AUSTRALIAN PRODUCT INFORMATION
CellCept® (mycophenolate mofetil)

1. NAME OF THE MEDICINE
Mycophenolate mofetil

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
CellCept 250 mg capsules contain 250 mg mycophenolate mofetil.

CellCept 500 mg tablets contain 500 mg mycophenolate mofetil.

CellCept 500 mg powder for concentrate for solution for infusion contains 500mg mycophenolate mofetil (as hydrochloride salt).

CellCept 1 g/5 ml powder for oral suspension contains 1 g mycophenolate mofetil per 5 mL when reconstituted.

For the full list of excipients, see section 6.1. List of excipients.

3. PHARMACEUTICAL FORM
CellCept 250mg capsules
Capsules, hard.
CellCept capsules: oblong, blue/brown, branded with black "CellCept 250" on the capsule cap and "Roche" name on the capsule body.

CellCept 500 mg tablets
Film coated tablets.
CellCept tablets: lavender coloured caplet-shaped tablet, engraved with "CellCept 500" on one side and "Roche" name on the other.

CellCept 500 mg powder for concentrate for solution for infusion
Powder for concentrate for solution for infusion.
Sterile lyophilised white to off-white powder for infusion.
CellCept 500 mg powder for concentrate for solution for infusion must be reconstituted and further diluted with glucose intravenous infusion 5% prior to administration to the patient. Reconstitution and dilution with 5% glucose intravenous infusion as recommended yields a slightly yellow solution of mycophenolate mofetil, 6 mg/mL.

CellCept 1 g/5 ml powder for oral suspension.
Powder for oral suspension
White to off-white powder for oral suspension

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
CellCept is indicated for the prophylaxis of solid organ rejection in adults receiving allogeneic organ transplants.

CellCept is indicated for the prophylaxis of organ rejection in paediatric patients (2 to 18 years) receiving allogeneic renal transplants.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

The initial dose of CellCept should be given as soon as clinically feasible following transplantation. Intravenous administration is recommended in those patients unable to take oral medication. However, oral administration should be initiated as soon as possible.

Adults

Renal Transplantation

The recommended dose in renal transplant patients is 1 g administered orally or intravenously twice daily (2 g daily dose).

Cardiac Transplantation

The recommended dose in cardiac transplant patients is 1.5 g administered orally or intravenously twice daily (3 g daily dose).

Hepatic Transplantation

The recommended dose in hepatic transplant patients is 1 g administered intravenously twice daily (2 g daily dose) followed by 1.5 g administered orally twice daily (3 g daily dose) (See CellCept IV below).

Other Transplants

The recommended dose in other transplants is 2 to 3g per day depending on the level of immunosuppression required.

Paediatrics (2 to 18 years)

The recommended dose for renal transplant patients is 600 mg/m^2 of mycophenolate mofetil (MMF) administered orally twice daily (up to a maximum of 2 g daily).

CellCept may be administered in combination with ciclosporin and corticosteroids.

Complete blood counts should be performed weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If neutropenia develops (ANC < 1.3x10^9/L), dosing with CellCept should be interrupted or the dose should be reduced and the patient carefully observed (see section 4.4 Special warnings and precautions for use). Patients should be advised to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

In renal transplant patients with severe chronic renal impairment (GFR < 25 mL/min/1.73m^2) outside of the immediate post-transplant period, doses of CellCept greater than 1 g administered twice a day should be avoided. No data are available in cardiac or hepatic allograft recipients with severe chronic renal impairment. These patients should also be carefully observed. No dose adjustments are needed in patients experiencing delayed renal allograft function post-operatively.

No dosage adjustment is required in the elderly or in renal transplant patients with hepatic parenchymal disease.

No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

Method of Administration

Preparation and Administration of CellCept IV

CellCept IV is an alternative dosage form recommended for patients unable to take CellCept capsules, tablets and oral suspension. CellCept IV should be administered within 24 hours following transplantation. Although CellCept IV administration has been studied for up to 14 days, patients should be switched to oral CellCept as soon as they can tolerate oral medication.

CellCept IV should be reconstituted and diluted to a concentration of 6 mg/mL with 5% glucose intravenous infusion prior to use. A two-step reconstitution and dilution process is required to prepare the infusion solution to the recommended concentration of 6 mg/mL (see below). It must be administered by slow intravenous infusion over a period of no less than 2 hours.

Caution: Cellcept IV solution must not be administered by rapid or bolus intravenous injection.

Two vials of CellCept IV are used for preparing each 1 g dose. Three vials of CellCept IV are used for preparing each 1.5 g dose.

1 gram dose (two vials)
Step 1.

1. Withdraw 5% glucose intravenous infusion from the bag so that 140 mL remains (e.g. for a 250 mL bag, withdraw 110 mL).
2. Use 28 mL of this withdrawn glucose solution to reconstitute the two vials by injecting 14 mL of 5% glucose intravenous infusion into each vial (using aseptic techniques).
3. Gently shake the vials to dissolve the drug.
4. Inspect the resulting solution for particulate matter and discolouration prior to further dilution. Discard any vial in which particulate matter or discolouration are observed.

Step 2.

1. Further dilute the contents of the **two** reconstituted vials (prepared in step 1) by adding both to the 140 mL bag of 5% glucose intravenous infusion for a total volume of 168 mL and a final concentration of 6 mg/mL.
2. Inspect the infusion solution for particulate matter or discolouration. Discard the infusion solution if particulate matter or discolouration is observed.

1.5 gram dose (three vials)
Step 1.

1. Withdraw 5% glucose intravenous infusion from the bag so that 210 mL remains (e.g. for a 250 mL bag, withdraw 40 mL and discard).
2. Prepare 42 mL of 5% glucose intravenous infusion to reconstitute the three vials by injecting 14 mL of 5% glucose intravenous infusion into each vial (using aseptic techniques).
3. Gently shake the vials to dissolve the medicine.
4. Inspect the resulting solution for particulate matter and discolouration prior to further dilution. Discard any vial in which particulate matter or discolouration are observed.

Step 2.

1. Further dilute the contents of the **three** reconstituted vials (prepared in step 1) by adding them to the 210 mL bag of 5% glucose intravenous infusion for a total volume of 252 mL and a final concentration of 6 mg/mL.
2. Inspect the infusion solution for particulate matter or discolouration. Discard the infusion solution if particulate matter or discolouration are observed.

<u>Preparation and Administration of Oral Suspension</u>
It is recommended that CellCept oral powder for suspension be reconstituted by the Pharmacist prior to dispensing to the patient.

CellCept powder for oral suspension should not be mixed with any other medication.

1. Tap the closed bottle several times to loosen the powder
2. Measure 94 mL of purified water in a graduated cylinder
3. Add approximately half of the total amount of purified water to the bottle and shake well for about 1 minute
4. Add the remainder of water and shake the closed bottle well for about 1 minute
5. Remove the cap and push bottle adapter into neck of the bottle
6. Close bottle with cap tightly. This will assure the proper seating of the bottle adapter in the bottle

7. Write the date of expiration of the constituted oral suspension on the bottle label. (The shelf life of the reconstituted oral suspension is 60 days from date of preparation).

Note: If required CellCept Oral Suspension can be administered via a nasogastric tube with a minimum interior diameter of 1.7 mm.

The deliverable volume of the oral suspension is 165 mL and contains 33 doses of 1 g/5 mL mycophenolate mofetil. After reconstitution, each bottle will contain a volume greater than 165 mL to allow for wastage due to inaccessible suspension. Each dose is administered using the 5 mL plastic oral dispenser provided (2 per carton). Discard any unused suspension 60 days after reconstitution.

4.3 CONTRAINDICATIONS

CellCept is contraindicated in patients with a history of hypersensitivity, including anaphylaxis, to mycophenolate mofetil (MMF), to mycophenolic acid (MPA) or any component of the drug product.

CellCept intravenous (IV) solution is contraindicated in patients with known hypersensitivity to polysorbate 80.

CellCept is contraindicated during pregnancy due to its mutagenic and teratogenic potential (see section 4.6 Fertility, pregnancy and lactation).

CellCept is contraindicated in women of childbearing potential not using highly effective contraceptive methods (see section 4.6 Fertility, pregnancy and lactation).

CellCept is contraindicated in women who are breastfeeding (see section 4.6 Fertility, pregnancy and lactation).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Female patients of childbearing potential must use effective contraception before, during and for 6 months after receiving CellCept. CellCept is contraindicated during pregnancy and during breastfeeding (see section 4.6 Fertility, pregnancy and lactation).

Men should not donate semen during therapy and for 90 days following discontinuation of CellCept.

Caution: CellCept IV solution must not be administered by rapid or bolus intravenous injection.

Neoplasms

As with other patients receiving immunosuppressive regimes involving combinations of medicines, patients receiving CellCept as part of an immunosuppressive regime are at an increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than the use of any specific agent. Approximately 1% of patients receiving CellCept with other immunosuppressive agents in the controlled studies of prevention of rejection have developed lymphoproliferative disease or lymphoma. As immunosuppression increases the risk of skin cancer, patients should also be advised to limit their exposure to sunlight and other sources of UV light by wearing protective clothing and using sunscreen with a high protection factor.

Infections

Over suppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections and sepsis. In the controlled studies for the prevention of rejection, the incidence of fatal infection was similar in patients receiving CellCept or control therapy

in combination with other immunosuppressive agents. There was a higher incidence of fatal infection in the liver transplant study (5%) compared with the other studies (2%).

Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation or infections caused by polyomaviruses. Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. Cases of progressive multifocal leukoencephalopathy (PML) associated with the JC virus, sometimes fatal, have been reported in CellCept-treated patients. Hemiparesis, apathy, confusion, cognitive deficiencies and ataxia were the most frequent clinical features observed. The reported cases generally had risk factors for PML, including concomitant immunosuppressant therapies and impaired immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated. Consideration should be given to reducing the amount of immunosuppression in patients who develop PML. In transplant patients, physicians should also consider the risk that reduced immunosuppression represents to the graft.

BK virus-associated nephropathy has been observed during the use of CellCept in patients post-renal transplant. This infection can be associated with serious outcomes, sometimes leading to renal graft loss. Patient monitoring may help detect patients at risk of BK virus-associated nephropathy. Due to the cytostatic effect of CellCept on B- and T-lymphocytes, increased severity of COVID-19 may occur. Dose reduction or discontinuation of CellCept should be considered for patients who develop evidence of BK virus-associated nephropathy, or in cases of clinically significant COVID-19.

Blood and Immune System

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with CellCept in combination with other immunosuppressive agents. The mechanism for mycophenolate mofetil-induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppression regimen are also unknown. In some cases, PRCA was found to be reversible with dose reduction or cessation of CellCept therapy. In transplant patients however, reduced immunosuppression may place the graft at risk.

