes of the infusion being stopped and the estimated T1/2 was less than 2 minutes. Following oral dosing, levels of the parent compound were very low or unmeasurable.

After IV infusion, the plasma MPA C_{max} showed an inverse relationship to the duration of the infusion. MPA C_{max} after the 80 minute and 3 hour infusions were higher than for oral dosing but the opposite was true after the 6 hour infusion. MPA AUC was not dependent on the rate of infusion, but declined by approximately one-third (22–35%) during transition from IV to oral dosing. Urinary excretion of MPA ranged between 0.424 and 2.87% and values were similar for the 3 different regimens.

The MPAG C_{max} values after IV infusion were similar for the 80 minute and 3 hour infusion, but somewhat lower after 6 hours. MPAG AUC₀₋₁₂ appears to decrease over the 7 days of IV dosing and was similar among patients during the transition from IV to oral dosing. These data show that both AUC₀₋₁₂ and the C_{max} for MPA tend to rise as oral MMF therapy continues, with the AUC₀₋₁₂ and C_{max} increasing 2.9 and 2.7-fold from day 14 to ≥9 months (Table 5).

Table 5: Summary of plasma MPA pharmacokinetic parameters for patients receiving oral MMF dose adjusted to 2g bd (MYCS2378)

Pharmacokinetic Parameter	Timepoint	N	Mean±SD
AUC ₀₋₁₂ (µg•h/ml)	Day 14	37	28.7 ±11.5
	Month 3	31	62.3 ±24.6
	≥9 Months	10	82.5 ±33.6
C _{max} (µg/ml)	Day 14	38	9.64 ±6.31
	Month 3	31	22.6 ±12.4
	≥9 Months	11	25.6 ±8.48

Study MYCS2646

This is the pivotal clinical efficacy study supporting this application. For details of study design see the *Clinical efficacy* section of this report. From a total of 277 patients treated with MMF, 22 patients participated in 12-hour pharmacokinetic assessments with 22 pharmacokinetic profiles collected on the last morning of IV MMF (day 5–14 post-transplant), 21 after the first oral dose and 14 at 6 months posttransplantation. All 22 patients received 1g IV dose, 20 patients were given 1.5 g of MMF and 1 patient 1.0 g as their first oral dose and at 6 months, 6 patients were on 1.5 g bd of MMF and 8 patients were receiving doses ranging between 0.25 and 1.0 g bd.

In this study, comparison between the last day of IV MMF dosing and the first day of oral MMF dosing showed that the mean MPA AUC₀₋₁₂ for the 1 g bd IV dose was similar to that for the 1.5 g bd oral dose. After 6 months of oral dosing, there was approximately a 1.6-fold (non dose adjusted data)

and a 2-fold (dose adjusted data) increase in MPA AUC_{0-12} compared to the first day of oral dosing. A similar trend was observed for MPAG (Table 6).

Table 6. Pharmacokinetic parameters by treatment regimen for patients receiving oral doses adjusted to 1.5 g (MYCS2646)

Treatment Regimen	Parameter	N	Mean (SD)		
			C_{max} ($\mu\text{g/ml}$)	T_{max} (h)	AUC_{0-12} ($\mu\text{g}\cdot\text{h/ml}$)
IV infusion 1.0 g bd, last day of IV dosing	MPA	22	17.0 \pm 12.7	1.50 \pm 0.517	34.0 \pm 17.4
	MPAG	22	70.7 \pm 36.0	2.38 \pm 0.584	616 \pm 407
Oral 1.5 g bd, ^a first day of oral dosing	MPA	21	13.2 \pm 6.64	1.13 \pm 0.430	31.0 \pm 14.3
	MPAG	21	90.9 \pm 45.1	2.36 \pm 0.991	809 \pm 485
Oral 1.5 g bd, ^a month 6	MPA	14	29.3 \pm 17.2	1.07 \pm 0.60	60.6 \pm 18.4
	MPAG	14	109 \pm 37.2	2.74 \pm 1.37	940 \pm 379

^a Dose adjusted

Conclusions on the pharmacokinetic studies

The data from several studies provides re-assurance that in the short term the pharmacokinetic profiles of MPA and MPAG following both oral and IV MMF are appropriate for patients following liver transplant and that transfer from IV to oral therapy in the post-operative period is unlikely to result in any significant change in immunosuppressive activity. Data from studies ICM 1812 and 1813 indicate that even during refractory rejection episodes where liver function may be impaired, there is no greater risk of higher concentration of MPA and MPAG than in similar patients following renal transplant.

In the early post-operative oral period MPA AUC_{0-12} , following 1.5 g bd of oral MMF is somewhat lower in liver recipients than in post-renal and post-cardiac transplant patients. However, for all the indications the AUC_{0-12} and the C_{max} for MPA tend to rise as therapy continues but this increase is greatest following liver transplant. The clinical expert report states that further rises beyond 6 months are unlikely to occur, but this statement is based on the result from only 10 patients.

Some patients experience a degree of liver failure or dysfunction and it may not be appropriate for them to receive the proposed MMF dose. The proposed daily dose of MMF in the immediate post-operative period is 1 g bd for IV and 1.5 g bd for oral administration. These doses were based on comparison with pharmacokinetic values (particularly AUC_{0-12}) in other transplant types. In the immediate post-operative period (up to 11days), the mean AUC_{0-12} for hepatic patients was 29.2 $\mu\text{g}\cdot\text{hr/ml}$ and 27.2 $\mu\text{g}\cdot\text{hr/ml}$ for renal patients.

During the first 15 days after a liver transplant, some patients had external drainage of bile (though a T-tube) which would reduce the entero-hepatic circulation of MPAG and thus reduce the AUCs of MPA. As between 16% and 24% of the administered MMF is excreted as MPAG via the T-tube, this proportion would not be available for re-circulation, resulting in reduced bioavailability of the active compound.

However, in the pivotal study, patients who had external biliary drainage and/or post-operative hepatic impairment received the same MMF dose schedule as other patients and there are no data to indicate that their clinical outcome was any different from the whole patient population, although this was not a pre-determined sub-group analysis.

PK/PD relationship

There are no studies specifically designed to evaluate the PK/PD relationship of MMF following hepatic transplant. The MAH has provided some extrapolations from data on 99 patients in the pivotal study MYCS 2646. It is concluded that there is no evidence of a PK/PD relationship between the AUC

of MPA and biopsy proven rejection (BPR) after liver transplant. In addition, it is stated that there is no evidence of a relationship between MPA AUC and the occurrence of adverse reactions commonly associated with MMF (diarrhoea, nausea, vomiting and leucopenia). However, in the hepatic transplant patients only one MPA AUC was obtained for each patient and the patient numbers were small.

These data contrast with the experience in renal transplant patients where there is a strong inverse correlation between the plasma AUC of MPA and the probability of acute rejection. However, in cardiac transplant patients no such relationship was established, probably because of the inadequacy of the biopsy findings as a marker of cardiac rejection.

It would be of value to have a firmly established PK/PD relationship as it would assist the clinician in managing possible rejection episodes, however, the clinical data show that patients can be managed satisfactorily in the absence of an established PK/PD relationship.

Dosing considerations in the late post-operative period

At 6 months following hepatic transplant, the 3g/day dose of MMF gives MPA AUCs that are 1.6 to 2-fold higher than those from patients given 2g/day post-renal transplant. Comparative data show a mean MPA AUC₀₋₁₂ of 53.5µg •hr/ml for renal patients at 9 months and 52.5µg •hr/ml at months 6 to beyond 9 months for post-hepatic graft patients. The pivotal study allowed dose adjustment based on clinical judgment and during the first 6 months post-transplant, the median dose was 2.5g/day and was 2.4g/day during the first 12 months post-transplant. These MMF doses gave satisfactory efficacy when compared to AZA. Because of the serious consequences of rejection, it is important that under-dosing does not occur, but prevention of under-dosing should not be at the expense of a greater than necessary frequency of adverse events. The MAH have provided data on the frequencies of leucopenia, nausea and vomiting over time (up to 6 months) and although no formal analyses can be made, there was no evidence suggesting that the MMF dose was higher in patients developing these types of adverse events. In conclusion, there are no safety or efficacy data indicating that the dose of MMF proposed in the late post-operative period needs to be revised because of the rise in the mean MPA AUC₀₋₁₂ in the first 6 to 9 months after a hepatic transplant. In addition, the SPC states that treatment with CellCept should be carried out by appropriately qualified transplant specialists who, in the clinical situation, would determine the most appropriate doses of CellCept in conjunction with other immunosuppressant agents depending on the patient's clinical condition.

Potential interaction with Tacrolimus

Tacrolimus is currently authorised for primary immunosuppression in hepatic transplant recipients and for allograft rejection resistant to conventional immunosuppressant regimens. As the concurrent use of the two products is not contra-indicated, they will sometimes be used together, and it is therefore important that the prescriber is informed of any pharmacokinetic interactions that may have clinical relevance.

One specific study (MYCS 063) has been submitted to support the proposal to add information on concurrent use of MMF and tacrolimus in post-hepatic transplant patients. The open multiple dose cross-over study was designed to assess the effect of oral MMF (1.5g bid for 7 days) on pharmacokinetics of oral tacrolimus (at a normal dose of 2mg bid) in 12 patients considered stable (6 months or more) after a hepatic transplant.

