

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CellCept 250 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg mycophenolate mofetil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules, hard (capsules)

Oblong, blue/brown, branded with black "CellCept 250" on the capsule cap and "Roche" on the capsule body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CellCept is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adult and paediatric (1 to 18 years of age) patients receiving allogeneic renal, cardiac or hepatic transplants.

4.2 Posology and method of administration

Treatment should be initiated and maintained by appropriately qualified transplant specialists.

Posology

Adults

Renal transplant

Treatment should be initiated within 72 hours following transplantation. The recommended dose in renal transplant patients is 1 g administered twice daily (2 g daily dose).

Cardiac transplant

Treatment should be initiated within 5 days following transplantation. The recommended dose in cardiac transplant patients is 1.5 g administered twice daily (3 g daily dose).

Hepatic transplant

Treatment of intravenous mycophenolate mofetil should be administered for the first 4 days following hepatic transplant, with oral mycophenolate mofetil initiated as soon after this as it can be tolerated. The recommended oral dose in hepatic transplant patients is 1.5 g administered twice daily (3 g daily dose).

Paediatric population (1 to 18 years)

The paediatric dosing information in this section applies to all oral formulations within the range of mycophenolate mofetil products, as appropriate. Different oral formulations should not be substituted without clinical supervision.

The recommended mycophenolate mofetil initial dose for paediatric renal, cardiac and hepatic transplant patients is 600 mg/m² (of body surface area (BSA)), administered orally, twice daily (initial total daily dose not to exceed 2 g, or 10 ml of the oral suspension).

The dose and product form should be individualised based on clinical assessment. If the recommended initial dose is well tolerated but does not achieve clinically adequate immunosuppression in paediatric cardiac and hepatic transplant patients, the dose can be increased to 900 mg/m² BSA twice daily (maximum total daily dose of 3 g, or 15 ml of the oral suspension). The recommended maintenance dose for paediatric renal transplant patients remains at 600 mg/m² twice daily (maximum total daily dose of 2 g or 10 ml of the oral suspension).

The mycophenolate mofetil powder for oral suspension should be used in those patients unable to swallow capsules and tablets and/or with a BSA lower than 1.25 m² due to the increased risk of choking. Patients with a BSA of 1.25 to 1.5 m² may be prescribed mycophenolate mofetil capsules at a dose of 750 mg twice daily (1.5 g daily dose). Patients with a BSA greater than 1.5 m² may be prescribed mycophenolate mofetil capsules or tablets at a dose of 1 g twice daily (2 g daily dose). As some adverse reactions occur with greater frequency in this age group (see section 4.8) compared with adults, temporary dose reduction or interruption may be required; these will need to take into account relevant clinical factors including severity of reaction.

Use in special populations

Elderly

The recommended dose of 1 g administered twice a day for renal transplant patients and 1.5 g twice a day for cardiac or hepatic transplant patients is appropriate for the elderly.

Renal impairment

In renal transplant patients with severe chronic renal impairment (glomerular filtration rate < 25 ml/min/1.73 m²), outside the immediate post-transplant period, doses greater than 1 g administered twice a day should be avoided. These patients should also be carefully observed. No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively (see section 5.2). No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Severe hepatic impairment

No dose adjustments are needed for renal transplant patients with severe hepatic parenchymal disease. No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

Treatment during rejection episodes

Adults

Mycophenolic acid (MPA) is the active metabolite of mycophenolate mofetil. Renal transplant rejection does not lead to changes in MPA pharmacokinetics; dose reduction or interruption of treatment is not required. There is no basis for dose adjustment following cardiac transplant rejection. No pharmacokinetic data are available during hepatic transplant rejection.

Paediatric population

No data are available for treatment of first or refractory rejection in paediatric transplant patients.

Method of administration

For oral use.

Precautions to be taken before handling or administering the medicinal product.

Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits, capsules should not be opened or crushed to avoid inhalation or direct contact with skin or mucous membranes of the powder contained in the capsules. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.