Patients receiving CellCept should be instructed to immediately report any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

Patients on CellCept should have complete blood counts weekly during the first month of treatment, twice monthly for the second and third months, then monthly through the first year. In particular, patients receiving CellCept should be monitored for neutropenia. The development of neutropenia may be related to CellCept, concomitant medications, viral infection or some combination of these causes. If neutropenia develops (absolute neutrophil count $< 1.3 \times 10^3/\mu L$), dosing with CellCept should be interrupted or the dose reduced and the patient should be carefully observed.

0.5% of patients receiving CellCept 2 g for prevention of rejection in renal transplantation, 2.8% of patients receiving CellCept 3 g in cardiac transplantation and 3.6% of patients receiving CellCept 3 g in hepatic transplantation, developed severe neutropenia (absolute neutrophil count [ANC] $< 5 \times 10^8/L$).

Patients should be advised that during treatment with CellCept vaccinations may be less effective and the use of live attenuated vaccines should be avoided (see section 4.5 Interactions with other medicines and other forms of interactions). Influenza vaccination may be of value. Physicians should refer to the national guidelines for influenza vaccination.

Patients should not donate blood during therapy and for at least 6 weeks following discontinuation of CellCept.

Gastrointestinal

CellCept has been associated with an increased incidence of digestive system adverse events, including uncommon cases of gastrointestinal tract ulceration, haemorrhage, and perforation (colon, gall bladder) in post-marketing surveillance, CellCept should be administered with caution in patients with active serious digestive system disease. Gastrointestinal tract bleeding (requiring hospitalisation) has been observed in approximately 1.4% of patients treated with CellCept 2 g in renal transplantation, 2.8% of patients receiving 3 g in cardiac transplantation and in 5.4% of patients receiving CellCept 3 g in hepatic transplantation. Gastrointestinal tract perforations have rarely been observed. Most patients were also receiving other drugs that are associated with these complications (see section 4.8 Adverse effects (Undesirable effects)). It should be noted that patients with active peptic ulcer disease were excluded from enrolment in studies with MMF.

Since CellCept is an IMPDH (inosine monophosphate dehydrogenase) inhibitor, on theoretical grounds it should be avoided in patients with rare hereditary deficiency of hypoxanthine guanine phosphoribosyl transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Interactions

Caution should be exercised when switching combination therapy from regimens containing immunosuppressants which interfere with MPA enterohepatic recirculation e.g. ciclosporin, to others devoid of this effect e.g. tacrolimus, sirolimus, belatacept, or vice versa, as this might result in changes of MPA exposure. Drugs which interfere with MPA's enterohepatic cycle e.g. cholestyramine, antibiotics should be used with caution due to their potential to reduce the plasma levels and efficacy of CellCept (see section 4.5 Interactions with other medicines and other forms of interactions).

Therapeutic drug monitoring of MPA may be appropriate when switching combination therapy (e.g. from ciclosporin to tacrolimus or vice versa) or to ensure adequate immunosuppression in patients with high immunological risk (e.g. risk of rejection, treatment with antibiotics, addition or removal of an interacting medication).

Azathioprine: It is recommended that CellCept should not be administered concomitantly with azathioprine because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied.

Hypersensitivity Reactions

Post-marketing cases of serious hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with CellCept with or without concomitant therapies, premedication, and/or a previous history of hypersensitivity reaction. These reactions generally occur within minutes to a day after initiating CellCept. It is recommended that if signs or symptoms of anaphylactic reaction occur, CellCept should be discontinued permanently. The patients should be provided appropriate medical treatment immediately and monitored until the symptoms resolve. See also sections 4.3 Contraindication and 4.8 Adverse Effects (Undesirable Effects).

Phenylketonurics

CellCept oral suspension contains aspartame, a source of phenylalanine (0.56 mg phenylalanine per mL suspension). Therefore, care should be taken if CellCept oral suspension is administered to patients with phenylketonuria.

Use in renal impairment

Patients with severe chronic renal impairment (GFR < 25 mL/min/1.73m²) who have received single doses of CellCept showed increased plasma AUCs of MPA and MPAG relative to patients with lesser degrees of renal impairment or normal healthy patients. Patients with severe chronic renal impairment should be carefully monitored and administration of doses of CellCept greater than 1g twice daily should be avoided (see sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties).

In patients with delayed graft function post-transplant, mean MPA AUC_{0-12} was comparable, but MPAG AUC_{0-12} was 2 - 3 fold higher, compared to that seen in post-transplant patients without delayed graft function. In the three controlled studies of prevention of rejection, there were 298 of 1 483 patients (20%) with delayed graft function. Although patients with delayed renal allograft function have a higher incidence of certain adverse events (anaemia, thrombocytopenia, hyperkalaemia) than patients without delayed graft function, these events were not more frequent in patients receiving CellCept than azathioprine or placebo. No dose adjustment is recommended for these patients, however, they should be carefully observed.

In renal transplant patients with severe chronic renal impairment, administration of doses greater than 1 g twice daily should be avoided.

Paediatric Use

Based on a safety and pharmacokinetics study in renal paediatric patients, no significant differences in pharmacokinetic parameters in comparison to adult patients were observed. Paediatric patients experienced a higher incidence of certain adverse events (see section 4.8 Adverse effects (Undesirable effects)). Data are insufficient to establish safety and efficacy in children below the age of two years.

Use in the Elderly

Elderly patients may be at an increased risk of adverse events such as certain infections (including CMV tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared with younger individuals. Elderly patients (over 65 years) may generally be at increased risk of adverse reactions due to immunosuppression. Pharmacokinetic behaviour of CellCept in the elderly has not been formally evaluated.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drug interaction studies with MMF have been conducted with aciclovir, antacids, belatacept, cholestyramine, ciclosporin, ganciclovir, oral contraceptives, proton pump inhibitors, sirolimus, tacrolimus, telmisartan and trimethoprim/sulfamethoxazole. Drug interaction studies have not been conducted with other medicines that may be commonly administered to renal, cardiac or hepatic transplant patients.

<u>Aciclovir</u>

Following single dose administration of MMF (1 g) and aciclovir (800 mg) to normal healthy subjects, higher MPAG (8.6%) and aciclovir (17.4%) plasma AUCs were observed when MMF was administered with aciclovir in comparison to the administration of each drug alone. As MPAG plasma concentrations are increased in the presence of renal impairment, as are aciclovir concentrations, the potential exists for the mycophenolate and aciclovir or its prodrugs e.g. valaciclovir to compete for tubular secretion and thus further increases in concentrations of both drugs may occur.

Antacids with Magnesium and Aluminium Hydroxides
Absorption of a single dose of MMF (2.0 g) was decreased when aluminium/magnesium hydroxide antacids were administered concomitantly to rheumatoid arthritis patients. The C_{max} and 24 hour AUC values for MPA were 33% and 17% lower, respectively than when MMF was administered alone under fasting conditions.

Antibiotics
Antibiotics eliminating β-glucuronidase-producing bacteria in the intestine (e.g. aminoglycoside, cephalosporin, fluoroquinolone, and penicillin classes of antibiotics) may interfere with MPAG/MPA enterohepatic recirculation thus leading to reduced systemic MPA exposure. Information concerning the following antibiotics is available:

Ciprofloxacin or Amoxicillin plus Clavulanic Acid:
Reductions in pre-dose (trough) MPA concentrations of 54% have been reported in renal transplant recipients in the days immediately following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. Effects tended to diminish with continued antibiotic use and cease after discontinuation. The change in pre-dose level may not accurately represent changes in overall MPA exposure; therefore, clinical relevance of these observations is unclear.

Norfloxacin ⁄and Metronidazole
The combination of norfloxacin and metronidazole reduced the MPA AUC following a single dose of CellCept.

Trimethoprim ⁄ and Sulfamethoxazole
Following single dose administration of MMF (1.5 g) to healthy male volunteers pretreated for 10 days with trimethoprim 160 mg ⁄ and sulfamethoxazole 800 mg, no effect on the bioavailability of MPA was observed.

Cholestyramine
Following single dose administration of 1.5 g MMF in normal healthy subjects pretreated with 4 g three times daily of cholestyramine for 4 days, there was a mean 40% reduction in the AUC of MPA (see section 5.2 Pharmacokinetic Properties). In view of the significant reduction in the AUC of MPA by cholestyramine, caution should be used with the concomitant use of CellCept and any drug which interferes with enterohepatic circulation because of the potential to reduce the efficacy of CellCept.

Ciclosporin
Ciclosporin pharmacokinetics (at doses of 275 to 415 mg/day) were unaffected by single and multiple doses of 1.0 g MMF twice daily in stable renal transplant patients. The mean (±SD) dose normalised AUC_{0-12h} of MPA after 14 days and 3 months of multiple doses of CellCept and ciclosporin in 17 renal transplant patients were 43 ± 11µg.h/mL.g and 56 ± 31µg.h/mL.g, respectively. However, ciclosporin interferes with MPA enterohepatic recycling, resulting in reduced MPA exposures by 30-50% in renal transplant patients treated with CellCept and ciclosporin compared with patients receiving sirolimus or belatacept and similar doses of CellCept. Conversely, changes of MPA exposure should be expected when switching patients from ciclosporin to one of the immunosuppressants which do not interfere with MPA's enterohepatic cycle.

Drugs affecting glucuronidation
Concomitant administration of drugs inhibiting glucuronidation of MPA may increase MPA exposure (e.g., increase of MPA $AUC_{0-\infty}$ by 35% was observed with concomitant administration of isavuconazole). Caution is therefore recommended when administering these drugs concomitantly with CellCept.

Telmisartan
Concomitant administration of telmisartan and CellCept resulted in an approximately 30% decrease of mycophenolic acid (MPA) concentrations. Telmisartan changes MPA's elimination by enhancing

PPAR gamma (peroxisome proliferator-activated receptor gamma) expression which in turn results in an enhanced UGT1A9 expression and activity.

Sirolimus
A study in 36 renal transplant patients demonstrated that concomitant administration of CellCept (1 g twice daily) and sirolimus resulted in the mean (± SD) AUC_{0-12h} of MPA after 14 days and 3 months were 81 ± 36 and 71 ± 26 µg.h/mL.g respectively. Another study using 45 renal transplant patients demonstrated that a significant proportion of patients (10 of 30) who received the combination of sirolimus and CellCept were withdrawn with symptoms consistent with MPA or sirolimus toxicity.

Monitoring of MPA levels should be performed in renal graft recipients co-treated with sirolimus because of the risk of overexposure to this immunosuppressive agent.

Ganciclovir
Following single dose administration in stable renal transplant patients, no pharmacokinetic interaction was observed between MMF (1.5 g) and IV ganciclovir (5 mg/kg). However, as MPAG plasma and ganciclovir concentrations are increased in the presence of renal impairment, the potential exists for the two medicines to compete for tubular secretion, and thus further increases in concentrations of both medicines may occur. In patients with renal impairment in which MMF and ganciclovir or its prodrugs (e.g. valganciclovir) are co-administered, patients should be carefully monitored. However, with MPA no substantial alteration of MPA pharmacokinetics is anticipated and dose adjustment of MMF is not required.