Tacrolimus and its major metabolite (13 de-methylated tacrolimus - M1) exhibited substantial variability in their pharmacokinetic parameters. However, the C_{max} for tacrolimus was similar when used alone and in combination with MMF, and its AUC₀₋₂₄ increased by approximately 15% when co-administered with MMF compared to tacrolimus alone. Its T_{max} decreased about 50% however, this difference was shown to be due to an artefact related to the computation methodology. When recalculated, in view of the number of patients that had different morning and afternoon doses of tacrolimus, T_{max} values were similar when comparing co-administration with MMF versus tacrolimus alone. For M1, the C_{max}, T_{max} and AUC₀₋₂₄ all decreased when tacrolimus was given with MMF. Very little data are available on the metabolites of MMF in post-hepatic patients treated concurrently with tacrolimus.

In study MYCS 063, MMF was not given alone so pooled data from study MYCS 2378 and 2646 have been submitted for 9 patients at the ≥6 month post-transplant time point. This cross-over study

showed that the MPA C_{max} was the same with or without tacrolimus, whilst MPA AUC_{0-12} was approximately 13% higher with tacrolimus. MPAG C_{max} , T_{max} & AUC_{0-12} were all lower with tacrolimus.

Although the dose of tacrolimus used in study MYCS 063 was lower than that recommended (4 versus 7-14 mg/day), it reflects the dose that would be used in clinical practice in stable patients in conjunction with another immunosuppressant such as MMF. In addition, in the clinical situation, tacrolimus concentrations would be monitored to ensure adequate dosing.

Two patients had markedly low tacrolimus AUC and C_{max} whereas one patient had relatively high C_{max} . However, There appears to be no satisfactory explanation for these findings as each of the patients had a normal physical examination and their laboratory and biochemical profiles and concomitant medication were the same throughout the study. The tacrolimus product information recommends monitoring of tacrolimus blood levels and these values would be taken into account with the patient's condition when making dose changes. Therefore, in the clinical situation, patients are not likely to be at undue risk.

In study MYCS 063, there was a trend towards an MMF-induced increase in the AUC of tacrolimus (15%), however it was considered that this is not a real effect of MMF on the pharmacokinetic parameters of tacrolimus because 15% is within usual pharmacokinetic fluctuations, the study (MYCS 063) has many potential biases and because the 15% difference is negligible compared with the potential increase in immunosuppressant effect when MMF and tacrolimus are used concurrently; long-term safety and efficacy studies are required

Study MYCS 063 is not an ideal study and there are methodological flaws. However, it was a pilot study and any deficiencies need to be considered in the light of the proposed addition to the SPC that states that the pharmacokinetic data on concurrent use of tacrolimus and CellCept are very limited. Additionally, the inclusion of the study findings (possible increase in tacrolimus AUC) in the *Interaction with other medicinal products and other forms of interaction* section of the SPC will re-enforce the importance of measuring tacrolimus levels if the clinician considers that the combination of MMF and tacrolimus is required.

In conclusion, there are very limited pharmacokinetic data available and in spite of all the limitations of the study there is an indication that the AUC of tacrolimus may be increased if used in conjunction with MMF after a liver transplant. This information has been included in the SPC to make physicians aware of the importance of monitoring tacrolimus concentrations.

Potential interactions with other medication

Following liver transplant, the potential for drug-drug interactions may increase. Twelve (12) products were taken by patients in the post-liver transplant study (MYCS 2646) that were not used concurrently with MMF in the study in cardiac transplant patients. However, no new class of drug was taken in study MYCS 2646 and the adverse events profile between the 2 groups was largely similar.

There was no evidence from study MYCS 2646 that there are drugs given to a patient following a liver transplant that are likely to cause a drug-drug interaction with MMF that is not already known and clinically relevant interactions with drugs commonly used in conjunction with CellCept are unlikely to occur, particularly in the immediate post-operative period.

Clinical efficacy (Hepatic transplant)

The MAH has supplied one pivotal study (MYCS 2646) and 9 uncontrolled supportive studies that include patients having hepatic transplants. However, 2 of these supportive studies are not complete and therefore have not been analysed. Of the remainder, 3 are pharmacokinetic studies and the remainder provide a limited or negligible contribution to the efficacy analysis.

Main hepatic transplant study (Study MYCS2646)

This was a randomised double-blind multi-centre study in patients receiving their first liver transplant and compared the efficacy of IV MMF followed by oral MMF plus cyclosporin and corticosteroids versus IV AZA followed by oral AZA plus cyclosporin and corticosteroids

Study MYCS 2646 is completed and report has been submitted by MAH. This report submitted presents analyses of the two co-primary end-points and the secondary end-points for the blinded phase of the study (first year of a 3-year study).

Patients with hepatitis B and liver cancer were not eligible for the study because the management of these patients changes rapidly and treatment may affect transplant outcomes.

The primary objectives of the study were:

- Rejection at 6 months: To determine whether MMF is superior to AZA in reducing the proportion of patients with one or more episode of biopsy proven and treated rejection or graft loss in the first 6 months post-transplant; and
- Graft loss at 12 months: To determine whether MMF is non-inferior to AZA in reducing the proportion of patients with graft loss in the first 12 months post-transplant.

Although, at the time of the application, there did not appear to be a single regimen for use in liver transplant recipients, AZA is a well-recognised treatment used in combination with corticosteroids and/or other immunosuppressants to enhance the survival of organ transplants. Therefore it was reasonable to have superiority defined for one primary efficacy variable and non-inferiority for another.

Liver biopsies taken to determine acute rejection were reviewed by both a local pathologist (who was aware of the patient's clinical condition) and a central reviewer (who was not). The interpretation of the local pathologist was used in the decision to treat the patient and the study was powered based on the assumed rejection rates as assessed by local pathologists. The data from the central review were prospectively established as supporting data with their main purpose to ensure that there was reasonable agreement in assessing rejection by biopsy. Graft loss was defined as death or re-transplant.

The primary rejection endpoint was modified once during the study when all patients had reached at least 6 months post-transplant (i.e. in the blinded phase of the study). The originally defined rejection endpoint included biochemical abnormalities (abnormal liver function tests) suggestive of rejection and this was removed. The reason was that it was considered that rejection was a clinical rather than a biochemical decision.

There were 10 secondary objectives relating to the first 12 months of the study (blinded phase). The majority (7) of these relate to rejection and death/re-transplant and can be considered to be subsets of the two co-primary objectives. Two of these variables relate to time from transplant to biopsy-proven and treated rejection, and time to graft loss. The final secondary objective was the maintenance dose of corticosteroids required.

In addition PK parameters were measured and the evaluation of safety included collecting data on adverse events, medically serious adverse events, opportunistic infections and malignancies.

Results

The planned enrollment was 550 patients and a total of 565 patients (287 and 278 patients randomised to AZA and MMF respectively) were entered into the study. The transplant groups were balanced for demographics and other characteristics determined at study entry. The results presented both the co-primary efficacy variables and the majority of the secondary variables related to the blinded (first year) phase of the study.

There was a very high withdrawal rate from the study (54% from the MMF arm; 53.7% from the AZA arm) with the greatest withdrawal in the first month (approximately 20% of all patients). Although the withdrawal rate was similar between the groups, in the pivotal study of MMF and AZA in post-cardiac transplant patients withdrawals were approximately half that occurring in study MYCS 2646. The mean cyclosporin concentrations were higher in patients who were prematurely withdrawn in both treatment groups and at all time points (day 7 to 12 months), compared with patients who were not withdrawn. However, the variability of the results limits the value of these findings and the data do not indicate a direct relationship between the trough cyclosporin concentrations and withdrawal from the study. Thus, there appears to be no definitive reason for the difference in withdrawal rates. It is important to note, however, that withdrawal rates were similar across treatment arms and this is considered to be the most relevant comparison.

Patients were randomised to the MMF group and received 1g IV of MMF in a 2 hour transfusion bid starting within 24 hours of transplant continuing for a minimum of 4 days to a maximum of 14 days. Once oral medication could be tolerated, patients switched to oral MMF 1.5g bid. The AZA group received AZA once a day at a dose, between 1 and 2mg/kg/day, selected by the investigators with the first dose within 24 hours of transplant. Patients were initiated on either oral or IV AZA; IV AZA was continued until oral medication was tolerated but unlike MMF there was no minimum duration. The doses of cyclosporin and corticosteroids were determined by the usual practice of the respective centre. Of the 565 patients entered, 564 patients received study drug. The dose of oral MMF and AZA could be reduced if adverse events occurred.

Approximately 1/3rd of the patients in the AZA group received less than 4 days IV treatment. There are no data on the equivalence between IV and oral MMF during the first 4 post-transplant days for MMF whereas there is a reasonable degree of equivalence between the proposed IV dose (1g bd) and the oral dose (1.5g bd) after 4-10 days of IV MMF. Therefore a statement was included in the SPC recommending that after liver transplantation patients will remain on IV CellCept for 4 days with oral therapy initiated as soon as the patient can tolerate oral medication (see SPC for the IV formulation, section 4.2, *Posology and method of administration*).