4.3 Contraindications

- CellCept should not be given to patients with hypersensitivity to mycophenolate mofetil, mycophenolic acid or to any of the excipients listed in section 6.1. Hypersensitivity reactions to this medicinal product have been observed (see section 4.8).
- Treatment should not be given to women of childbearing potential who are not using highly effective contraception (see section 4.6).
- Treatment should not be initiated in women of childbearing potential without providing a pregnancy test result to rule out unintended use in pregnancy (see section 4.6).
- Treatment should not be used in pregnancy unless there is no suitable alternative treatment to prevent transplant rejection (see section 4.6).
- Treatment should not be given to women who are breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

Neoplasms

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including CellCept, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.8). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

As general advice to minimise the risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Infections

Patients treated with immunosuppressants, including mycophenolate mofetil, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis (see section 4.8). Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation and infections caused by polyomaviruses (BK virus associated nephropathy, JC virus associated progressive multifocal leukoencephalopathy PML). Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. Mycophenolic acid has a cytostatic effect on B- and T-lymphocytes, therefore an increased severity of COVID-19 may occur, and appropriate clinical action should be considered.

There have been reports of hypogammaglobulinaemia in association with recurrent infections in patients receiving mycophenolate mofetil in combination with other immunosuppressants. In some of these cases, switching mycophenolate mofetil to an alternative immunosuppressant resulted in serum IgG levels returning to normal. Patients on mycophenolate mofetil who develop recurrent infections should have their serum immunoglobulins measured. In cases of sustained, clinically relevant hypogammaglobulinaemia, appropriate clinical action should be considered taking into account the potent cytostatic effects that mycophenolic acid has on T- and B-lymphocytes.

There have been published reports of bronchiectasis in adults and children who received mycophenolate mofetil in combination with other immunosuppressants. In some of these cases, switching mycophenolate mofetil to another immunosuppressant resulted in improvement in respiratory symptoms. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect on the lung. There have also been isolated reports of interstitial lung disease and

pulmonary fibrosis, some of which were fatal (see section 4.8). It is recommended that patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, are investigated.

Blood and immune system

Patients receiving mycophenolate mofetil should be monitored for neutropenia, which may be related to the treatment itself, concomitant medications, viral infections, or some combination of these causes. Patients taking mycophenolate mofetil should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If neutropenia develops (absolute neutrophil count $< 1.3 \times 10^3/\mu\text{l}$), it may be appropriate to interrupt or discontinue mycophenolate mofetil.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil in combination with other immunosuppressants. The mechanism for mycophenolate mofetil induced PRCA is unknown. PRCA may resolve with dose reduction or cessation of mycophenolate mofetil therapy. Changes to mycophenolate mofetil therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimise the risk of graft rejection (see section 4.8).

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

Patients should be advised that, during treatment with mycophenolate mofetil, vaccinations may be less effective, and the use of live attenuated vaccines should be avoided (see section 4.5). Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

Gastrointestinal

Mycophenolate mofetil has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, haemorrhage and perforation. Treatment should be administered with caution in patients with active serious digestive system disease.

Mycophenolate is an IMPDH (inosine monophosphate dehydrogenase) inhibitor. Therefore, 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 of mycophenolate and its efficacy (see also section 4.5).

It is recommended that mycophenolate mofetil should not be administered concomitantly with azathioprine because such concomitant administration has not been studied.

The risk/benefit ratio of mycophenolate mofetil in combination with sirolimus has not been established (see also section 4.5).

Therapeutic drug monitoring

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).

Special populations

Paediatric population

Very limited post-marketing information indicates a higher frequency of the following adverse events in patients under 6 years of age compared to older patients:

- lymphomas and other malignancies, particularly of post-transplant lymphoproliferative disorder in cardiac transplant patients.
- blood and lymphatic system disorders including anaemia and neutropenia in cardiac transplant patients. This applies for children under 6 years of age compared to older patients and compared to paediatric hepatic/renal transplant recipients.
Patients taking mycophenolate mofetil should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If neutropenia develops, it may be appropriate to interrupt or discontinue mycophenolate mofetil.
- gastrointestinal disorders including diarrhoea and vomiting.
Treatment should be administered with caution in patients with active serious digestive system disease.