Iron
In a study involving 16 healthy volunteers, no clinically relevant interaction was found between CellCept and iron supplements when administered in a fasting state. In the same study, a 15% reduction in MPA AUC was observed when CellCept and iron were administered simultaneously with food. In an earlier study involving 7 healthy volunteers, a significant reduction in MPA AUC was observed when CellCept and iron were administered in a fasting state. To avoid any possible interactions, iron supplements should be administered at least 3 hours following CellCept.

Live Vaccines
Live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished.

Oral Contraceptives
A study of co-administration of CellCept (1 g twice daily) and combined oral contraceptives containing ethinylestradiol (0.02 - 0.04 mg) and levonorgestrel (0.05 - 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 - 0.1 mg) conducted in 18 women with psoriasis over 3 menstrual cycles showed no clinically relevant influence of CellCept on serum levels of progesterone, LH and FSH, thus indicating no influence of CellCept on the ovulation-suppressing action of the oral contraceptives. The pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by coadministration of CellCept (see section 4.6 Fertility, pregnancy and lactation, Use in Pregnancy).

Proton Pump Inhibitors (PPIs)
Decreased MPA exposure has been observed when PPIs, including lansoprazole and pantoprazole, were administered with CellCept. The clinical impact of reduced MPA exposure on organ rejection has not been established in transplant patients receiving PPIs and CellCept. Because clinical relevance has not been established, PPIs should be used with caution when co-administered to transplant patients being treated with CellCept.

Rifampicin
After correction for dose, a 70% decrease in MPA exposure (AUC_{0-12h}) has been observed with concomitant rifampicin administration in a single heart-lung transplant patient. It is therefore recommended to monitor MPA exposure levels and to adjust CellCept doses accordingly to maintain clinical efficacy when the drugs are administered concomitantly.

Tacrolimus
The AUC and C_{max} of MPA, the active metabolite of CellCept, were not significantly affected by co-administration with tacrolimus, in stable hepatic transplant patients initiated on CellCept and tacrolimus. In contrast, there was an increase of approximately 20% in tacrolimus AUC when multiple doses of CellCept (1.5g twice daily) were administered to patients taking tacrolimus.

However, in renal transplant patients, tacrolimus concentration did not appear to be altered by CellCept.

Sevelamer and Other Calcium-Free Phosphate Binders
Concomitant administration of sevelamer and CellCept in adults and paediatric patients decreased the C_{max} and AUC_{0-12} of MPA by 30% and 25% respectively. There are no data on CellCept with phosphate binders other than sevelamer. This data suggest that sevelamer and other calcium-free phosphate binders should preferentially be given two hours after CellCept intake to minimise impact on the absorption of MPA.

Other Interactions
The measured value for renal clearance of MPAG indicates removal occurs by renal tubular secretion as well as glomerular filtration. Consistent with this, co-administration of probenecid, a known inhibitor of tubular secretion, with MMF in monkeys raises plasma AUC of MPAG by 3-fold. Thus, other medicines known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility
MMF had no effect on fertility of male rats at oral doses up to 20 mg/kg/day or on female rats at oral doses up to 4.5mg/kg/day (0.8 and 0.1 times the expected maximum clinical dose based on AUC values respectively). A female fertility and reproduction study conducted in rats caused malformations (see Use in Pregnancy below). Malformations (including anophthalmia, agnathia, and hydrocephaly) occurred in the first generation offspring of female rats treated with oral doses of mycophenolate mofetil in the absence of maternal toxicity. No effect was seen on the fertility of male rats treated with mycophenolate mofetil.

Use in Pregnancy - Category D
CellCept is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraceptive methods due to its mutagenic and teratogenic potential. (see section 4.3 Contraindications). CellCept is a human teratogen with an increased risk of spontaneous abortions (mainly in the first trimester) and congenital malformations in case of maternal exposure during pregnancy (see section 4.8 Adverse effects (Undesirable effects)). In the medical literature, the risk of spontaneous abortions have been reported as 45% to 49% following mycophenolate mofetil exposure, compared to a reported rate between 12% and 33% in solid organ transplant patients treated with other immunosuppressants.

Congenital malformations (including multiple malformations in individual newborns) have been reported in 23% to 27% of live births in mycophenolate mofetil exposed pregnancies in published

literature. For comparison the risk of malformations is estimated at approximately 2% of live births in the overall population and at approximately 4% to 5 % in solid organ transplant patients treated with immunosuppressants other than mycophenolate mofetil.

Congenital malformations, including multiple malformations have been reported post-marketing in children of patients exposed to mycophenolate mofetil in combination with other immunosuppressants during pregnancy. The following malformations were most frequently reported:

- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;
- Abnormalities of the ear (e.g. abnormally formed or absent external/middle ear) and eye (e.g. coloboma, microphthalmos);
- Malformations of the fingers (e.g. polydactyly, syndactyly, brachydactyly);
- Cardiac abnormalities such as atrial and ventricular septal defects;
- Oesophageal malformations (e.g. oesophageal atresia);
- Nervous system malformations (such as spina bifida).

These findings were consistent with teratology studies performed in rats and rabbits where fetal resorptions and malformations occurred in absence of maternal toxicity.

Embryofoetal development studies were conducted with MMF in rats (0.6, 2, 6 mg/kg/day on gestation days 7-16, and 0.5, 1.5 and 4.5 mg/kg/day from prior to conception to weaning) and rabbits (10, 30, 90 mg/kg/day on gestation days 7-19). Foetal resorptions and malformations occurred in rats at doses of 4.5mg/kg/day or more (0.1 times the expected maximum human dose based on AUC values) and in rabbits at 90 mg/kg/day (0.1 times the expected maximum human dose based on AUC values), in the absence of maternal toxicity.

The observed malformations in rats or rabbits were highly predictive of human malformations. Animal malformations with reported human correlates can be broadly classified as facial defects (including cleft palate, agnathia), eye abnormalities (including anopthalmia, micropthalmia), cardiac malformations (including ectocardia), nervous system malformations (including hydrocephaly), abdominal and thoracic wall defects (including umbilical and diaphragmatic hernia), kidney and lung defects (including renal agenesis, ectopic kidney and lung hypoplasia), reproductive organ defects (cryptorchidism) and skeletal malformations. Additional animal malformations included spleen and adrenal gland defects (aplasia, dysplasia).

The no-effect levels for teratogenicity in rats and rabbits were 2 and 30 mg/kg/day, respectively. A peri and postnatal study in rats administered MMF 1, 3 or 10 mg/kg/day from gestation day 17 to weaning showed no adverse effects.

Before the start of treatment, female and male patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention, and planning.

Use in Lactation

Limited data show that MPA may be excreted in human breast milk. Due to the potential for serious adverse reactions in nursing infants, CellCept is contraindicated during breastfeeding (see section 4.3 Contraindications).

Pregnancy Testing

Prior to starting therapy with CellCept, female patients of childbearing potential must have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL; The second test should be performed 8-10 days after the first one and immediately before starting CellCept. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should they become pregnant.

Contraception

Females

Women of childbearing potential should use two reliable forms of contraception simultaneously, at least one of which must be highly effective, before beginning CellCept therapy, during therapy, and for 6 months following discontinuation of therapy, unless abstinence is the chosen method of contraception.

Males

Limited clinical evidence is currently available on paternal exposure to CellCept.

Non-clinical evidence shows that the dose of mycophenolate that could be transferred via the seminal fluid to a potentially pregnant partner is 30-fold lower than the concentration without teratogenic effects in rats, and 200-fold lower than the lowest teratogenic concentration in rats. Therefore, the risk of harm mediated via seminal fluid is considered negligible. However, genotoxic effects have been observed in animal studies at exposures exceeding the human therapeutic exposures by approximately 2.5-times. Thus, the risk of genotoxic effects on sperm cells cannot completely be excluded.

In absence of sufficient data to exclude a risk of harm to the fetus conceived during or directly after the treatment of the father, the following precautionary measure is recommended. Sexually active men are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomized men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. In addition, female partners of male patients are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of CellCept.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

CellCept may have a moderate influence on the ability to drive and use machines.
Patients should be advised to use caution when driving or using machines if they experience adverse drug reactions such as somnolence, confusion, dizziness, tremor or hypotension during treatment with CellCept (see 4.8 Adverse Effects (Undesirable Effects)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The adverse event profile associated with the use of immunosuppressive medicines is often difficult to establish owing to the presence of underlying disease and the concurrent use of many other medications. The principal adverse reactions associated with the administration of CellCept in combination with ciclosporin and steroids include diarrhoea, leucopenia, sepsis and vomiting, and there is evidence of a higher frequency of certain types of infections, such as tuberculosis and atypical mycobacterial infection. Uncommon but serious life-threatening infections such as meningitis and infectious endocarditis have been reported.

The incidence of adverse events for CellCept was determined in 3 randomised comparative double blind trials in prevention of rejection in renal transplant patients. However, due to the lower overall reporting of events in the placebo-controlled prevention of rejection study, these data were not combined with the other two active-controlled prevention trials, but are instead presented separately.

Patients in the double blind studies of the prevention of renal allograft rejection were treated for up to a minimum of 1 year, with approximately 53% of the patients having been treated for more than 1 year. The adverse events, reported as probably or possibly related to study medication at an incidence of greater than or equal to 3% of patients in either of the CellCept 2 g or 3 g treatment groups are presented below, for the two active-controlled studies combined, and for the one placebo-controlled study.