Rejection at 6 months

In the first 6 months post-transplant the proportion of first biopsy proven and treated rejection or graft loss (either in study or after termination) was 38.1% for the MMF group and 47.7% for the AZA group (Cochran-Mantel-Haenszel adjusted for centre $P=0.0196$; RR MMF/AZA=0.80). These results with the other secondary rejection endpoints are shown in Table 7. All the rejection end-points included patients experiencing graft loss; graft loss without rejection occurred in 8.6% (23) patients on MMF and 9.4% (27) patients on AZA. Approximately 60% of graft loss occurred in the first 3 months post-transplant.

The findings of the study are somewhat confounded when considering acute rejection endpoints. When judged by the local pathologists, who were aware of the patients clinical condition, MMF was shown to be statistically significantly superior ($p=0.02$) to AZA although the size of the additional benefit was not great (by 6 months 48% of the patients on AZA and 38% on MMF had acute rejection episodes). This difference in the acute rejection end-point had narrowed by 12 months.

Acute rejection episodes when the biopsies were read centrally were no longer statistically significant ($p=0.2$) when compared with the on-site reading of biopsies despite a positive trend in favour of the MMF group. When comparing the findings of the two groups of pathologists, there was 86% concordance ($\kappa = 0.789$) and in 75 out of the total 78 cases showing disagreement, the discordance resulted from the local pathologist indicating rejection whilst the central reviewer did not. It is considered that the local review most closely reflects the post-marketing use of the product (*i.e.*, a pathologist aware of the patient's clinical condition when reviewing the biopsy). Therefore more emphasis is normally given to the local analysis, since this determines the patient's further medical management.

The 6 month data regarding the cumulative incidence of biopsy-proven and treated rejection, excluding graft loss, was 40.0% for AZA and 31.0% for MMF. The Kaplan-Meier estimates show separation of the curves occurring from before 1 month. These data show that when patients with graft loss are excluded the findings are in line with the primary rejection variables already considered acceptable in the pivotal study.

When event-free survival was compared between both treatment groups for this endpoint, the difference was no longer statistically significant at the 5% level (logrank $p=0.0593$). However, this p-value was considered to be sufficiently supportive of a treatment difference, and that the apparent inconsistency with the primary analysis had no important implications.

Graft loss at 12 months

Graft losses were primarily deaths and the overall rate of re-transplantation during the first 12 months was 4.4%. As far as graft loss and survival are concerned, events were observed in 39/278 *versus* 42/287 patients for MMF *versus* AZA, respectively and non-inferiority of MMF was demonstrated to a pre-defined degree (the lower acceptable limit for the difference was -10% for the difference in graft loss rates). The observed difference was +0.45% with a lower limit of - 5.1%, providing no evidence of inferiority of MMF in this respect with a suitable degree of precision. The time to graft loss was

also similar between the 2 groups. In the hepatic study the death rates were similar for both the MMF and AZA groups (10.4% and 12.9% respectively) whereas in the cardiac study the rates were 6.2% and 11.4% respectively. However, there are no major differences between the 2 groups in the pivotal study regardless of the differing death rates in the post-cardiac transplant study.

Additional efficacy analyses

In terms of additional immunosuppression required at 6 months and 12 months, there was a tendency for additional corticosteroids (36.7% *versus* 46.7% and 39.2% *versus* 49.1%, for MMF *versus* AZA at 6 and 12 months respectively) and for OKT₃ (3.6% *versus* 8.0% and 4.0% *versus* 8.0%, for MMF *versus* AZA at 6 and 12 months respectively) to be required more frequently in the AZA group than in the MMF group. ATG was infrequently used in either group.

Various subgroup analyses of the primary efficacy variables were carried out. Graft loss by age, racial sub-group, gender or presence of hepatitis C virus, showed no clinically relevant differences compared to the total study population. Rejection tended to decrease with age and was higher in women, however, this is a pattern seen with other transplant patients regardless of type of immunosuppression used.

The results based on the efficacy endpoints broken down by the proportion of deaths and of re-transplants, and the level of severity and the outcome of biopsy-confirmed treated rejections seen in each treatment group were provided. The incidence of first and second rejection episodes was provided: a total of 7.3% of AZA patients and 5.4% of MMF patients experienced a second rejection episode in the first 12 months post-transplant. These additional analyses did not alter the overall evidence of efficacy from study MYCS 2646.

The incidence of rejection was lower than expected, particularly in the AZA group, although the incidence of rejection in the pivotal study did not appear to differ from that in other liver transplant studies. From the data provided it appears that rejection episodes were not directly related to cyclosporin trough levels. The mean levels over time (day 7 to 6 months) showed no consistent pattern between the treatment groups and rejection status.

The addition of selected results from the pivotal study to the SPC is not essential for the safe and effective use of the product in the proposed indication and as with any data taken out of context may not be helpful to prescribers. The current section 5.1 is in line with the European guidelines.

Additional information from the MAH stated that some discrepancies had been noted at one centre. In summary, 3 patients who did not have chronic hepatitis B or positive hepatitis B antigens recorded on the case report form were marked as having positive hepatitis B status on the patient information sheet. In addition, 1 positive and 3 negative biopsy findings were not included in the study report. A document providing the background to the findings with a summary of the discrepancies identified and an erratum to study MYCS 2646 was subsequently provided.

The correction of the identified discrepancies resulted in a few minor changes that had no practical consequences. Primary end-points were not involved. Only one change to a secondary end-point was involved and this change had no impact on statistical significance and minimal impact on estimates. Therefore, the identified discrepancies did not affect the interpretation of the study. There were no additional concerns about the quality of the data of this centre or the study and overall, the MAH undertook appropriate remedial action.

Table 7. Rejection Endpoints during the first 6 months (MYCS2646)

	AZA (N = 287)	MMF (N = 278)	Relative Risk (MMF/AZA)	P-value
Primary endpoint*				
Biopsy-proven and treated rejection or graft loss	137 (47.7%)	106 (38.1%)	0.80	0.02
Secondary endpoints*				
Biopsy-proven rejection	147 (51.2%)	117 (42.1%)	0.82	0.03
Treated rejection	152 (53.0%)	123 (44.2%)	0.84	0.04
Biopsy-proven and treated rejection with biochemical abnormalities suggestive of rejection	136 (47.4%)	103 (37.1%)	0.78	0.01
Biopsy-proven rejection with biochemical abnormalities suggestive of rejection	142 (49.5%)	112 (40.3%)	0.81	0.02
Treated rejection with biochemical abnormalities suggestive of rejection	151 (52.6%)	120 (43.2%)	0.82	0.02
OKT ₃ - or ATG-treated rejection	57 (19.9%)	40 (14.4%)	0.73	0.09

*Includes Events Post Study Withdrawal

Clinical safety (Hepatic transplant)

Because of the discrepancy in study withdrawals (mainly due to adverse events), comparisons were made where relevant, with study MYCS 1864 which was similar to MYCS 2646 in oral dose and patient numbers but was carried out in cardiac transplant patients. IV MMF was not used in the cardiac transplant study and also in study MYCS 1864 some patients had been followed up for 2.5 years whereas most patients in the liver transplant study had only been followed up for 18 months.

Adverse events, serious adverse events and deaths

The following 5 events occurred with a >5% frequency in the MMF group (*versus* AZA) – abdominal pain, pain (not further specified), increased creatinine, oedema and constipation. There are no major differences between the pattern and type adverse events occurring with IV MMF and IV AZA. The high overall frequency (97.8% for MMF; 91.3% for AZA) is almost certainly due to the fact they were collected in the immediate post-operative period and consequently are adverse events rather than adverse drug reactions. No comparisons between the adverse event profile of IV and oral MMF and AZA were provided, however because of the differences in base-line (ie patients' condition, concurrent medication etc) this is unlikely to be of significant relevance.

There were concerns as the increases in AUC and C_{max} of MPA (the active moiety of MMF) during long-term use were greater and extended for longer after hepatic transplant than following cardiac and renal transplant with a consequent increased risk of toxicity.

Although these data are not conclusive, there is no direct evidence that the rising AUC₀₋₁₂ of the active metabolite (MPA) over the first 6-9 months post-transplant results in an increased frequency of adverse events such as leucopenia and infections. The data provided show that approximately a quarter of the first reports of leucopenia associated with MMF occur in the first month post transplant and approximately 90% are reported in the first 6 months with similar values shown for sepsis. In addition, the pattern of cumulative reports is similar for AZA. The data on malignancies is not clear cut but does not indicate a great increase in frequency with 1.5g bid compared with 1g bid.

The overall frequency of leucopenia was 45.8% in the MMF group and 39.0% in the AZA group. However, this did not appear to lead to increased adverse sequelae. In addition, the CellCept SPC recommends regular blood count monitoring and provides advice on action that should be taken if leucopenia develops.

The frequency of severe neutropenia was higher with MMF than with AZA (3.6% vs 0.7%) as was the frequency of herpes virus infection (10.1% vs 5.9%). Although there are differences in the frequencies of specific post-transplant infections between the MMF and AZA groups, there is no direct evidence that MMF increases the risk of major infections when compared with AZA or produces a significant risk for patients.