Elderly population

Elderly patients may be at an increased risk of adverse events such as certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared with younger individuals (see section 4.8).

Teratogenic effects

Mycophenolate is a powerful human teratogen. Spontaneous abortion (rate of 45% to 49%) and congenital malformations (estimated rate of 23% to 27%) have been reported following mycophenolate mofetil exposure during pregnancy. Therefore, treatment is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejection. Female patients of childbearing potential should be made aware of the risks and follow the recommendations provided in section 4.6 (e.g. contraceptive methods, pregnancy testing) prior to, during, and after therapy with mycophenolate mofetil. Physicians should ensure that women taking mycophenolate mofetil understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult their physician if there is a possibility of pregnancy.

Contraception (see section 4.6)

Because of robust clinical evidence showing a high risk of abortion and congenital malformations when mycophenolate mofetil is used in pregnancy, every effort to avoid pregnancy during treatment should be taken. Therefore, women with childbearing potential must use at least one form of reliable contraception (see section 4.3) before starting mycophenolate mofetil therapy, during therapy, and for six weeks after stopping the therapy, unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred to minimise the potential for contraceptive failure and unintended pregnancy.

For contraception advice for men see section 4.6.

Educational materials

In order to assist patients in avoiding foetal exposure to mycophenolate and to provide additional important safety information, the Marketing Authorisation Holder will provide educational materials to healthcare professionals. The educational materials will reinforce the warnings about the teratogenicity of mycophenolate, provide advice on contraception before therapy is started and guidance on the need for pregnancy testing. Full patient information about the teratogenic risk and the

pregnancy prevention measures should be given by the physician to women of childbearing potential and, as appropriate, to male patients.

Additional precautions

Patients should not donate blood during therapy or for at least 6 weeks following discontinuation of mycophenolate mofetil. Men should not donate semen during therapy or for 90 days following discontinuation of mycophenolate mofetil.

Sodium contents

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Aciclovir

Higher aciclovir plasma concentrations were observed when mycophenolate mofetil was administered with aciclovir in comparison to the administration of aciclovir alone. The changes in MPAG (the phenolic glucuronide of MPA) pharmacokinetics (MPAG increased by 8%) were minimal and are not considered clinically significant. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are aciclovir concentrations, the potential exists for mycophenolate mofetil and aciclovir, or its prodrugs, e.g. valaciclovir, to compete for tubular secretion and further increases in concentrations of both substances may occur.

Antacids and proton pump inhibitors (PPIs)

Decreased MPA exposure has been observed when antacids, such as magnesium and aluminium hydroxides, and PPIs, including lansoprazole and pantoprazole, were administered with mycophenolate mofetil. When comparing rates of transplant rejection or rates of graft loss between mycophenolate mofetil patients taking PPIs vs. mycophenolate mofetil patients not taking PPIs, no significant differences were seen. These data support extrapolation of this finding to all antacids because the reduction in exposure when mycophenolate mofetil was co-administered with magnesium and aluminium hydroxides is considerably less than when mycophenolate mofetil was co-administered with PPIs.

Medicinal products that interfere with enterohepatic recirculation (e.g. cholestyramine, ciclosporin A, antibiotics)

Caution should be used with medicinal products that interfere with enterohepatic recirculation because of their potential to reduce the efficacy of mycophenolate mofetil.

Cholestyramine

Following single dose administration of 1.5 g of mycophenolate mofetil to normal healthy subjects pre-treated with 4 g TID of cholestyramine for 4 days, there was a 40% reduction in the AUC of MPA (see section 4.4 and section 5.2). Caution should be used during concomitant administration because of the potential to reduce efficacy of mycophenolate mofetil.

Ciclosporin A

Ciclosporin A (CsA) pharmacokinetics are unaffected by mycophenolate mofetil.

In contrast, if concomitant CsA treatment is stopped, an increase in MPA AUC of around 30% should be expected. CsA interferes with MPA enterohepatic recycling, resulting in reduced MPA exposures by 30-50% in renal transplant patients treated with mycophenolate mofetil and CsA compared with patients receiving sirolimus or belatacept and similar doses of mycophenolate mofetil (see also section 4.4). Conversely, changes of MPA exposure should be expected when switching patients from CsA to one of the immunosuppressants which does not interfere with MPA's enterohepatic cycle.