Table 1 - Adverse Events in Prevention of Renal Allograft Rejection

	Active - Controlled Studies			*Placebo - Controlled Study*		
	Azathioprine *1-2 mg/kg/day or 100-150 mg/day* (n = 326)	**CellCept *2 g/day* (n = 336)**	**CellCept *3 g/day* (n = 330)**	**Placebo (n = 166)**	**CellCept *2 g/day* (n = 165)**	**CellCept *3 g/day* (n = 160)**
Digestive System						
Diarrhoea	12.6%	17.9%	23.3%	9.6%	9.1%	13.1%
Constipation	11.0	12.2	7.9	1.2	3.0	1.3
Dyspepsia	8.9	10.4	7.3	1.8	1.2	0.6
Oral Moniliasis	11.0	9.8	12.1	6.6	6.1	3.1
Nausea	10.7	9.5	12.1	2.4	2.4	4.4
Nausea And Vomiting	7.7	6.0	5.2	1.2	0.6	0
Vomiting	4.6	5.1	4.8	1.2	1.2	1.9
Oesophagitis	2.1	4.2	4.8	0.6	0	0
Gastritis	0.6	4.2	3.0	1.2	1.2	2.5
Flatulence	3.4	3.9	1.8	0	1.8	0
Liver Function Tests Abnormal	2.5	3.0	2.1	6.0	3.0	3.1
Gastrointestinal Moniliasis	1.8	3.0	2.4	0	1.8	1.3
Gastroenteritis	0.3	1.5	1.8	1.8	2.4	4.4
Infection	0.6	0.9	3.3	1.2	1.8	2.5
Body as a Whole						
Abdominal Pain	9.2	13.4	12.1	7.2	6.7	5.6
Sepsis	11.7	12.5	12.7	13.3	21.8	17.5
Infection	6.1	4.5	6.1	12.7	12.7	15.0
Fever	2.8	4.5	4.2	1.8	2.4	3.1
Headache	4.0	3.9	2.7	0.6	0	0
Pain	2.1	3.6	1.8	1.8	0.6	0.6
Flu Syndrome	0.6	0.9	0.6	2.4	3.6	5.0
Asthenia	1.8	1.8	3.0	0.6	0	0
Urogenital System						
Urinary Tract Infection	10.7	13.4	11.5	37.3	45.5	44.4
Pyelonephritis	0.3	0.3	0.3	3.0	3.6	1.9
Haemic and Lymphatic System						
Leucopenia	22.1	19.0	31.2	3.0	9.7	11.9
Thrombocytopenia	9.5	6.0	4.8	3.0	4.2	2.5
Anaemia	3.4	6.0	4.8	0.6	1.2	2.5
Leucocytosis	2.5	2.1	3.6	0	0	0.6

	Active - Controlled Studies			*Placebo - Controlled Study*		
	Azathioprine *1-2 mg/kg/day or 100-150 mg/day* (n = 326)	**CellCept *2 g/day* (n = 336)**	**CellCept *3 g/day* (n = 330)**	**Placebo (n = 166)**	**CellCept *2 g/day* (n = 165)**	**CellCept *3 g/day* (n = 160)**
Respiratory System						
Infection	3.1	3.6	4.5	7.8	13.9	11.9
Pneumonia	1.2	2.1	1.5	10.8	3.6	10.6
Bronchitis	0.3	1.5	0.6	8.4	8.5	11.3
Pharyngitis	0.9	0.9	2.7	4.2	2.4	3.1
Metabolic and Nutritional Disorders						
Lactic Dehydrogenase Increased	4.9	5.1	5.2	0	0	0
Hypophosphataemia	4.3	5.4	5.2	0	0	0
SGPT Increased	2.8	3.9	3.0	1.2	1.2	1.9
Alkaline Phosphatase Increased	1.8	4.2	2.7	0.6	0	1.9
Hyperlipidaemia	3.1	3.3	3.0	0	0.6	0
SGOT Increased	1.5	2.7	3.3	0	0	0
Creatinine Increased	0.9	0.3	0.6	1.2	1.8	3.1

Patients in a double blind study of the prevention of cardiac allograft rejection were treated for up to a minimum of 1 year. The adverse events, reported as probably or possibly related to study medication at an incidence of greater than or equal to 3% of patients in either of the CellCept 3 g or azathioprine treatment groups are presented below (Table 2).

Table 2 - Adverse Events in Prevention of Cardiac Allograft Rejection with an Incidence of ≥ 3% in Either Treatment Arm

	Active - Controlled Cardiac Study	
	CellCept *3 g/day* (n = 289)	**Azathioprine *1.5-3.0 mg/kg/day* (n = 289)**
Digestive System		
Nausea	21.8	17.6
Diarrhoea	14.2	11.8
Oral Moniliasis	11.4	11.8
Vomiting	9.7	11.4
Dyspepsia	7.3	5.5
Constipation	5.5	6.6
Flatulence	3.1	5.5
Gastritis	5.2	2.8
Nausea And Vomiting	3.5	3.1
Anorexia	3.8	2.4
Liver Damage	3.1	3.1
Liver Function Tests Abnormal	3.1	2.1
Haemic and Lymphatic System		
Leucopenia	26.0	36.3
Anaemia	6.2	7.6

	Active - Controlled Cardiac Study	
	CellCept	**Azathioprine**
	3 g/day	***1.5-3.0 mg/kg/day***
	(n = 289)	**(n = 289)**
Thrombocytopenia	3.5	6.6
Body as a Whole		
Sepsis	9.7	10.0
Headache	7.3	9.0
Abdominal Pain	7.6	7.3
Infection	8.7	5.9
Fever	1.0	3.1
Metabolic and Nutritional Disorders		
Bilirubinaemia	6.2	7.3
SGPT Increased	3.8	4.2
SGOT Increased	2.4	4.2
Alkaline Phosphatase Increased	2.4	3.8
Lactic Dehydrogenase Increased	2.8	3.5
Respiratory System		
Infection	2.4	4.2
Pneumonia	1.7	3.1
Nervous System		
Insomnia	3.1	2.1
Urogenital System		
Urinary Tract Infection	4.2	4.5

Patients in a double blind study of the prevention of hepatic allograft rejection were followed for up to a minimum of 1 year. The adverse events reported as probably or possibly related to study medication at an incidence of greater than or equal to 3% of patients in either of the CellCept 3 g or azathioprine treatment groups are presented below (Table 3).

Table 3 - Adverse Events in Prevention of Hepatic Allograft Rejection with an Incidence of ≥ 3% in Either Treatment Arm

	Active - Controlled Hepatic Study	
	CellCept	**Azathioprine**
	3 g/day	***1-2 mg/kg/day***
	(n = 277)	**(n = 287)**
Digestive System		
Diarrhoea	28.2	25.4
Nausea	26.7	19.9
Vomiting	11.9	12.2
Oral Moniliasis	9.4	9.8
Dyspepsia	6.5	10.1
Hepatitis	4.7	8.0
Anorexia	7.9	4.5
Constipation	5.4	4.5
Flatulence	5.4	3.1
Liver Function Tests Abnormal	4.0	3.1
Gastrointestinal moniliasis	2.5	4.2
Infection	3.2	2.8
Melaena	3.2	2.8

	Active - Controlled Hepatic Study	
	CellCept ***3 g/day*** **(n = 277)**	**Azathioprine** ***1-2 mg/kg/day*** **(n = 287)**
Haemic and Lymphatic System		
Leucopenia	42.2	35.2
Anaemia	12.6	19.9
Thrombocytopenia	14.4	16.0
Hypochromic Anaemia	6.1	4.2
Leucocytosis	4.3	4.9
Body as a Whole		
Sepsis	18.8	20.2
Abdominal Pain	15.9	11.5
Fever	8.7	9.4
Infection	7.9	9.4
Headache	7.6	7.3
Peritonitis	3.2	4.9
Abdomen Enlarged	4.0	3.5
Asthenia	2.2	3.1
Respiratory System		
Infection	4.0	6.6
Respiratory Moniliasis	4.3	5.6
Pneumonia	4.7	2.4
Nervous System		
Insomnia	5.1	4.5
Tremor	3.6	2.1
Urogenital System		
Urinary Tract Infection	7.6	9.4
Cardiovascular System		
Hypertension	6.5	2.8
Skin and Appendages		
Herpes Simplex	9.4	5.6
Herpes Zoster	4.0	4.9

The following adverse events, considered by the investigator to be possibly or probably related to drug treatment and not mentioned in any of the tables above or in text pertaining to infections or malignancy following, were reported with an incidence of less than 3% in one or more of the CellCept 2 g or 3 g (renal) active-controlled cohorts (n = 336, n = 330), the CellCept 2 g or 3 g (renal) placebo-controlled cohorts (n = 165, n = 160), less than 1.4% in the CellCept 3 g (cardiac) active-controlled cohort (n = 289), or less than 1.4 % in the CellCept 3 g (hepatic) active-controlled cohort study (n = 277).

Digestive System*:* colitis (sometimes caused by cytomegalovirus), ileus, duodenal ulcer, rectal disorder, stomach ulcer, duodenitis, gastrointestinal haemorrhage, mouth ulceration, dysphagia, peptic ulcer, cholecystitis, gastrointestinal disorder, ulcerative stomatitis, cheilitis, large intestine perforation, periodontal abscess, haemorrhagic gastritis, gum hyperplasia, stomatitis, eructation, haemorrhagic pancreatitis, intestinal necrosis, intestinal perforation, intestinal ulcer, gingivitis, glossitis, oesophageal ulcer, pancreatitis, apthous stomatitis, enteritis, faecal impaction, stomach atony, haematemesis, duodenal ulcer haemorrhage, proctitis, rectal haemorrhage, gastrointestinal carcinoma, faecal

incontinence, pancreas disorder, stomach ulcer haemorrhage, cholangitis, hepatic failure, perforated peptic ulcer, ulcerative colitis.

Body as a Whole: back pain, ciclosporin level increased, chest pain, reaction unevaluable, accidental injury, abscess, lab test abnormal, cyst, neoplasm, chills, face oedema, malaise, substernal chest pain, carcinoma, moniliasis, chills and fever, sarcoma, adenoma, granuloma, lack of drug effect, syncope, pelvis pain, pain, oedema, drug level increased, drug level decreased, injection site reaction, injection site inflammation, injection site hypersensitivity.

Urogenital System: dysuria, cystitis, haematuria, infection, oliguria, urinary frequency, pyuria, kidney abscess, abnormal kidney function, urethritis, urogenital carcinoma, kidney pain, nephritis, urethral pain, urinary urgency, urinary tract disorder, hydronephrosis, epididymitis, kidney tubular necrosis, urogenital occlusion, bladder neoplasm, urinary incontinence, vaginal moniliasis, kidney failure, urine abnormality.

Reproductive System: vaginal moniliasis, metrorrhagia, prostatic disorder, amenorrhoea, balanitis, cervix disorder, endometrial carcinoma, vaginal haemorrhage, impotence, breast pain, gynaecomastia, penis disorder.

Skin and Appendages: alopecia, fungal dermatitis, skin benign neoplasm, rash, acne, cutaneous moniliasis, pruritus, infection, urticaria, cellulitis, sweating, haemorrhage (skin and appendages), vesiculobullous rash, skin disorder, skin hypertrophy, skin ulcer, furunculosis, injection site inflammation, maculopapular rash, petechial rash, seborrhoea, skin carcinoma, skin discolouration.

Haemic and Lymphatic System: pancytopenia, polycythemia, thrombocythemia, agranulocytosis, lymphoma like reaction, decreased immunoglobulins, ecchymosis, thrombotic thrombocytopenic purpura, epistaxis, haemorrhage, petechia, abnormal WBC, blood dyscrasia, haemolytic anaemia, lymphadenopathy, hepatitis B serum antigen positive, reticuloendothelial hyperplasia, marrow hyperplasia, coagulation disorder, haemolysis.