The death rate on MMF which was less than for AZA following cardiac transplant was equivalent to AZA in the pivotal study supporting this application. There were a total of 75 deaths (from 565 patients) at any time post-transplant in study MYCS 2646. Overall the death rate was similar between the two treatment groups (35, 12.6% MMF *versus* 40, 13.9% AZA) and the causes of death are shown in Table 8. The death rate 1 year post-transplant in the cardiac study (MYCS 1864) was 11.4% (33/289) for MMF and 6.2% (18/289) for the AZA group.

The most frequent cause of death was infection/sepsis with the next most frequent cause “other” which includes primary graft failure and multi-organ failure. During the 12 months post-transplant, there were 66 on study and post-termination deaths (29, 10.5% from MMF group *versus* 37, 12.9% from AZA group) with the primary cause of death again due to infection/sepsis. Also at 12 months, 24 patients died on study and 7 within 15 days of study termination; of these 31 patients 13 (4.7%) were in the MMF group 18 (6.3%) in the AZA group.

Table 8. Cause of death at anytime post-transplant (including deaths post-study withdrawal)

	AZA (1-2mg/kg/day) (N = 287)	MMF (1.5g bd) (N = 278)
No. of patients	287	
Total deaths	40 (13.9%)	35 (12.6%)
Cardiovascular event	3 (1.0%)	6 (2.2%)
Cancer	2 (0.7%)	1 (0.4%)
Infection/sepsis	21 (7.3%)	15 (5.4%)
Pulmonary embolism	2 (0.7%)	0
Cerebro-vascular event	2 (0.7%)	1 (0.4%)
Graft rejection	1 (0.3%)	0
Other	9 (3.1%)	12 (4.3%)

Adverse events leading to withdrawal

In study MYCS 2646, the main reasons for withdrawal were related to safety, and the proportion of withdrawals was high compared with an equivalent study in post-cardiac transplant patients. A similar number of patients were withdrawn from each group (94, 33.9% on MMF *versus* 95, 33.1% on AZA) due to adverse events, intercurrent illness or laboratory abnormalities during the first 12 months of treatment. Most of the adverse events occurred with similar frequency between the groups. Table 9 shows the adverse events in which there was a 2% or more difference between the groups.

Table 9. Adverse events leading to withdrawal $\geq 2\%$ difference across treatment arms (study MYCS2646)

Adverse event	AZA (N = 287)	MMF (N = 277)
Leucopenia	7.3%	10.1%
Nausea	1.4%	4.3%
Abdominal pain	0.3%	2.5%
Sepsis	3.8%	1.8%

In the cardiac transplant study (MYCS1864) events lead to premature discontinuation due to an adverse event, intercurrent illness or laboratory abnormality was 14.5% in the MMF group and 15.6% in the AZA group.

Malignancies

The MAH reported that the risk of developing a malignancy (a long-term effect of immunosuppression) is not unduly increased by doses of MMF of either 2g or 3g daily. From study MYC2646, 4.2% of patients on AZA and 3.2% of patients on MMF had developed malignancies by 1 year post-transplant. The absolute numbers are too small to determine any pattern of specific tumours and the duration of immunosuppression too short to provide a definitive reporting rate for malignancies. Similar malignancy rates were noted in MYCS 1864 (post-cardiac transplant study).

Medically serious events

During the first 12 months of the study of liver transplant patients, severe neutropenia was considerably more frequent (approximately 5-fold) in the MMF group whereas severe hepatitis and severe thrombocytopenia occurred more often in the AZA group (Table 10).

Table 10. Medically serious events (study MYCS 2646)

	AZA (N = 287)	MMF (N = 277)
Severe neutropenia	2 (0.7%)	10 (3.6%)
Severe thrombocytopenia	36 (12.5%)	19 (6.9%)
Severe hepatitis	58 (20.2%)	44 (15.9%)
GI perforation/GI bleed	15 (6.2%)	19 (6.8%)

Opportunistic infections

The frequency of opportunistic infections was similar between the groups (MMF, 43.2% *versus* AZA, 45.5%). The most common infections are shown in Table 11.

Table 11. Most common infections (study MYCS 2646)

	AZA (N = 287)	MMF (N = 277)
Candida (mucocutaneous)	17.4%	18.4%
CMV viraemia/syndrome	12.2%	14.1%
Herpes simplex	5.9%	10.1%
CMV tissue invasion	8.0%	5.8%

Discussion on clinical aspects and benefit/risk assessment (Hepatic transplant)

CellCept has proven evidence of efficacy in preventing acute transplant rejection after renal and cardiac transplants, so its immunosuppressive activity would be expected to extend to liver transplant recipients. The pivotal study MYCS 2646 showed CellCept to be superior ($p=0.02$) to AZA (which is known to enhance graft survival including hepatic transplants) when considering the primary end-point of acute rejection as defined by local pathologists. From a statistical viewpoint, the finding is robust as it did not depend critically on how the end-point was defined, it was based on a proper intention-to-treat analysis, the pattern of withdrawals was explored and nothing was found to cast doubt on the findings with the protocol amendment having been shown not to influence the outcome.

There is a negative aspect of the evidence relating to the end-point of acute rejection determined by central review of the biopsies, as a positive trend rather than superiority was shown. However, the local pathologist who was in possession of clinical as well as biopsy findings, will most closely reflect the post-marketing situation in which the product would be used. In addition, most of the differences resulted from the local pathologist indicating rejection and although patients should not be subjected to unnecessary immunosuppression, the benefits of treating rejection episodes early in order to prevent chronic rejection, graft loss or death may outweigh any additional immunosuppressant burden.

Concerning graft loss and survival, the non-inferiority of MMF *versus* AZA was demonstrated. The frequency and causes of deaths were similar in the both groups.

In addition to the statistical issues, clinically there were some concerns about the very high withdrawal rate (over 50%) in the first 12 months of the study. These withdrawals were mainly due to adverse events and were similar in number and type between the two study groups. This rate is approximately twice that in a similar study following heart transplantation. This discrepancy has not been satisfactorily explained, the only major difference between the two studies was the use of IV study medication in the immediate post-operative period for the liver transplant recipients and the data provided does not permit a direct analysis of adverse events occurring whilst on IV study medication. Nevertheless, more importance is given to the comparison across the two randomised treatment arms, rather than the comparison with a different study.

The pharmacokinetic findings provide re-assurance that the profiles of the metabolites of MMF are, in the short term, appropriate for patients following liver transplant. In addition, there does not appear to be any undue risk of reduced or increased immunosuppressive activity occurring when patients are transferred from IV to oral CellCept.

In study MYCS 2646, there were 12 products taken by patients post-transplant that were not used concurrently with MMF in the cardiac transplant study. Most of the drugs taken by the post-hepatic transplant patients were those taken in conjunction with MMF in other studies. No new class of drug was taken in study MYCS 2646 and the adverse events profile between the 2 groups was largely similar. There is no evidence from study MYCS 2646 that there are drugs given to a patient following a liver transplant that are likely to cause a drug-drug interaction with MMF that is not already known.

For drug-drug interactions only limited data have been provided. With the importance of an effectively functioning liver in metabolising drugs additional data providing re-assurance that drugs and classes of drugs commonly used in conjunction with CellCept would be useful in supporting this application. Considering tacrolimus which, although not specifically indicated for concurrent use with CellCept, may be used in high doses in rejection episodes, the relevant study used a dose of tacrolimus that was lower than that used clinically. The clinical relevance of the potential pharmacokinetic interaction needs to be clearly established.

The average dose of tacrolimus used in study MYC 063 was 4mg/day which is lower than the currently recommended dose of tacrolimus for adults (7-14mg daily). Although the dose of tacrolimus used in study MYCS 063 was less than that recommended in the tacrolimus product information, it is likely to reflect clinical practice in stable patients in conjunction with another immunosuppressant such as MMF.

Reassurance that relatively high increases in C_{max} and AUC seen with long-term MMF dosing will not produce increased frequency of adverse reactions (particularly neutropenia) following liver transplant was provided. There were relatively high increases in C_{max} and AUC with long-term MMF dosing. The volume of distribution (V_d) was not calculated as patients did not receive IV MMF long-term. Clearance values for MPA (active moiety of MMF) and MPAG (inactive metabolite) have been

provided for the final IV and the first oral doses of MMF (ie the change over to oral dosing in immediate post-transplant period), and for the oral dose at 6 months. For MPA, the mean clearance shows similar values after IV dosing with MMF and at 6 months of oral dosing, whilst clearance on the first day of oral MMF was higher than at the other 2 time-points. For MPAG, clearance values were similar at all 3 time-points.

In isolation, these data have limited relevance, however, there would be concerns if changes in clearance and volume of distribution over time had an adverse effect on safety or efficacy of MMF used after hepatic transplant. The issue of the altered pharmacokinetic parameters over time and the frequency of adverse events is addressed in detail in the *Clinical safety, Adverse events, serious adverse events and deaths* section of this report and as the MPA levels rise over time, it would not be expected that efficacy would be affected.

In the cardiac transplant study, the death rate was lower with MMF (*versus* AZA), whereas equivalent death rates were noted in the liver transplant study. Although the proportion of patients developing adverse events when CellCept is used in liver transplant recipients was relatively high, the safety profile was basically similar between the patients on MMF and on AZA in the pivotal study.