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 about 50% have been reported in renal transplant recipients in the days immediately following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. This effect tended to diminish with continued antibiotic use and to cease within a few days of antibiotic discontinuation. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

Norfloxacin and metronidazole

In healthy volunteers, no significant interaction was observed when mycophenolate mofetil was concomitantly administered with norfloxacin or metronidazole separately. However, norfloxacin and metronidazole combined reduced the MPA exposure by approximately 30% following a single dose of mycophenolate mofetil.

Trimethoprim/sulfamethoxazole

No effect on the bioavailability of MPA was observed.

Medicinal products that affect glucuronidation (e.g. isavuconazole, telmisartan)

Concomitant administration of drugs affecting glucuronidation of MPA may change MPA exposure. Caution is therefore recommended when administering these drugs concomitantly with mycophenolate mofetil.

Isavuconazole

An increase of MPA exposure ($AUC_{0-\infty}$) by 35% was observed with concomitant administration of isavuconazole.

Telmisartan

Concomitant administration of telmisartan and mycophenolate mofetil resulted in an approximately 30% decrease of MPA concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression, which in turn results in an enhanced uridine diphosphate glucuronyltransferase isoform 1A9 (UGT1A9) expression and activity. When comparing rates of transplant rejection, rates of graft loss or adverse event profiles between patients on mycophenolate mofetil with and without concomitant telmisartan medication, no clinical consequences of the pharmacokinetic drug-drug interaction were seen.

Ganciclovir

Based on the results of a single dose administration study of recommended doses of oral mycophenolate mofetil and intravenous ganciclovir and the known effects of renal impairment on the pharmacokinetics of mycophenolate mofetil (see section 4.2) and ganciclovir, it is anticipated that co-administration of these agents (which compete for mechanisms of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics is anticipated and mycophenolate mofetil dose adjustment is not required. In patients with renal impairment in whom mycophenolate mofetil and ganciclovir or its prodrugs, e.g. valganciclovir, are co-administered, the dose recommendations for ganciclovir should be observed and patients should be monitored carefully.

Oral contraceptives

The pharmacodynamics and pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by co-administration of mycophenolate mofetil (see also section 5.2).

Rifampicin

In patients not also taking ciclosporin, concomitant administration of mycophenolate mofetil and rifampicin resulted in a decrease in MPA exposure (AUC_{0-12h}) of 18% to 70%. It is recommended to monitor MPA exposure levels and to adjust mycophenolate mofetil doses accordingly to maintain clinical efficacy when rifampicin is administered concomitantly.

Sevelamer

Decrease in MPA C_{max} and AUC_{0-12h} by 30% and 25%, respectively, were observed when mycophenolate mofetil was concomitantly administered with sevelamer without any clinical consequences (i.e. graft rejection). It is recommended, however, to administer mycophenolate mofetil at least one hour before or three hours after sevelamer intake to minimise the impact on the absorption of MPA. There are no data on mycophenolate mofetil with phosphate binders other than sevelamer.

Tacrolimus

In hepatic transplant patients initiated on mycophenolate mofetil and tacrolimus, the AUC and C_{max} of MPA, the active metabolite of mycophenolate mofetil, were not significantly affected by co-administration with tacrolimus. In contrast, there was an increase of approximately 20% in tacrolimus AUC when multiple doses of mycophenolate mofetil (1.5 g BID) were administered to hepatic transplant patients taking tacrolimus. However, in renal transplant patients, tacrolimus concentration did not appear to be altered by mycophenolate mofetil (see also section 4.4).

Live vaccines

Live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished (see also section 4.4).

Paediatric population

Interaction studies have only been performed in adults.

Potential interaction

Co-administration of probenecid with mycophenolate mofetil in monkeys raises plasma AUC of MPAG by 3-fold. Thus, other substances known to undergo renal tubular secretion may compete with MPAG, and thereby raise plasma concentrations of MPAG or the other substance undergoing tubular secretion.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Pregnancy whilst taking mycophenolate mofetil must be avoided. Therefore, women of childbearing potential must use at least one form of reliable contraception (see section 4.3) before starting the therapy, during therapy, and for six weeks after stopping the therapy, unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred.