Respiratory System: sinusitis, cough increased, dyspnoea, rhinitis, respiratory abscess, interstitial pneumonia, lung carcinoma, lung disorder, asthma, laryngismus, laryngitis, pneumothorax, hypoxia, atelectasis, lung oedema, lung fibrosis, pleural effusion, pleural disorder.

Metabolic and Nutritional Disorders: gamma glutamyl transpeptidase increased, hypercholesterolaemia, hypokalaemia, acidosis, increased creatinine, bilirubinaemia, peripheral oedema, increased amylase, healing abnormal, hypocalcaemia, hyperglycaemia, albuminuria, weight loss, BUN increased, dehydration, decreased gamma globulin, hypercalcaemia, hypervolaemia, hypoproteinaemia, uremia, hyperkalaemia, hyperchloraemia, enzymatic abnormality, hypomagnesaemia, increased creatine phosphokinase, hyperuricaemia, hyponatraemia, diabetes mellitus, gout, respiratory acidosis, oedema, hypoglycaemia, cachexia, hyperphosphataemia.

Liver and Biliary System: liver damage, cholestatic jaundice, cholelithiasis.

Cardiovascular System: pulmonary embolus, thrombosis, palpitation, angina pectoris, vasodilatation, arterial thrombosis, cerebrovascular accident, phlebitis, atrial fibrillation, supraventricular tachycardia, cyanosis, cerebral ischaemia, hypotension, peripheral gangrene, tachycardia, arrhythmia, heart arrest, occlusion, shock, gangrene, deep thrombophlebitis, myocardial infarct, cardiomegaly, ventricular extrasystoles, ventricular tachycardia, cerebral ischaemia, myocarditis, endocarditis, heart failure, pulmonary hypertension, cardiomyopathy, electrocardiogram abnormal, pericardial effusion.

Central and Peripheral Nervous System: hypertonia, dizziness, anxiety, vocal cord paralysis, neuropathy, paraesthesia, convulsion, depression, confusion, amnesia, depersonalisation, encephalitis, psychosis, agitation, hallucinations, aphasia, delirium, encephalopathy, hyperaesthesia, nystagmus, speech disorder, thinking abnormal, vertigo, apathy, catatonic reaction, CNS neoplasia, delusions,

hemiplegia, hostility, hypokinesia, opisthotonos, paranoid reaction, personality disorder, somnolence, hypesthesia, emotional lability, hyperkinesia, manic reaction.

Special Senses: otitis media, infection, conjunctivitis, eye haemorrhage, blepharitis, ear pain, visual disturbance, lacrimation disorder, corneal ulcer, deafness, diplopia, retinal disorder, taste loss, keratitis, retinitis, ear disorder, vestibular disorder, eye disorder, taste perversion, tinnitus, otitis externa, amblyopia, abnormal vision, eye pain, photophobia.

Musculo-Skeletal System: arthralgia, bone pain, leg cramps, myalgia, bone necrosis, joint disorder, myasthenia, myopathy, osteoporosis.

Endocrine: sialadenitis, hormone level altered, hypothyroidism.

Up to 0.5% (regardless of investigator assessment of causality) of patients receiving CellCept 2 g for prevention of renal allograft rejection developed severe neutropenia (absolute neutrophil count (ANC) < 5 x 10^8/L). Up to 2.8% (regardless of investigator assessment of causality) of cardiac transplant patients receiving CellCept 3 g and up to 3.6% (regardless of investigator assessment of causality) of patients receiving CellCept 3 g in hepatic transplantation developed severe neutropenia.

Cytomegalovirus (CMV) tissue invasive disease was more common in renal transplant patients receiving CellCept 3 g/day (8 - 12%) than in those receiving CellCept 2 g/day (4 - 8%) or control therapy (2 - 6%) in the three controlled studies for prevention of renal allograft rejection (percentage incidences have been determined regardless of investigator assessment of causality). In the placebo-controlled renal study, there was an increased incidence of *Herpes simplex* and *Herpes zoster* infections in patients receiving CellCept compared to placebo. In addition, the incidence of overall infection with Candida and CMV viraemia/syndrome were similar in the three treatment groups. The following table shows the incidence of select opportunistic infections in the prevention of rejection trials:

Table 4 - Viral and Fungal Infections in Controlled Studies in Prevention of Renal, Cardiac or Hepatic Transplant Rejection

	Renal Studies			**Cardiac Study**		**Hepatic Study**	
	CellCept 2 g/day	**CellCept** 3 g/day	**Azathioprine** 1-2 mg/kg^{-1}/day^{-1} or 100-150 mg/day	**CellCept** 3 g/day	**Azathioprine** 1.5-3 mg/kg^{-1}/day^{-1}	**CellCept** 3 g/day	**Azathioprine** 1-2 mg/kg^{-1}/day^{-1}
	(n = 336) %	**(n = 330)** %	**(n = 326)** %	**(n = 289)** %	**(n = 289)** %	**(n = 277)** %	**(n = 287)** %
Herpes simplex	16.7	20.0	19.0	20.8	14.5	10.1	5.9
CMV							
Viraemia/ syndrome	13.4	12.4	13.8	12.1	10.0	14.1	12.2
Tissue invasive disease	8.3	11.5	6.1	11.4	8.7	5.8	8.0
Herpes zoster	6.0	7.6	5.8	10.7	5.9	4.3	4.9
Cutaneous disease	6.0	7.3	5.5	10.0	5.5	4.3	4.9
Candida	17.0	17.3	18.1	18.7	17.6	22.4	24.4

	Renal Studies			Cardiac Study		Hepatic Study	
	CellCept 2 g/day	**CellCept** 3 g/day	**Azathioprine** 1-2 $mg/kg^{-1}/day^{-1}$ or 100-150 mg/day	**CellCept** 3 g/day	**Azathioprine** 1.5-3 $mg/kg^{-1}/day^{-1}$	**CellCept** 3 g/day	**Azathioprine** 1-2 $mg/kg^{-1}/day^{-1}$
	(n = 336)	**(n = 330)**	**(n = 326)**	**(n = 289)**	**(n = 289)**	**(n = 277)**	**(n = 287)**
Mucocutaneous	15.5	16.4	15.3	18.0	17.3	18.4	17.4

The following other opportunistic infections occurred with an incidence of less than 4% in CellCept patients in the above azathioprine-controlled studies: Herpes zoster, visceral disease; Candida, urinary tract infection, fungemia/ disseminated disease, tissue invasive disease; Cryptococcosis; Aspergillus/Mucor; Pneumocystis carinii.

In the placebo-controlled renal transplant study, the same pattern of opportunistic infection was observed compared to the azathioprine-controlled renal study, with a notably lower incidence of Herpes simplex and CMV tissue-invasive disease.

In the three controlled studies for prevention of rejection in renal transplantation, similar rates of fatal infections/sepsis (< 2%) have occurred in patients receiving CellCept or control therapy in combination with other immunosuppressive agents. In the controlled cardiac transplant study, fatal infections occurred in 2.4% of patients receiving CellCept 3 g compared to 4.5% of patients receiving azathioprine, both in combination with other immunosuppressive agents. In the controlled hepatic transplant study, fatal infection/sepsis occurred in 5.4% of patients receiving CellCept 3 g compared to 7.3% receiving azathioprine, both in combination with other immunosuppressive agents.

As with other patients receiving immunosuppressive regimes involving combinations of drugs, patients receiving CellCept as part of an immunosuppressive regime are at an increased risk of developing lymphomas and other malignancies, particularly of the skin. Within 3 years post-transplant, lymphoproliferative disease or lymphoma developed in patients receiving CellCept in immunosuppressive regimes in 0.6% of patients receiving 2 g daily in the controlled studies of prevention of renal rejection compared to placebo (0%) and azathioprine groups (0.6%).

The incidence of malignancies among the 1 483 patients enrolled in controlled trials for the prevention of renal allograft rejection was low, and similar to the incidence reported in the literature for renal allograft recipients. There was a slight increase in the incidence of lymphoproliferative disease in the MMF treatment groups compared to the placebo and azathioprine groups. Table 5 summarises the incidence of malignancies observed in the prevention of rejection trials.

Table 5 - Malignancies Observed in Prevention of Renal, Cardiac and Hepatic Rejection Trials No. of patients (%) with one or more malignancies (Regardless of Investigator Assessment of Causality)

	Renal Studies				**Cardiac Study**		**Hepatic Study**	
	Placebo	**Azathio-prine** ***1-2 mg/kg/day or 100-150 mg/day***	**CellCept** ***2 g/day***	**CellCept** ***3 g/day***	**Azathio-prine** ***1.5-3 mg/kg/day***	**CellCept** ***3 g/day***	**Azathio-prine** 1-2 mg/kg/day	**CellCept** ***3 g/day***
	(n=166)	**(n=326)**	**(n=501)**	**(n=490)**	**(n=289)**	**(n=289)**	**(n=287)**	**(n=277)**
Lymphoma/ lympho-proliferative disease	0	0.3	0.6	1.0	2.1	0.7	0	0.4
Non-melanoma skin carcinoma	0	2.4	4.0	1.6	2.8	4.2	2.1	2.2
Other malignancy	1.8	1.8	0.8	1.4	2.1	2.1	2.4	0.7

Three year safety data in renal and cardiac transplant patients indicated that the overall incidence of malignancy was comparable between CellCept and azathioprine groups. Hepatic transplant patients were followed for at least 1 year but less than 3 years.

Adverse Events Profile for Intravenous Administration

The adverse event profile of CellCept administered intravenously was determined from a single, double blind, controlled comparative study of the safety of CellCept 2 g/day administered intravenously or orally in the immediate post-transplant period (administered for the first 5 days). The potential venous irritation of CellCept administered intravenously was evaluated by comparing the adverse events attributable to a peripheral venous infusion of CellCept with those observed in the IV placebo group; patients in the latter group received active medication by the oral route.

Adverse events attributable to peripheral venous infusion were phlebitis and thrombosis, both observed at 4% in patients treated with CellCept intravenously.

In the active controlled study in hepatic transplant patients, 2 g daily of CellCept intravenous were administered in the immediate post-transplant period (up to 14 days). The safety profile of intravenous CellCept was similar to that of intravenous azathioprine.

Paediatric Adverse Events

The type and frequency of adverse drug reactions in a clinical study of 100 paediatric patients 3 months to 18 years of age given 600 mg/m^2 MMF orally twice daily were generally similar to those observed in adult patients given 1 g CellCept twice daily with the exception that paediatric patients had a higher proportion of diarrhoea, anaemia, sepsis and leucopenia.

Post-Marketing Experience

Infections: *uncommon:* Serious life threatening infections such as meningitis, Protozoal infections and infectious endocarditis have been reported occasionally and there is evidence of a higher frequency of certain types of serious infections such as tuberculosis and atypical mycobacterial infections.