In summary, overall the rates of deaths, withdrawals, malignancies and medically serious events in liver transplant patients did not differ between patients receiving MMF and AZA, but, severe neutropenia was considerably more frequent (5-fold increase) in patients on MMF. This finding needs to be balanced against a 1.8-fold increase of severe thrombocytopenia and a 1.3-fold increase of severe hepatitis with AZA. In addition the increased frequency of neutropenia with MMF did not appear to be translated into increased rates of infection and the SPC provides a recommended regimen for monitoring blood counts.

Clinical pharmacology

The clinical pharmacokinetic data submitted with this application provides re-assurance that in the immediate post-operative period the pharmacokinetic profile of both the active metabolite (MPA) and the inactive metabolite (MPAG) following both oral and IV MMF are appropriate for patients post-liver transplant. Also, transfer from IV to oral therapy from 4 days post-operatively onwards is unlikely to result in any significant change in immunosuppressive efficacy. However, data are not available for the first 4 days post-transplant which is the time when potential liver dysfunction is likely to be greatest. Therefore, a recommendation in the SPC states that IV CellCept should continue for the first 4 days following hepatic transplant with oral therapy initiated as soon after this as it can be tolerated.

There are only very limited data on the concurrent use of tacrolimus with CellCept and this is adequately reflected in the SPC. An option would be not to have any information at all in the SPC relating to the use of tacrolimus and CellCept following hepatic transplant. However, as there is already information on tacrolimus and CellCept post-renal graft and the drugs are not contra-indicated, a clinician may consider that a patient who is in danger of losing his/her graft may require additional immunosuppression and needs to use the two drugs concurrently. A statement in the SPC warns the prescriber of the lack of data in post-hepatic graft and indicates that the tacrolimus AUC may be increased.

The proposed doses of 1g bd for IV CellCept and 1.5g bd for oral CellCept gives a satisfactory efficacy without undue risk of adverse events in both the immediate and late post-transplant period.

Clinical efficacy

On the data from the pivotal study, MMF was shown to be statistically significantly superior ($p=0.02$) to AZA when acute rejection end-points were assessed by local pathologists (but with only a positive trend when centralised readings were used). For graft loss and survival non-inferiority of MMF compared to AZA was demonstrated. The new information on data discrepancies from one centre does not affect the robustness of the study findings.

Although not specifically studied, patients with hepatitis B and liver cancer will require immunosuppression following liver transplantation, regardless of potentially poorer survival because of their underlying condition. It seems appropriate that the results of the pivotal study were not diluted by inclusion of these patients. However, in the clinical situation the use of MMF is managed by

transplant experts, therefore it is not unreasonable that it could be used, if appropriate, following a hepatic transplant in patients with hepatitis B and liver cancer.

Clinical Safety

The safety in the proposed doses and for the proposed indication is acceptable. The MAH provided the follow up to study MYCS 2646 in the form of the final study report to the CPMP by 1st quarter 2002. The CPMP concluded there are no major differences between treatment groups...

CPMP Recommendation

The CPMP considered this Type II variation to be acceptable and agreed on the proposed wordings to be introduced into the Summary of Product Characteristics and reflected into the Package Leaflet, based on the observations and the appropriate conclusions.

Paediatric renal transplant programme

At the time of the application, approximately 650 paediatric renal transplants were performed annually in the EU and approximately 550 in the USA. The regimens currently used in children are similar to those for adults, *i.e.*, AZA in addition to cyclosporin and corticosteroids, with lymphocyte antibody induction therapy (ATG, ALG or OKT3) often added immediately post-transplant.

Younger children often need higher doses of cyclosporin to maintain adequate blood levels. Following renal transplant, one-year graft survival rates in Europe are 61-81% in children (*versus* 75-83% in adults). Acute rejection has been reported to develop in 40-70% of children treated with cyclosporine-AZA containing regimens with most occurring in the first 3 months post-transplant. As with adults, acute rejection is the most important predictor of subsequent chronic rejection in children.

The causes of end-stage renal failure differ between adults and children, however the only aetiologies that are considered to impact on graft survival are focal glomerulosclerosis, which occurs more frequently in children than adults (8% vs 3%) and congenital nephrotic syndrome. Several factors not directly related to the pathogenesis of renal failure also affect graft loss. Graft survival is poorer in very young children (< 3 years) and as this often results from vascular thrombosis, it may be due to mechanical factors resulting from placing a relatively large organ in a small child. Children under 6 years of age have higher incidence of non-specific cellular immune responsiveness which is likely to be the reason they are reported to experience more episodes of acute rejection than adults and consequently are often treated with more intense immunosuppression.

Data from two single-arm paediatric post renal transplant studies were provided. The pivotal study (MYCS 2675) included 100 paediatric patients. An additional pharmacokinetic study (MYCS 2190) included 40 paediatric patients. The age groups used in these studies were 3 months to 6 years, 6 to 12 years and 12 to 18 years (the cut-off points were selected prior to the circulation of the European guidelines). The clinical development for paediatric use was based extensively on the benefit/risk profile already established in adults. Comparisons were made with two studies that compared MMF to AZA in adults, retrospective series of non-MMF patients as well as published data and a postmarketing study.

The safety database consists of the 140 paediatric patients in the 2 studies with comparisons made with adult patients on CellCept following renal transplant. Additionally, data on incidence of malignancies were available from a postmarketing study with 346 MMF-treated patients.

Because of the limited data in children under the age of 2 years, this age group was excluded by the MAH from the scope of this variation.

Clinical Pharmacology (Paediatric renal transplant)

Pharmacokinetic data from the two studies in paediatric patients (MYCS 2190 and MYCS 2675) have been submitted to support this application. Only a subset of paediatric patients in study MYCS 2675 had pharmacokinetic parameters measured.

Rationale for dose selection

The rationale for dose selection based on pharmacokinetic parameters relied on the assumption that the metabolism and mechanism of action of MMF in paediatric patients would be similar to adults (as is the course of graft rejection). In adults, a strong inverse correlation between the plasma MPA

AUC₀₋₁₂ and the probability of acute rejection has been observed. Data from study MYC 058 (in adult patients) were used to select the target MPA AUC₀₋₁₂ for paediatric patients following a renal graft. Adjusting the dose to 1 g bid (the currently authorised dose for adult renal transplant patients), the mean of the individual AUC₀₋₁₂ values in study MYC 058 on days 3, 7 and 11 post-transplant was 27.2 ± 11.6 micrograms•hour/ml. In 2 other studies in adults (MYC 1866 and ICM 1753) for the first 40 days post-transplant following 1 g of MMF bid, the mean AUC₀₋₁₂ of MPA was 27.3 ± 10.9 micrograms•hour/ml. Therefore, a mean AUC₀₋₁₂ level of approximately 27 micrograms•hour/ml was selected as suitable for paediatric patients post renal transplant. Because of substantial inter-subject variability, it was considered that there would be better dosing schedule if body surface area (BSA) were used rather than weight to calculate dose.

Paediatric renal transplant study MYCS 2190

MYCS 2190 was a non-randomised study designed to evaluate pharmacokinetics, safety and tolerability of MMF in patients aged between 3 months and 18 years. The primary objective was to assess the pharmacokinetics in the first year of treatment and safety for the 3 years of the study. Paediatric patients weighing at least 5.4 kg and who were having a single first or second renal transplant (cadaver or living donor) were entered. Patients were stratified into 3 age groups (3 months to less than 6 years; 6 years to less than 12 years; 12 years to 18 years).

Patients were accrued concurrently across age strata and a total of 40 patients received one or more doses of MMF. The dose levels were 15, 23 or 30 mg/kg of MMF (capsules) bid in combination with cyclosporin and corticosteroids. Sample collection was planned on days 1, 5, 7, 9, 11, 14 and 21 and at months 3, 6, 9 and 12. For patients who received 23 mg/kg, the mean MPA AUC₀₋₁₂ was 28.1 (± 11.9) micrograms•hour/ml. Two patients had IV MMF (each a single dose). The pharmacokinetic data at months 3-12, consisting of a single trough level of MPA and MPAG, expectedly showed an increase in AUC at 3 and 9 months compared with days 7 and 14.

The study was terminated early because it was considered that from the pharmacokinetic data collected it was possible to make a specific dose recommendation (23 mg/kg bid). This was then used in the extension of the study (MYCS 2190v2).

Because of the substantial inter-patient variability noted in study MYCS 2190, additional analyses were performed in order to extrapolate MPA AUC₀₋₁₂ when the MMF dose was calculated using BSA. Using linear regression of MPA AUC₀₋₁₂ versus dose from study MYCS 2190 and adult data, the dose of CellCept of 600 mg/m² gave a projected MPA AUC₀₋₁₂ of 28.2 micrograms•hour/ml (the nearest value to 27.2 micrograms•hour/ml, selected as suitable for paediatric patients post-renal transplant). By calculating the dose on BSA the coefficient of variation could be reduced by about 10%.

Paediatric renal transplant study MYCS 2675

In this single-arm study, 600 mg/m² bid up to 1 g bid were administered to paediatric patients following renal transplant.