Pregnancy

Mycophenolate mofetil is contraindicated during pregnancy unless there is no suitable alternative treatment to prevent transplant rejection. Treatment should not be initiated without providing a negative pregnancy test result to rule out unintended use in pregnancy (see section 4.3).

Female patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations at the beginning of the treatment and must be counselled regarding pregnancy prevention and planning.

Before starting treatment, women of childbearing potential should have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/ml in order to exclude unintended exposure of an embryo to mycophenolate. It is recommended that the second test should be performed 8-10 days after the first test. For transplants from deceased donors, if it is not possible to perform two tests 8-10 days apart before treatment starts (because of the timing of transplant organ availability), a pregnancy test must be performed immediately before starting treatment and a further test 8-10 days later. Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported). Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.

Mycophenolate is a powerful human teratogen, with an increased risk of spontaneous abortions and congenital malformations in case of exposure during pregnancy;

- Spontaneous abortions have been reported in 45 to 49% of pregnant women exposed to mycophenolate mofetil, compared to a reported rate of between 12 and 33% in solid organ transplant patients treated with immunosuppressants other than mycophenolate mofetil.
- Based on literature reports, malformations occurred in 23 to 27% of live births in women exposed to mycophenolate mofetil during pregnancy (compared to 2 to 3% of live births in the overall population and approximately 4 to 5% of live births in solid organ transplant recipients treated with immunosuppressants other than mycophenolate mofetil).

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

- Abnormalities of the ear (e.g. abnormally formed or absent external ear), external auditory canal atresia (middle ear);
- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;
- Abnormalities of the eye (e.g. coloboma);
- Congenital heart disease such as atrial and ventricular septal defects;
- Malformations of the fingers (e.g. polydactyly, syndactyly);
- Tracheo-oesophageal malformations (e.g. oesophageal atresia);
- Nervous system malformations such as spina bifida;
- Renal abnormalities.

In addition, there have been isolated reports of the following malformations:

- Microphthalmia;
- Congenital choroid plexus cyst;
- Septum pellucidum agenesis;
- Olfactory nerve agenesis.

Studies in animals have shown reproductive toxicity (see section 5.3).

Breast-feeding

Limited data shows that mycophenolic acid is excreted in human milk. Because of the potential for serious adverse reactions to mycophenolic acid in breast-fed infants, treatment is contraindicated in nursing mothers (see section 4.3).

Men

The limited clinical evidence available does not indicate an increased risk of malformations or miscarriage following paternal exposure to mycophenolate mofetil.

MPA is a powerful teratogen. It is not known if MPA is present in semen. Calculations based on animal data show that the maximum amount of MPA that could potentially be transferred to woman is so low that it would be unlikely to have an effect. Mycophenolate has been shown to be genotoxic in animal studies at concentrations exceeding the human therapeutic exposures only by small margins, such that the risk of genotoxic effects on sperm cells cannot completely be excluded.

Therefore, the following precautionary measures are recommended: sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 90 days after cessation of mycophenolate mofetil. Male patients of reproductive potential should be made aware of and discuss with a qualified healthcare professional the potential risks of fathering a child.

Fertility

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. The systemic exposure at this dose represents 2 – 3 times the clinical exposure at the recommended clinical dose of 2 g/day in renal transplant patients and 1.3 – 2 times the clinical exposure at the recommended clinical dose of 3 g/day in cardiac transplant patients. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (including anophthalmia, agnathia, and hydrocephaly) in the first generation offspring in the absence of maternal toxicity. The systemic exposure at this dose was approximately 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

4.7 Effects on ability to drive and use machines

Mycophenolate mofetil has moderate influence on the ability to drive and use machines. Treatment may cause somnolence, confusion, dizziness, tremor or hypotension, and therefore patients are advised to use caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

Diarrhoea (up to 52.6%), leukopenia (up to 45.8%), bacterial infections (up to 39.9%) and vomiting (up to 39.1%) were among the most common and/or serious adverse reactions associated with the administration of mycophenolate mofetil in combination with ciclosporin and corticosteroids. There is also evidence of a higher frequency of certain types of infections (see section 4.4).