Cases of Progressive Multifocal Leukoencephalopathy (PML), sometimes fatal, have been reported in CellCept treated patients. The reported cases generally had risk factors for PML, including concomitant immunosuppressant therapies and impaired immune function.

BK virus-associated nephropathy has been observed in patients treated with CellCept. This infection can be associated with serious outcomes, sometimes leading to renal graft loss.

Neoplasm benign, malignant and unspecified (including cysts and polyps): Lymphoma, lymphoproliferative disorder.

Gastrointestinal: *uncommon:* pancreatitis, isolated cases of intestinal villous atrophy, colitis (sometimes caused by cytomegalovirus).

Congenital Disorders: congenital malformations have been reported post marketing in children of patients exposed to CellCept in combination with other immunosuppressants during pregnancy (see section 4.6 Fertility, pregnancy and lactation).

Pregnancy, Puerperium and Perinatal Conditions: Cases of spontaneous abortions mainly in the first trimester in patients exposed to mycophenolate mofetil have been reported (see section 4.6 Fertility, pregnancy and lactation).

Blood and Immune System: Cases of pure red cell aplasia (PRCA) and hypogammaglobulinemia have been reported in patients treated with CellCept in combination with other immunosuppressive agents. Serious hypersensitivity reactions including anaphylactic reactions have been reported in CellCept treated patients.

Respiratory, thoracic and mediastinal disorders: Bronchiectasis, interstitial lung disease, pulmonary fibrosis.

Vascular disorders: Lymphocele.

General disorders and administration site conditions: De novo purine synthesis inhibitors-associated acute inflammatory syndrome is a newly described paradoxical pro-inflammatory reaction associated with mycophenolate and other purine synthesis inhibitors, characterized by fever, arthralgias, arthritis, muscle pain and elevated inflammatory markers. Anecdotal literature reports showed rapid improvements following discontinuation of the drug.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Reports of overdoses with MMF have been received from clinical trials and during post-marketing experience. In many of these cases no adverse events were reported. In those overdose cases in which adverse events were reported, the events fall within the known safety profile of the drug. However, isolated serious adverse events including a fatal case were observed during post-marketing experience.

It is expected that an overdose of MMF could possibly result in over-suppression of the immune system and increase susceptibility to infections and bone marrow suppression (see section 4.4 Special warnings and precautions for use). If neutropenia develops, dosing with CellCept should be interrupted or the dose reduced (see section 4.4 Special warnings and precautions for use).

MPA cannot be removed by haemodialysis. However, at high MPAG plasma concentrations (> 100 μg/mL), small amounts of MPAG are removed. Bile acid sequestrants, such as cholestyramine, can remove MPA by increasing excretion of the drug (see section 5.2 Pharmacokinetic properties).

Treatment of overdosage should consist of general supportive measures.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia) or the National Poisons Centre on 0800 POISON (0800 764766) (New Zealand).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: immunosuppressive agents. ATC code L04AA06

Mechanism of Action

Mycophenolic acid (MPA) is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) which inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Based on Chinese hamster inosine-5'-monophosphate dehydrongenase (IMPDH) in complex with inosine-5'-monophosphate (IMP) and mycophenolic acid (MPA), the mechanism by which MPA inhibits the enzymic activity of IMPDH (human type II) appears to be related to the ability of MPA to structurally mimic both the nicotinamide adenine dinucleotide cofactor and a catalytic water molecule. This prevents the oxidation of IMP to xanthos-5'-monophosphate, the committed step in the de novo guanosine nucleotide biosynthesis. Human type II and Chinese hamster IMPDH differ by six amino acids but have similar enzymatic characteristics. MPA has more potent cytostatic effects on lymphocytes than on other cells because T- and B-lymphocytes are dependent for their proliferation on de novo synthesis of purines, whereas other cell types can utilise salvage pathways. Depletion of guanosine nucleotides leads to the inhibition of glycosylation of adhesion molecules on lymphocytes, a process also considered an action of mycophenolate mofetil.

Mycophenolate mofetil (MMF) has been demonstrated in experimental animal models to prolong the survival of allogeneic transplants (kidney, heart, liver, intestine, limb, small bowel, pancreatic islets, and bone marrow). MMF has also been shown to reverse ongoing acute rejection in the canine renal and rat cardiac allograft models. Mycophenolate mofetil also inhibited proliferative arteriopathy in experimental models of aortic and heart allografts in rats, as well as in primate cardiac xenografts. MMF was used alone or in combination with other immunosuppressive agents in these studies.

In experimental animals, MMF has been demonstrated to prevent inflammatory responses that are immunologically mediated, and to delay tumour development and prolong survival in models of xenogeneic human to mouse and syngeneic murine tumours in vivo.

MMF, the 2-morpholinoethyl ester of MPA is rapidly absorbed following oral administration and hydrolysed to form free MPA, which is the active metabolite. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation.

Addition of guanosine or deoxyguanosine reverses the cytostatic effects of MPA on lymphocytes, showing the specificity of action of the drug. MPA also suppresses antibody formation by B-lymphocytes. By depletion of guanosine nucleotides, MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells. By this mechanism, MPA may inhibit recruitment of leucocytes into sites of inflammation and graft rejection.

MMF did not inhibit early events in the activation of human peripheral blood mononuclear cells such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but did block the coupling of these events to DNA synthesis and proliferation.

Animal studies have shown that mortality in rats with Pneumocystis carinii pneumonia is higher during combined treatment with MMF and trimethoprim/sulfamethoxazole than with either drug alone. MMF did not interfere with the ability of trimethoprim/sulfamethoxazole to reduce the incidence of P. carinii cysts in surviving animals, and reduced the incidence of cysts when administered by itself.

Clinical trials

Prevention of Acute Renal Rejection Episodes

The safety and efficacy of CellCept as adjunctive therapy for the prevention of organ rejection following allogeneic renal transplants were assessed in three randomised, double-blind, multicentre trials.

These studies compared two dose levels of CellCept (1 g twice daily and 1.5 twice daily) with azathioprine (2 studies) or placebo (1 study) when administered in combination with ciclosporin and corticosteroids to prevent acute rejection episodes. One study also included antithymocyte globulin (ATGAM®) induction therapy.

The primary efficacy endpoint was the proportion of patients in each treatment group who experienced biopsy-proven acute rejection or treatment failure (defined as early termination from the study for **any** reason without prior biopsy-proven rejection) within the first six months after transplantation. CellCept, when administered with ATGAM® induction (one study) and with ciclosporin and corticosteroids (all three studies) was shown to be superior to the following three therapeutic regimens: (1) ATGAM® induction / azathioprine / ciclosporin / corticosteroids, (2) azathioprine / ciclosporin / corticosteroids, and (3) ciclosporin / corticosteroids. The superior efficacy of CellCept as adjunctive therapy, when compared to azathioprine or placebo, was demonstrated by a reduction in the incidence of first biopsy-proven acute rejection episode or treatment failure within the first 6 months following transplantation. In addition, CellCept reduced the incidence of first biopsy-proven acute rejection episodes within the first six months after transplantation.

In Table 6 below, the percentages for first biopsy-proven rejection alone have not been adjusted for patients who terminated prematurely before experiencing a biopsy-proven rejection episode.

Table 6 - Incidence of Biopsy Proven-Rejection or Treatment Failure

Induction, Azathioprine-Controlled (n = 499 patients)	**Azathioprine 1-2 mg/kg/day (n = 166 patients)**	**CellCept 2 g/day (n = 167)**	**CellCept 3 g/day (n = 166)**
First biopsy-proven rejection episode or treatment failure	47.6%	31.1%	31.3%
First biopsy-proven rejection episode alone	38.0%	19.8%	17.5%

No Induction, Azathioprine-Controlled	**Azathioprine 100-150 mg/day (n = 166)**	**CellCept 2 g/day (n = 173)**	**CellCept 3 g/day (n = 164)**

(n = 503 patients)			
First biopsy-proven rejection episode or treatment failure	50.0%	38.2%	34.8%
First biopsy-proven rejection episode alone	35.5%	19.7%	15.9%

No Induction, Placebo-Controlled (n = 491 patients)	Placebo (n = 166)	CellCept 2 g/day (n = 165)	CellCept 3 g/day (n = 160)
First biopsy-proven rejection episode or treatment failure	56.0%	30.3%	38.8%
First biopsy-proven rejection episode alone	46.4%	17.0%	13.8%

In these three studies, the proportion of patients requiring antilymphocyte therapy for treatment of rejection during the first 6 months following transplantation was smaller among patients receiving CellCept 2 g per day (5.5 to 10.3%) or CellCept 3 g per day (3.1 to 5.4%) than among patients receiving azathioprine or placebo (15 to 21%).

Six and twelve-month patient survival and graft survival was somewhat higher in the patients receiving CellCept in comparison to either azathioprine or placebo. The cumulative proportions of patients who had died or lost their graft by 6 and 12 months' post-transplant were as follows:

Table 7 - Cumulative Incidence of Combined Graft Loss & Patient Death at 6 (12) Months

Study	Control (Azathioprine or Placebo)	CellCept 2 g/day	CellCept 3 g/day
Induction, Azathioprine-Controlled	10.4% (12.2%)	5.5% (8.5%)	8.5% (11.5%)
No Induction, Azathioprine-Controlled	11.7% (13.6%)	8.8% (11.7%)	6.7% (11.0%)
No Induction, Placebo-Controlled	10.2% (11.5%)	6.7% (8.5%)	8.8% (10.0%)

Treatment of Refractory Renal Rejection

The safety and efficacy of CellCept as adjunctive therapy for the treatment of refractory organ rejection following allogeneic renal transplants was assessed in one randomised, open-label, multicentre trial. This study was designed to evaluate whether CellCept at a dose of 1.5 g twice daily was superior to high dose IV steroids. In this study, all patients continued to receive concomitant maintenance oral corticosteroids and ciclosporin. The control group received IV methylprednisolone (5 mg/kg/day for 5 days followed by an oral course with tapered doses of corticosteroids); the control patients also generally received azathioprine. A total of 150 patients were enrolled (73 assigned to receive IV steroids; 77 assigned to receive CellCept). Patients enrolled in this study had recurrent or persistent

allograft rejection following treatment with either Orthoclone OKT3®, ATGAM®, or antilymphocyte globulin for at least 7 days, the last day of which occurred within 28 days prior to entry into the study. In addition, patients showed renal biopsy findings consistent with acute rejection at study entry. Serum creatinine concentrations were 442 μmol/L or lower at study entry.