From the total patient population of 100, 55 had pharmacokinetic profiles for MPA and MPAG measured at day 7 and months 3 and 9. Patients were stratified into one of the three defined age groups. The study showed that with a dose of MMF of 600 mg/m² (the currently proposed dose), AUCs in paediatric patients of 1-18 years of age in the immediate post-transplant period were scattered around the (adult) target AUC. The 7 day values for the 3 main age categories varied between 26.3 and 33.2 micrograms•hour/ml. The late post-transplant, AUC₀₋₁₂ values show the rise over time seen in all post-transplant patients (Table 12).

Table 12. Adjusted MPA AUC₀₋₁₂ (micrograms•hour/ml) by age group (MYCS 2675)

	No.	Day 7	Month 3	No.	Month 9
< 6 yr.	17	27.4 ± 9.54	49.7 ± 18.2	12	60.9 ± 10.7
6 to < 12 yr.	17	33.2 ± 12.1	61.9 ± 19.6	11	66.8 ± 21.2
12 to 18 yr.	21	26.3 ± 9.14	53.6 ± 20.2	14	56.7 ± 14.0

Comparisons with adult population

Results from these studies were compared with those from study MYCS 058 in adult renal transplant patients taking 1 g bid of CellCept. For the immediate post-operative period in paediatric patients the dose of 23 mg/kg bid (study MYCS 2190) provided an MPA AUC₀₋₁₂ scattered around 27.2 micrograms•hour/ml. In MYCS 2675 (where the dose was 600mg/m²), at day 7 there were more values above 27.2 micrograms•hour/ml than below. However, a similar pattern was noted in adult renal patients in the first 11 days post-transplant. As with all organ transplants, the MPA AUC₀₋₁₂ values rose over time reaching a plateau between 3 and 9 months. The late-transplant values from the paediatric patients (MYCS 2675) increased by approximately 2-fold and this falls within the range of the values occurring in adults.

Drug –drug interactions

Interaction studies have not been performed in the paediatric population. There were only 4 agents (diazoxide, lidocaine/prilocaine cream, pentobarbital and somatropin) taken by paediatric patients in the first 12 months following renal transplant that were not taken by adults in the pivotal studies. There was no known pharmacokinetic mechanism indicating that a drug-drug interaction between these drugs and MMF was likely.

Pharmacodynamics

The metabolism of MMF to the active moiety MPA and its subsequent metabolism to the inactive MPAG are crucial in the prevention of graft rejection regardless of age and organ transplanted. Exploratory analyses did not reveal a PK/PD relationship between MPA pharmacokinetics and efficacy (acute rejection). MPA AUC₀₋₁₂, C_{max} and C_{min} (i.e. trough MMF levels) were not good predictors of rejection in the first 12 months post-transplant. PK/PD analyses were also attempted for safety issues (especially leucopenia, sepsis, anaemia, diarrhoea) using linear regression. The only finding was an association between MPA C_{max} and diarrhoea but this was no longer statistically significant if adjusted for age. In conclusion, although in adults following renal transplant, there was a strong inverse correlation between the plasma AUC₀₋₁₂ and the probability of acute rejection, this was not demonstrated in paediatric patients.

Discussion on clinical pharmacokinetics and pharmacodynamics

Paediatric renal transplant programme

In paediatric patients of 2 years and above, the pharmacokinetic data provided some re-assurance that the proposed dose (600 mg/m²) may provide an AUC₀₋₁₂ which was similar to that in adults in the immediate (< 40 days) and the late post-transplant period. In adults these values were associated with acceptable efficacy in prevention of rejection and graft loss. However, for paediatric patients aged between 6 and 12 years, all the MPA AUC₀₋₁₂ values were above the target of 27.2 micrograms•hour/ml.

Clinical efficacy (Paediatric renal transplant)

Study MYCS 2675 was submitted as the pivotal efficacy study and study MYCS 2190 as supporting study. No randomised comparative data were provided. Retrospectively collected series, a post-marketing study and published data from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) were also provided.

Paediatric renal transplant study MYCS 2675

This was a single-arm, open label study of MMF oral suspension in paediatric patients following renal transplant. The study was carried out in 15 sites in the USA, Australia and Europe. The main objectives of the study were to evaluate the safety, tolerability and pharmacokinetics of MMF suspension. The efficacy endpoints included prophylaxis of acute rejection at 6 months, patient and graft survival at 6 and 12 months and immunosuppressive treatment for rejection at 6 months.

Patients were stratified into one of three defined age groups: 3 months to < 6 years, 6 to < 12 years and 12 to 18 years. Patients with recurrent focal segmental glomerular sclerosis were not eligible because of their high risk of graft loss. Patients with HIV or with active hepatitis B were also excluded.

The dose of MMF suspension was 600 mg/m² bid (up to 1 g bid), with treatment starting as early as 24 hours pre-transplant but no later than 72 hours post-transplant. After 9 months patients could switch to capsules if desired with the following doses:

- patients with a BSA of 1.25-1.5 m² received 750 mg (3 × 250 mg capsules) bid
- patients with a BSA > 1.5 m² received 1 g (4 × 250 mg capsules) bid

In addition to MMF, patients were treated with cyclosporin plus a corticosteroid. Each study centre's standard practice was followed regarding the use of anti-lymphocyte antibody induction therapy.

Biopsy specimen were reviewed both centrally and locally, with the local assessment the primary method for assessing BPR. In patients with signs and symptoms characteristic of rejection and in those who received a full-course of anti-rejection treatment but who did not have biopsy confirmation, a diagnosis of "presumed rejection" was made.

Results

A total of 100 patients were entered into the study following either a single first or second renal allograft.

The 6 months BPR results are shown in Table 13. A quarter of the patients had first BPR or presumed rejection during the first 6 months post transplant with no major differences between age groups, although paediatric patients below the age of 6 years had a tendency for fewer first rejection episodes.

For graft loss and death at 12 months, the overall incidence was 7 (7%) with 5 graft losses and 2 deaths. Neither of the 2 deaths were considered to be related to MMF (see *Clinical safety section* of this report). Four of the 5 graft loss patients were aged 12-18 years. Three patients lost their transplanted kidneys as a result of technical complications and 1 patient started anti-rejection therapy prior to starting study MMF.

Table 13. Rejection endpoints at 6 months (MYCS 2675, using paediatric criteria)

	< 6 yr. (n=33) No. (%)	6 to < 12 yr. (n=34) No. (%)	12 to 18 yr. (n=33) No. (%)	Total (n=100) No. (%)
BPR	6 (18.2)	9 (26.5)	9 (27.3)	24 (24.0)
BPR or presumed rejection	7 (21.2)	9 (26.5)	9 (27.3)	25 (25.0)

In the study half the paediatric patients had kidneys from living-related donors (which is expected to reduce rejection episodes and increase graft survival). An analysis of efficacy by donor type of the pivotal study was carried out (Table 14). The prevalent source of graft was cadaveric in Europe (81%) whereas in North America most grafts were of living-related source (69%).

Historical data were provided to suggest that acute rejection in paediatric patients treated with cyclosporin regimens was between 58 and 62% between 1982 to 1996 both in Europe and the USA compared with 11-31% in study MYCS 2675.

Table 14. BPR or presumed rejection at 6-month by donor type and Continent (MYCS 2675)

	Europe	North America	Australia	All
Cadaveric	8/26 (31%)	2/18 (11%)	--	10/44 (23%)
Living-related	0/6 (--)	12/44 (27%)	2/4 (50%)	14/54 (26%)
Living-unrelated	--	1/2 (50%)	--	1/2 (50%)
All	8/32 (25%)	15/64 (23%)	2/4 (50%)	25/100 (25%)

Paediatric renal transplant study MYCS 2190

The primary objectives of this study were pharmacokinetics and safety but secondary objectives were the proportion of patients with at least one biopsy-proven rejection episode in the first 6 months and the incidence of graft and patient survival at 1 and 3 years. A total of 14/40 patients (35%) experienced BPR or presumed rejection in the first 6 months. Two patients had graft loss on day 48 and day 53 post-transplant and there were no study deaths.

Comparison of efficacy results in paediatric patients with similar studies in adults

The rejection criteria used for adult patients were less stringent than the paediatric criteria. Borderline rejection (Banff grade I) was considered as rejection in paediatric patients but not in adults. Borderline rejection treated with a full course of immunosuppressant therapy was considered as “presumed rejection” in adults. Acute rejections after study withdrawal were excluded from the adult studies whilst those in the paediatric studies were not. A comparison of the 6-month rejection episodes in adults and paediatric patients is shown in Table 15.