The primary efficacy endpoint was graft and patient survival at 6 months post-enrolment. CellCept was shown to be clinically effective in this study as evidenced by a 45% reduction in the number of patients who died or lost their graft. By 6 months post-enrolment, 26% of the IV steroid group and 14.3% of the CellCept group had died or experienced graft loss. Eighteen patients (25%) receiving high dose IV steroids and 9 patients (12%) receiving CellCept lost their graft in the 6 months after enrolment. One patient (1.4%) receiving high dose IV steroids and 2 patients (2.6%) receiving CellCept died in the 6 months after enrolment. Fewer patients receiving CellCept (10.4%) required treatment with anti-lymphocyte preparations in the 6 months after enrolment, compared to those receiving high dose IV steroids (24.7%).

Prevention of Renal Rejection in Paediatrics

In a multicentre open-label, safety, tolerability and pharmacokinetic study of CellCept oral suspension 600 mg/m^2 twice daily (up to 1 g twice daily) in combination with ciclosporin and corticosteroids in the US, Europe and Australia, 100 patients aged 3 months to 18 years of age received treatment for the prevention of renal allograft rejection. The primary efficacy endpoint was the proportion of patients experiencing an acute rejection episode in the first 6 months post-transplant. Results were analysed after 1 year and it was shown that CellCept was well tolerated in paediatric patients (see section 4.8 Adverse effects (Undesirable effects)), and the pharmacokinetics profile was similar to that seen in adult patients dosed with 1 g twice daily CellCept capsules (see section 5.2 Pharmacokinetic properties, Special populations). The rate of biopsy-proven rejection was similar across the age groups (3 months to < 6 years, 6 to < 12 years, 12 to 18 years). The overall biopsy-proven rejection rate at 6 months and the combined incidence of graft loss (5%) and patient death (2%) at 12 months post-transplant were similar to the rates observed in adult renal transplant patients. Results out to 36 months post-transplant in children are currently under investigation.

Prevention of Cardiac Allograft Rejection

In a randomised, double-blind, parallel active-controlled multicentre study to compare the safety and efficacy of MMF 1.5 g twice daily with azathioprine 1.5 - 3 mg/kg/day, both in combination with ciclosporin and corticosteroids, 650 patients were randomised to the two arms. The primary endpoints investigated were (1) prevention of biopsy-proven acute rejection with haemodynamic compromise during the first six months following transplantation and (2) prevention of death or retransplantation during the first year following cardiac transplantation. 72 patients were withdrawn prior to administration and without knowledge of the assigned therapy primarily because of perioperative adverse events, inability to take oral medication or death. Therefore, 289 patients received study medication in each arm.

Patients in the CellCept arm had a lower incidence of death or retransplantation, however this difference was within the protocol-defined range of equivalence, being a ± 10% mortality difference.

CellCept and azathioprine did not differ significantly at 6 months in biopsy-proven acute rejection with haemodynamic compromise.

Table 8 - Survival, acute rejection and composite endpoints.

Parameter	Azathioprine n = 289 %	CellCept n = 289 %
Survival Endpoint		
Death or retransplantation at 12 months post-transplant	11	6
Composite Failures at 12 months		
Death, ejection fraction < 30%, coronary stenosis or myocardial infarction	14	8
Acute Rejection Endpoints		
Patients with Rejection at 6 months post-transplant		
1. Including haemodynamic compromise [(1)]		
- with haemodynamic compromise	35	32
- with severe haemodynamic compromise (cardiogenic) [(2) , (3)]	17	11
2. By ISHLT Grade		
- grade 1A or greater	97	95
- grade 2A or greater	69	65
- grade 3A or greater	53	45
3. Including pulse treatment of rejection		
- biopsy proven rejection		
treated with pulse immunosuppressives [(4)]	71	64
- biopsy proven or presumed rejection		
treated with pulse immunosuppressives [(4)]	74	66
treated with OKT3 or ATG	21	15

(1) Haemodynamic compromise defined as one or more of the following:
Pulmonary capillary wedge pressure ≥ 20 mm or 25% increase
Cardiac index < 2.0 or 25% decrease
Ejection fraction ≤ 30%
Pulmonary artery saturation ≤ 60% or 25% decrease
Presence of S_3 gallop
Fractional shortening ≤ 20 % or 25% decrease
(2) Severe defined as requirement for inotropic support to manage any one of the clinical conditions listed above.
(3) Amongst patients who reached this acute rejection endpoint, no CellCept-treated patients died during 12 months, versus 8 AZA recipients during 6 months and 12 AZA recipients who died during 12 months.
(4) Pulse immunosuppressives being corticosteroids and if required OKT3 by protocol-defined regimen (according to ISHLT biopsy grade and degree of haemodynamic compromise).

Prevention of Hepatic Allograft Rejection

The safety and efficacy of CellCept was assessed in a randomised, double-blind, parallel, active-controlled, multicentre study in hepatic transplant patients. This study compared the use of MMF 1 g twice daily intravenously for up to 14 days followed by 1.5 g twice daily orally against azathioprine 1 - 2 mg/kg/day intravenously followed by 1 - 2 mg/kg/day orally, both in combination with ciclosporin and corticosteroids. 565 patients were randomised into the two arms, 278 patients in the CellCept group and 287 patients in the azathioprine group.

The two primary endpoints investigated were (1) the proportion of patients who experienced, in the first 6 months post-transplantation, (a) one or more episodes of biopsy-proven and treated rejection or (b) death/retransplantation, and (2) the proportion of patients with graft loss (death/retransplantation) during the first 12 months post-transplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection and for the occurrence of graft loss (death/retransplantation) for 1 year.

In the primary analyses CellCept in combination with corticosteroids and ciclosporin was superior to azathioprine for prevention of acute rejection (p = 0.02) in the 6 months following transplant and equivalent to azathioprine for survival or graft loss in the 12 months following transplant.

Table 9 - Two primary endpoints investigated

	Azathioprine n =287 (%)	**CellCept n=278 (%)**	**Difference [95% CI]**
Biopsy-proven and treated rejection or death/retransplantation at 6 months	47.7	38.1	p=0.02
Death or retransplantation at 12 months	14.6	14.0	0.5(1) [-5.1, 6.0]

(1) Weighted point estimate of difference in proportions (azathioprine minus MMF). Met non inferiority criterion of a lower bound > - 10%.

The superiority of CellCept to azathioprine in the time to biopsy-proven and treated rejection or death/ retransplantation in the 6 months following transplant approached statistical significance (log-rank p = 0.06). The time to death/retransplantation in the 12 months following transplant was similar in the two treatment groups
(log-rank p = 0.86).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral and intravenous administration, MMF undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, mycophenolic acid (MPA). MMF is not measurable systemically in plasma following oral administration. Modest concentrations of the parent drug are detected in plasma samples during intravenous infusion, but concentrations decline rapidly after the completion of the infusion. The mean extent of absorption of MPA during multiple dosing (as measured by the area under the plasma-concentration time curve, AUC) increases in a dose proportionate manner over a daily dose range of 1 g to 4 g in renal transplant patients.

The administration of a 1.5 g dose of MMF by the intravenous (IV) and oral routes to healthy volunteers resulted in similar plasma MPA and inactive glucuronide of MPA (MPAG) total AUC values. Recovery of MPAG in urine was the same for both routes indicating complete absorption of oral MMF. The mean bioavailability of orally administered MMF, based on MPA AUC, was 94% relative to IV administration.

In a steady state study, the administration of 1 g twice daily of MMF by the IV and oral routes to renal transplant patients in the immediate post-transplant period, resulted in a MPA AUC that was approximately 29% higher for the IV formulation than achieved by the capsule. C_{max} was approximately 20% greater for IV.

The results of a single-dose bioequivalence study in 47 healthy volunteers indicated that the 500 mg tablet (x 2) was equivalent to the 250 mg capsule (x 4) with respect to the extent of absorption (AUC),

but not the rate of absorption (C_{max}). The C_{max} for MPA of the tablet was 28% lower than that for the capsule.

In a two-way, randomised, cross-over, bioequivalence study of MMF oral suspension and capsules, a 1 g dose of MMF suspension was bioequivalent to the 250 mg capsule (x 4) with respect to C_{max} , $t_{½}$, AUC_{last}, $AUC_{0-\infty}$ and K_{el}. T_{max} was marginally shorter for the oral suspension.

Food had no effect on the extent of absorption (MPA AUC) of MMF when administered as 1.5 g twice daily doses to renal transplant patients. However, the C_{max} for MPA was decreased by 40% in the presence of food.

The pharmacokinetic profile of MPA in cardiac patients is similar to that in renal patients.

Distribution

As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed approximately 6 to 12 hours post-dose. Co-administration of cholestyramine (4 g three times daily) with MMF is associated with a reduction in the AUC of MPA of approximately 40% as a result of decreased enterohepatic recirculation. The majority of the difference in the AUC is in the terminal portion of the MPA plasma concentration time profile.

At clinically relevant concentrations, MPA is 97% bound to plasma albumin.

Metabolism

MPA is metabolised principally by glucuronyl transferases (predominantly isoform UGT1A9) to form the pharmacologically inactive phenolic glucuronide of MPA (MPAG). *In vivo*, MPAG is converted back to free MPA via enterohepatic recirculation. A minor acylglucuronide (AcMPAG) is also formed. AcMPAG is pharmacologically active and is suspected to be responsible for some of MMF's side effects (diarrhoea, leucopenia).

Excretion

After oral administration, 93% of the dose was recovered from the urine and 6% from the faeces. The major metabolite of MMF excreted in urine is MPAG, which accounts for 87% of the oral MMF dose. Less than 1% of the dose was excreted as MPA in the urine. The following metabolites of the morpholino moiety are also recovered in the urine following oral administration of MMF: N-(2-carboxymethyl)-morpholine, N-(2-hydroxyethyl)-morpholine, and the N-oxide of N-(2-hydroxyethyl)-morpholine.

Mean ± SD apparent half-life and plasma clearance of MPA are 17.9 ± 6.5 hours and 193 ± 48 mL/min respectively following oral administration and 16.6 ± 5.8 hours and 177 ± 31 mL/min respectively following intravenous administration.

MPA's disposition depends on several transporters. Organic anion-transporting polypeptides (OATPs) and multidrug resistance-associated protein 2 (MRP2) are involved in MPA's disposition; OATP isoforms, MRP2 and breast cancer resistance protein (BCRP) are transporters associated with the glucuronides' biliary excretion. Multidrug resistance protein 1 (MDR1) is also able to transport MPA, but its contribution seems to be confined to the absorption process. In the kidney MPA and its metabolites inhibit renal organic anion transporters, with MPAG also being a substrate for OAT3.

Pharmacokinetics in Special Populations

Renal, Cardiac and Hepatic Transplant Patients

In renal, cardiac and hepatic transplant patients, mean steady state MPA AUC and C_{max} were up to 40% lower in the early post-transplant period (< 40 days post-transplant) compared to the late transplant period (3 - 6 months post-transplant).

In renal transplant patients, in the immediate post-transplant phase, mean steady state MPA AUC was 24% higher following 1 g twice daily intravenous MMF (over 2 hours) for 5 days compared with the same dose orally.