Table 15. Rejection endpoints in paediatric and adult studies (using adult criteria)

	Paediatric	Adult Studies			
	MYCS 2675	MYC 023		MYC 1886	
	MMF (0.750 - 1 g bd) n=100	MMF (1g bd) n=173	AZA (100-150 mg) n=166	MMF (1g bd) n=167	AZA (1-2 mg/kg/d) n=166
BPR at 6 months	19%	19.7%	35.5%	19.8%	38.0%
BPR or presumed rejection 6 months	22%	31.8%	48.2%	26.3%	45.8%
Graft loss and patient death at 12 months	7%	11.7%	13.6%	8.5%	12.2%

Retrospective and Published series

Comparative analyses for paediatric patients who had not received MMF were performed using historical data from 3 institutions (Germany, France, USA), stratified by age group and source of graft (cadaver *versus* living-related donor). Overall in the non-MMF patients, 60.7% of patients had cadaveric kidneys and 38.4% had kidneys from a living-related donor (*versus* 44% and 54% in study MYCS 2675). From the German centre (n=55) the rejection rates for each age group varied between

25% and 65% (overall 50%) whereas in France (n=30) the rates were approximately 30% for all age groups. No deaths were reported. Graft losses incidences were too low to make any comparisons.

Published efficacy data from the NAPRTCS were provided. The registry database contains data on 5,516 paediatric patients that have undergone renal transplantation during the period of 1987 to January 1998. The analysis shows a higher 6-month acute rejection rate (42 and 57% for living and cadaveric grafts, respectively) than occurred in study MYCS 2675 (27 and 23% respectively).

This is a prospective observational cohort study with a companion case-control study, the final report on both have been submitted end 2002. The main objective of the cohort study is to address the issue of whether MMF was associated with an increased risk of post-transplant lymphoproliferative disorders (PTLD) in comparison with alternative immunosuppressant regimens. The cohort study collected data from two transplant registries - the United Network Organ Sharing Registry (UNOS) from the USA and the Collaborative Transplant Study (CTS) registry in Europe and Canada. MMF patients were matched for age to non-MMF patients within ± 5 years. In UNOS registry, approximately half the patients had a cadaveric graft whereas the percentage was considerably higher in the CTS registry (72% in children on MMF and 81% in children on non-MMF regimens). The mean age was 13 years and 12 years in UNOS and CTS respectively.

The average duration of follow up in UNOS was 1.7 years (total person years of follow up =698) and in CTS 1.2 and 1.3 years for MMF and non-MMF respectively (total person years of follow up =328). There is no indication that children on MMF have a higher frequency of rejection episodes than those on non-MMF regimens with a trend towards less graft rejection with MMF (UNOS: 3.9% *versus* 5.5%; CTS: 0.7% *versus* 2.4% for MMF and non-MMF patients respectively). Graft rejection rates in the registries were considerably lower than in the pivotal study, MYCS 2675 where they varied between 18 and 27% (depending on age).

Discussion on clinical efficacy

Comparison with historical data in adults and comparison with an overall estimation of graft survival and acute rejection episodes from clinical practice in Europe indicate similar efficacy for MMF in the paediatric and adult populations. The precise efficacy of MMF-containing regimens compared to alternative regimens is difficult to establish in the paediatric population, in the absence of adequately controlled data. The historical controls presented suffer from the known pitfalls of retrospective series. The retrospective series presented come from a 15 year period (1984 and 1999) during which time there may well have been many changes in factors that could affect graft survival and the adverse event profiles of treatment. No control was exercised over patient selection. The patients included in the published data from the NAPRTCS registry in the US were also not considered sufficiently similar to the MYCS 2675 study to act as a robust control group in terms of efficacy.

Clinical safety (Paediatric renal transplant)

From the 140 patients in the 2 paediatric studies (MYCS 2675, MYCS 2190 and extension MYCS 2190v2), approximately 78% have received MMF for at least 12 months and approximately 11% (all from the supporting study MYCS 2190v2) for 3 years.

Adverse events, adverse drug reactions, serious adverse events and deaths

All 140 paediatric patients reported at least one adverse event. Those observed in more than 50% of the patients were fever (75%), pain (70%), hypertension (70%), diarrhoea (68.6%), vomiting (58.6%), respiratory infection (55.7%) and abdominal pain (55.0%). Selected adverse events are summarised in Table 16.

A total of 63 (45.0%) of paediatric patients developed opportunistic infections 58 (41.4%) in the first 12 months. Mucocutaneous *Candida* was more prevalent in the paediatric patients below the age of 6 years (22% *versus* 6.1% and 8.0% for the other age groups) whilst *Herpes zoster* and CMV tissue invasion increased with age.

Patients below the age of 6 years had a trend towards a higher incidence of diarrhoea, vomiting, anaemia and sepsis. The incidence of leucopenia was similar for both the younger age groups but higher than in the 12 to 18 year group. For these adverse events the general trend was a reduced incidence with increased age. However, the oldest paediatric patients showed a trend towards a greater incidence of pain, nausea, headache and tremor.

A total of 110 patients (78.6%) had adverse events possibly or probably related to MMF. Overall, severe adverse drug reactions occurred more frequently in the oldest age group (66% versus 56.4% in the whole population). Table 16 shows adverse events that were probably and/or possibly related to MMF.

Table 16. MMF: selected adverse events in paediatric and adult patients (first 12 months)

	Paediatric studies (MYCS2675, MYC2190)				Adult studies
	< 6 yr. (n=41) No. (%)	6 to < 12 yr. (n=49) No. (%)	12 to 18 yr. (n=50) No. (%)	Total (n=140) No. (%)	MYC1866 MYC023 Pooled (n=336) No. (%)
Related					
Diarrhoea	17 (41.5)	14 (28.6)	6 (12.0)	7 (26.4)	9 (17.6)
Leucopenia	10 (24.4)	13 (26.5)	8 (16.0)	31 (22.1)	61 (18.2)
Anaemia	9 (22.0)	4 (8.2)	3 (6.0)	16 (11.4)	19 (5.7)
Sepsis	8 (19.5)	8 (16.3)	7 (14.0)	23 (16.4)	46 (13.7)
Dose modification					
Diarrhoea	11 (26.8)	9 (18.4)	4 (8.0)	24 (17.1)	20 (6.0)
Leucopenia	10 (24.4)	14 (28.6)	8 (16.0)	32 (22.9)	62 (18.5)
Anaemia	4 (9.8)	2 (4.1)	1 (2.0)	7 (5.0)	4 (1.2)
Sepsis	2 (4.9)	4 (8.2)	3 (6.0)	9 (6.4)	20 (6.0)
Severe					
Diarrhoea	3 (7.3)	--	--	3 (2.1)	12 (3.6)
Leucopenia	4 (9.8)	3 (6.1)	2 (4.0)	9 (6.4)	10 (3.0)
Anaemia	4 (9.8)	3 (6.1)	4 (8.0)	11 (7.9)	50 (14.9)
Sepsis	1 (2.4)	1 (2.0)	2 (4.0)	4 (2.9)	20 (6.0)
Withdrawal					
Diarrhoea	1 (2.4)	1 (2.0)	--	2 (1.4)	--
Leucopenia	--	--	--	--	5 (1.5)
Anaemia	1 (2.4)	--	--	1 (0.7)	3 (0.9)
Sepsis	--	--	2 (4.0)	2 (1.4)	3 (0.9)

Abbreviations: *Related*, probably or possibly related; *Dose modification*, resulting in dose reduction or interruption; *Severe*, as graded; *Withdrawal*, resulting in premature withdrawal from study treatment.

Table 17. Adverse events with observed incidence \geq 10% possibly/probably related to MMF (first 12 months)

	< 6 yr. n = 41	6 to < 12 yr. n = 49	12 to 18 yr. n = 50	Adults n = 336
Diarrhoea	41.5%	28.6%	12.0%	17.6%
Leucopenia	24.4%	26.5%	16.0%	18.2%
Sepsis	19.5%	16.3%	14.0%	13.7%
Urinary tract infection	19.5%	4.1%	8.0%	16.4%
Herpes simplex	7.3%	12.2%	10.0%	15.2%
Abdominal pain	14.6%	12.2%	10.0%	13.7%
Constipation	--	--	--	12.2%
Infection	19.5%	4.1%	10.0%	6.8%
Anaemia	22.0%	8.2%	6.0%	5.7%

The majority of cases of sepsis were considered to be viral whilst infections were commonly upper respiratory tract infections. This finding needs to be considered in relation to the fact that paediatric renal patients are particularly at risk of infections both because of their previous lack of exposure to pathogens and because of their size surgery is more complex.

Overall in the paediatric studies, serious adverse events (including deaths, safety related withdrawals and malignancies) were observed in 26 (18.5%) of the 140 patients. Severe neutropenia, thrombocytopenia and GI bleeding occurred in 3, 1 and 4 patients, respectively. There were 2 (1.4%) cases of malignancy, both lymphoma/lymphoproliferative disorders, one occurring at 280 days and the other more than 3 years after the start of MMF. Both cases were reported in paediatric patients below the age of 6 years.

In the first 12 months of the paediatric studies, 2 patients died (one from pulmonary embolus and the other from acute haemorrhagic pancreatitis) and neither were considered to be related to MMF. Acute haemorrhagic pancreatitis occurred in a 2 year old male patient with a history of acute pancreatitis. The patient had septicaemia with *Candida* and *Klebsiella* and the cause of death was shock and acute haemorrhagic pancreatitis.