In cardiac transplant patients, administration of 1.5 g twice daily oral MMF resulted in mean steady state MPA AUC values similar to those found in renal transplant patients administered the same dose.

In hepatic transplant patients, administration of 1 g twice daily intravenous MMF followed by 1.5 g twice daily oral MMF resulted in mean steady state MPA AUC values similar to those found in renal transplant patients administered 1 g twice daily oral MMF.

Renal Impairment

In a single dose study (6 subjects per group), plasma MPA AUCs were up to 30% higher in subjects with mild to moderate renal impairment (GFR 25 - 80 mL/min/1.73m^2) and 75% higher in subjects with severe renal impairment (GFR < 25 mL/min/1.73m^2) than those subjects with normal renal function (GFR > 80 mL/min/1.73m^2). The mean increase in MPA AUC observed in subjects with severe renal impairment was comparable to the increase in MPA AUC seen when the dose of MMF is increased from a daily dose of 2 to 3 g (see section 4.2 Dose and method of administration). Multiple dosing of MMF in patients with severe chronic renal impairment has not been studied. In addition, the single dose plasma AUC of MPAG was 3 to 6 fold higher in subjects with severe renal impairment than in subjects with mild renal impairment or normal healthy subjects consistent with the known renal elimination of MPAG. No data are available on the safety of long-term exposure to this level of MPAG.

Delayed Renal Graft Function Post-Transplant

In patients with delayed renal graft function post-transplant, mean AUC_{0-12} of MPA was comparable to that seen in post-transplant patients without delayed graft function. However, mean plasma AUC_{0-12} of MPAG was 2- to 3-fold higher than post-transplant patients without delayed graft function. Also, with repeated dosing, plasma concentrations of MPAG accumulated, whereas accumulation of MPA occurred to a lesser degree, if at all. High plasma concentrations of MPAG may displace MPA from its protein binding sites resulting in a transient increase in the plasma concentration of free MPA in patients with delayed graft function.

No dose adjustment is recommended although close monitoring is advised.

Haemodialysis

The pharmacokinetics of MMF during haemodialysis are not altered. Haemodialysis does not remove MPA or MPAG. At high concentrations (> 100 μg/mL), haemodialysis removes only small amounts of MPAG.

Hepatic Impairment

In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation was relatively unaffected by hepatic parenchymal disease. Effects of hepatic disease on these processes probably depend on the particular disease. Hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.

Elderly Patients
Pharmacokinetics in the elderly have not been formally evaluated.

Paediatric Patients
The pharmacokinetic parameters of the MPA and MPAG were evaluated in 55 paediatric renal transplant patients aged 1 to 18 years given 600 mg/m^2 MMF orally twice daily (up to a maximum of 1 g twice daily). This dose achieved MPA AUC values similar to those seen in adult renal transplant patients receiving CellCept at a dose of 1 g twice daily in the early and late post-transplant period. MPA AUC levels across age groups were similar in the early post-transplant period out to 9 months post-transplant. There is limited pharmacokinetic data available for children aged less than 2 years.

Plasma-Binding
MPA, at clinically relevant concentrations, is 97% bound to plasma albumin. MPAG is 82% bound to plasma albumin at MPAG concentration ranges such as those normally seen in stable renal transplant patients; however at higher concentrations of MPAG which are seen in patients with delayed graft function or with severe renal insufficiency, the bound fraction *in vitro* decreases to 62%.

In vitro studies to evaluate the effect of several agents on the binding of MPA to human serum albumin (HSA) or plasma proteins showed that salicylate (at 250 μg/mL with HSA) and MPAG (at greater than or equal to 460 μg/mL with plasma proteins) increased the free fraction of MPA. At concentrations that exceeded what is encountered clinically, naproxen, digoxin, ciclosporin, theophylline, tacrolimus, tolbutamide, propranolol, warfarin, and prednisone did not increase the free fraction of MPA. MPA at concentrations as high as 100 μg/mL had little effect on the binding of warfarin, digoxin or propranolol but decreased the binding of theophylline from 53% to 45% and decreased the binding of phenytoin from 90% to 87%.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
MMF did not induce point mutations (Ames assay) or primary DNA damage (yeast mitotic gene conversion assay) in the presence or absence of metabolic activation. MMF did not cause chromosomal damage in vivo at oral doses up to 3000 mg/kg (mouse micronucleus aberration assay) or in vitro with or without metabolic activation at concentrations up to 5 μg/mL (Chinese hamster ovary cell [CHO] chromosomal aberration assay). Chromosome aberrations were present without metabolic activation in an initial CHO cell assay, but only at concentrations (249 to 300 μg/mL) that cause excessive cytotoxicity.

Carcinogenicity
A 104-week oral carcinogenicity study in mice with MMF at daily doses of 25, 75 or 180 mg/kg showed an increase above control levels in the incidence of lymphosarcomas in females at the highest two dose levels and in males at the highest dose level (1.1-1.9 times the expected maximum clinical dose based on AUC values). The incidence of lymphosarcomas in all mice remained within the range of that observed historically in this strain of mice. In a 104-week oral carcinogenicity study in rats, MMF in daily doses up to 15 mg/kg (0.6 times the expected maximum clinical dose based on AUC values) was not tumourigenic.

The incidence of lymphoma/lymphoproliferative disease and other malignancies is also increased in patients on immunosuppressive agents, and this appears to be related to the intensity or duration of immunosuppression rather than any specific immunosuppressant agent (see section 4.4 Special warnings and precautions for use).

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

CellCept 250 mg capsules

Pregelatinised maize starch
Croscarmellose sodium
Povidone
Magnesium stearate

Capsule shell
Gelatin
Sodium lauryl sulfate
Shellac
Potassium hydroxide
Silicon dioxide

Capsule shell dyes
Indigo carmine
Iron oxide red
Titanium dioxide
Iron oxide yellow
Iron oxide black

CellCept 500 mg tablets

Microcrystalline cellulose
Croscarmellose sodium
Povidone
Magnesium stearate
Talc
Opadry Lavender Y-5R-10272-A.

CellCept 500 mg powder for concentrate for solution for infusion

Polysorbate 80
Citric acid
Sodium chloride.

CellCept 1 g/5 ml powder for oral suspension

Sorbitol
Silicon dioxide
Sodium citrate
Soybean lecithin
Mixed fruit flavour
Xanthan gum
Aspartame
Methyl hydroxybenzoate
Citric acid anhydrous

6.2 INCOMPATIBILITIES

CellCept IV infusion solution should not be mixed or administered concurrently via the same catheter with other intravenous drugs or infusion admixtures.

CellCept IV is physically incompatible with the following infusion solutions: 0.9% Normal Saline, Ringer's and lactated Ringer's solutions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

CellCept 250 mg capsules should be stored below 25°C.

CellCept 500 mg tablets should be stored below 25°C and protected from moisture.

CellCept 500 mg powder for solution for infusion should be stored below 30°C. Reconstituted IV solution should be stored between 15 - 30°C for up to four hours.

CellCept oral suspension should be stored below 30ºC before reconstitution. The reconstituted oral suspension should be stored below 30ºC or may be refrigerated (2 - 8ºC) but should not be frozen. Discard any unused suspension 60 days after reconstitution.

6.5 NATURE AND CONTENTS OF CONTAINER

CellCept 250 mg capsules

Blister platforms of 10 (pack of 100)

CellCept 500 mg tablets

Blister platforms of 10 (pack of 100)

CellCept 500 mg powder for solution for infusion

20 mL clear glass vials with a grey rubber stopper and aluminium seals with plastic flip-off caps (pack of 4).

CellCept 1 g/5 ml powder for oral suspension.

Each bottle contains 35g mycophenolate mofetil in a 110 g powder for oral suspension, yielding 33 doses of 1 g/5 mL once reconstituted.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

CellCept oral administration

Mycophenolate mofetil has demonstrated teratogenic effects (see sections 4.4 Special warnings and precautions for use and 4.6 Fertility, Pregnancy and Lactation), therefore CellCept tablets and capsules should not be crushed or opened. Patients should also avoid inhalation or contact of the skin or mucous membranes with the powder contained in CellCept capsules and oral suspension (before and after reconstitution). If contact occurs, wash thoroughly with soap and water; should the eyes be affected, rinse eyes with plain water.

CellCept powder for oral suspension.

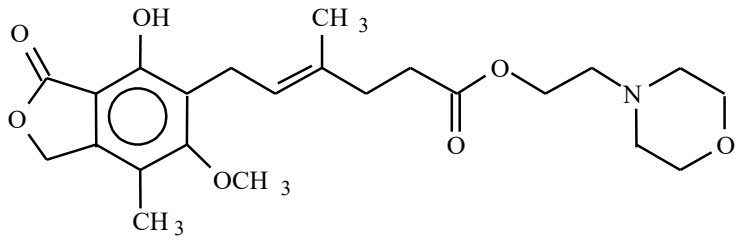
It is recommended that CellCept powder for suspension be reconstituted by the pharmacist prior to dispensing to the patient. Wearing disposable gloves is recommended during reconstitution and when wiping the outer surface of the bottle/cap and the table after reconstitution.

CellCept intravenous administration

Caution should be exercised in the handling and preparation of solutions of CellCept IV to avoid direct contact of prepared solution with skin or mucous membranes. If contact occurs, wash thoroughly with soap and water; should the eyes be affected, rinse eyes with plain water.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure



Mycophenolate mofetil is the 2-morpholinoethyl ester of mycophenolic acid. The chemical name for mycophenolate mofetil is 2-morpholinoethyl(*E*)-6-(1, 3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl) -4-methyl-4-hexenoate. It has an empirical formula of $C_{23}H_{31}NO_7$ and a molecular weight of 433.50.

Mycophenolate mofetil is a white to off-white crystalline powder. It is freely soluble in dimethyl sulfoxide, tetrahydrofuran, acetone, acetonitrile, dichloromethane, and ethyl acetate; soluble in methanol and propylene carbonate; sparingly soluble in anhydrous ethanol; slightly soluble in 2-propanol, diethyl ether, and very slightly soluble in hexane. It is practically insoluble in water (43 μg/mL at pH 7.4); the solubility increases in acidic medium (4.27 mg/mL at pH 3.6).

CAS number
115007-34-6

7. MEDICINE SCHEDULE (POISONS STANDARD)
Schedule 4 – Prescription Only Medicine

8. SPONSOR
Roche Products (New Zealand) Limited
PO Box 109113 Newmarket
Auckland 1149
NEW ZEALAND

Medical enquiries: 0800 276 243

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 – 34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

16 January 1997

10. DATE OF REVISION

21 September 2026

Summary table of changes

Section Changed	Summary of new information
4.4 and 4.6	Post-treatment contraception period for women of childbearing potential extended from 6 weeks to 6 months