A comparison during the first 12 months post-transplant with the adult studies with MMF following renal transplant (n = 336) was provided. Opportunistic infections occurred with similar frequencies in adult and paediatric patients (45.5% versus 41.4% respectively). The only infections showing a marked difference were CMV invasion which was twice as common in adults as in paediatric patients (8.6% versus 4.3%) and CMV infection which occurred three times as often (6.5% adults versus 2.1% paediatric patients). It was noted that following transplant, paediatric patients can be affected by the growth-suppressant effects of steroids and very young paediatric patients may be more susceptible to viral infections because they lack prior immunity. Apart from *Herpes simplex* and constipation (which was not reported in any of the paediatric patients), all other commonly reported adverse drug reactions to MMF occurred more frequently in paediatric patients below the age of 6 years when compared to adults. Severe diarrhoea and leucopenia occurred more frequently in paediatric patients than in adults. Diarrhoea, anaemia and infection (but not sepsis) occurred with considerably greater frequency in the younger patients (<6 years) when compared with the older paediatric patients or adults.

Withdrawal as a result of an adverse event, intercurrent illness, laboratory abnormality or death occurred in 16/140 patients (11.4% overall; 9.8% in the < 6 years, 12.2% in the 6 to < 12 year and 12.0% in the 12 to 18 years age group). No association with age was apparent. Adverse events leading to withdrawal were less frequent in paediatric patients than in adults (8.6% vs 12.8%) with the most frequent events being GI reactions. Cardiovascular reactions were more frequent in paediatric patients (3.6% vs 1.5%) because of an increased frequency of "thrombosis" and "heart arrest"

Dose modifications

Dose modifications in the pivotal study are reported in Table 18, for the first 12 months. A total of 49% of patients had an adverse event that resulted in a dose reduction/interruption of MMF. The median reduction was 33% and the duration ranged from 13-24 days but after dose interruption/reduction most patients returned to within 90% of their original MMF dose. The proportion of paediatric patients who had at least one decrease in MMF dose due to an adverse event differed according to the age group. The proportion decreased for increasing age groups (58% in the <6 year, 41% in 6-<12 year and 30% in 12-18 year group). In terms of median average daily MMF, a clear age trend was not considered to be present.

A greater percentage of paediatric patients had their MMF dose reduced or interrupted because of an adverse event (35.7% adults *versus* 50.7% paediatric patients). Within the paediatric population, dose reduction/interruption occurred more often in the youngest age group for leucopenia, diarrhoea and anaemia.

In the first 12 months of study MYCS 2675, 10 patients (7.1%) were withdrawn from the study because of the need for medication prohibited by the protocol. This was considerably greater than the 1% (4 patients) from the adult studies. In 8 of the 10 patients tacrolimus was used to replace cyclosporin (toxicity in 5 patients and chronic rejection in 3 patients) and in the remaining 2 cyclophosphamide was required to treat focal segmental glomerulosclerosis. The data provided give some re-assurance that corticosteroids doses used in the pivotal paediatric study are not markedly different from those used in routine clinical practice.

In the extension to MYCS 2190, 40 paediatric patients were treated with MMF for longer than 3 years and 70 for at least 2.5 years. These patients did not reveal any new or unexpected adverse events. In reference to MYCS 2675, the final study report provides with safety data of patients for 1.5 years for 49% of patients. It showed premature termination due to an adverse event (total 11, 11%) and 4 additional cases of opportunistic infection bringing the study total to 52 (52%), compared to 12-month data.

Table 18. MMF: Dose modifications, average daily and bid dose (MYCS 2675, first 12 months)

	< 6 yr. n=33	6 to < 12 yr. n=34	12 to 18 yr. n=33	Total n=100
Dose modifications:				
Dose modification for AE (No.)	21 (64%)	16 (47%)	12 (36%)	49
No dose modification (No.)	12 (36%)	18 (53%)	21 (64%)	51
Median average daily dose				
Dose modification for AE (mg/m ²)	1027	1015	1005	1020
No dose modification (mg/m ²)	1196	1197	1187	1194
Median average bid dose in mg/m ²				
% reduction (from 600 mg/m ²)	560 (7%)	578 (4%)	575 (4%)	576 (5%)

Abbreviations: AE, adverse event.

Dose of corticosteroids

The mean maintenance corticosteroids dose in the pivotal study MYCS 2675 was 0.2-0.3 mg/kg/day at 6 months post-transplant. Table 19 shows the maintenance corticosteroids dose in mg/kg/day by age

group at 6 and 12 months post-transplant. From the report of the NAPRTCS in 4,217 paediatric patients below the age of 18 years receiving cyclosporin and AZA, the approximate mean prednisone dose was 0.2 mg/kg/day.

Table 19. Study MYCS 2675: Mean maintenance corticosteroid dose

	< 6 yr.		6 to < 12 yr.		12 to 18 yr.	
	No	Mean ± SEM	No.	Mean ± SEM	No.	Mean ± SEM
Month 6	28	0.3 ± 0.03	29	0.2 ± 0.01	20	0.2 ± 0.01
Month 12	28	0.2 ± 0.01	26	0.2 ± 0.01	18	0.1 ± 0.01

Retrospective data

The data collected from the three centres differed to those from study MYCS 2675 in several respects such as definition of leucopenia in one centre, reporting of viral sepsis and exclusion of patients who died during the 1st year post-transplant in one centre. Leucopenia in the non-MMF patients from the French and German series occurred with a greater overall frequency (40 and 47% respectively) than in the study MYCS 2675 (25%). Anaemia was observed in all but one patient from the German and the US series (n=82) whilst it was only reported in 10% of the patients from the French centre (*versus* 36% in study MYCS 2675). The frequency of diarrhoea was 10%, 30% and 60% in the French, German and US series respectively. The overall rates of sepsis was similar for the non-MMF series from France (30%) and the USA (35%) and also to that in the MMF study (35%) but the profile by age group differed.

Discussion on clinical safety

The most common adverse drug reactions for CellCept differ according to the age of the patient. Severe leucopenia and severe diarrhoea were more common in paediatric patients whilst severe anaemia and sepsis were more frequent in adults. Regardless of severity, diarrhoea, leucopenia, anaemia and sepsis were observed with greater frequency in paediatric patients. Diarrhoea or anaemia required interruption or reduction of immunosuppressant therapy in all age groups (except anaemia in oldest paediatric patients) in the pivotal paediatric MMF study (diarrhoea 12%; anaemia 6%). The frequency of diarrhoea, which is of particular concern, may reflect the increased susceptibility of paediatric patients to viral infections. An age related increasing incidence of diarrhoea (and to a lesser extent leucopenia and anaemia) were also observed in non-MMF treated patients. However, no data were available to confirm an infective origin of diarrhoea. Viral gastro-enteritis post-transplant can precipitate rejection and diarrhoea of any cause can affect the absorption of cyclosporin.

Concerning safety aspects beyond 12 months, the data are very limited but do not indicate that the long-term use of MMF would result in major safety concerns.

Discussion on clinical aspects and benefit/risk assessment (Paediatric renal transplant)

The proposed dose produces AUC₀₋₁₂ values in paediatric patients above the age of 2 years that are similar those in adults. The proposed CellCept dose has only been validated by pharmacokinetic parameters. No PK/PD relationship in children has been established.

A comparison with efficacy data in adults indicates similar efficacy in the paediatric population. However, these results need to be viewed with caution as the efficacy results could be affected by the large proportion of paediatric patients (50%) with grafts from living-related donors in the MMF studies. No randomised double-blind study has been carried out in paediatric patients comparing CellCept as part of an immunosuppressant regimen *versus* an already established regimen used for renal transplants in paediatric patients.

Paediatric data showed differences in the ADR profile compared to adults, particularly in patients below 6 years. The individual reactions that occurred with greater frequency in paediatric patients

were diarrhoea, sepsis, leucopenia and anaemia. These could relate to the increased susceptibility of paediatric patients to infections or indicate a greater susceptibility of paediatric patients to the adverse effects of CellCept.

CPMP Recommendation

The CPMP considered this Type II variation to be acceptable and agreed on the proposed wordings to be introduced into the Summary of Product Characteristics based on the observations and the appropriate conclusions.

Renewal of the Marketing Authorisation

At the time of the 5-year renewal of the marketing authorisation, CellCept was approved in the following indications:

- CellCept 250 mg capsules, CellCept 500 mg tablets and CellCept 1 g/5 ml powder for oral suspension are indicated in combination with cyclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.
- CellCept 500 mg powder for concentrate for solution for infusion is indicated in combination with cyclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal or hepatic transplants.

The additional data reported in the clinical expert statement confirm the continued efficacy in the currently authorised indications. There are no data indicating that the current dosage regimens are inappropriate or need revision.

Additional long-term safety data have become available from ongoing studies, without revealing any new safety concerns or a change in the expected frequency of adverse events.

All PSURs since product launch have been submitted and assessed. In addition, an interim PSUR has been submitted with the renewal application. This covers the period 01 May to 31 August 2000. It is estimated that approximately 60,000 patients have received CellCept post-marketing with an additional 1,040 receiving the product in company sponsored clinical trials during this time period.

The MAH has agreed to submit PSUR 12 by June 2001 and to submit following PSURs on a yearly basis thereafter, until the next renewal date.

CPMP Recommendation

Based on the CPMP review of the available information, the CPMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered by consensus that the benefit/risk profile of CellCept continues to be favourable. The CPMP recommended the renewal of the Marketing Authorisation for CellCept.