Tabulated list of adverse reactions

The adverse reactions from clinical trials and post-marketing experience are listed in Table 1, by MedDRA system organ class (SOC) along with their frequencies. The corresponding frequency category for each adverse reaction is based on the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ to $< 1/1\ 000$) and very rare ($< 1/10\ 000$). Due to the large differences observed in the frequency of certain adverse reactions across the different transplant indications, the frequency is presented separately for renal, hepatic and cardiac transplant patients.

Table 1 Adverse reactions in studies investigating mycophenolate mofetil treatment in adults and adolescents, or through post-marketing surveillance

| Adverse reaction (MedDRA) System Organ Class | Renal transplant | Hepatic transplant | Cardiac transplant |
|---|---------------------|-----------------------|-----------------------|
| | Frequency | Frequency | Frequency |
| Infections and infestations | | | |
| Bacterial infections | Very Common | Very Common | Very Common |
| Fungal infections | Common | Very Common | Very Common |
| Protozoal infections | Uncommon | Uncommon | Uncommon |
| Viral infections | Very Common | Very Common | Very Common |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | | | |
| Benign neoplasm of skin | Common | Common | Common |
| Lymphoma | Uncommon | Uncommon | Uncommon |
| Lymphoproliferative disorder | Uncommon | Uncommon | Uncommon |
| Neoplasm | Common | Common | Common |
| Skin cancer | Common | Uncommon | Common |
| Blood and lymphatic system disorders | | | |
| Anaemia | Very Common | Very Common | Very Common |
| Aplasia pure red cell | Uncommon | Uncommon | Uncommon |
| Bone marrow failure | Uncommon | Uncommon | Uncommon |
| Ecchymosis | Common | Common | Very Common |
| Leukocytosis | Common | Very Common | Very Common |
| Leukopenia | Very Common | Very Common | Very Common |
| Pancytopenia | Common | Common | Uncommon |
| Pseudolymphoma | Uncommon | Uncommon | Common |
| Thrombocytopenia | Common | Very Common | Very Common |
| Metabolism and nutrition disorders | | | |
| Acidosis | Common | Common | Very Common |
| Hypercholesterolaemia | Very Common | Common | Very Common |
| Hyperglycaemia | Common | Very Common | Very Common |
| Hyperkalaemia | Common | Very Common | Very Common |
| Hyperlipidaemia | Common | Common | Very Common |
| Hypocalcaemia | Common | Very Common | Common |
| Hypokalaemia | Common | Very Common | Very Common |
| Hypomagnesaemia | Common | Very Common | Very Common |
| Hypophosphataemia | Very Common | Very Common | Common |
| Hyperuricaemia | Common | Common | Very Common |
| Gout | Common | Common | Very Common |
| Weight decreased | Common | Common | Common |
| Psychiatric disorders | | | |
| Confusional state | Common | Very Common | Very Common |
| Depression | Common | Very Common | Very Common |
| Insomnia | Common | Very Common | Very Common |
| Agitation | Uncommon | Common | Very Common |

| Adverse reaction (MedDRA) System Organ Class | Renal transplant | Hepatic transplant | Cardiac transplant |
|---|-----------------------------|-------------------------------|-------------------------------|
| Anxiety | Common | Very Common | Very Common |
| Thinking abnormal | Uncommon | Common | Common |
| Nervous system disorders | | | |
| Dizziness | Common | Very Common | Very Common |
| Headache | Very Common | Very Common | Very Common |
| Hypertonia | Common | Common | Very Common |
| Paresthesia | Common | Very Common | Very Common |
| Somnolence | Common | Common | Very Common |
| Tremor | Common | Very Common | Very Common |
| Convulsion | Common | Common | Common |
| Dysgeusia | Uncommon | Uncommon | Common |
| Cardiac disorders | | | |
| Tachycardia | Common | Very Common | Very Common |
| Vascular disorders | | | |
| Hypertension | Very Common | Very Common | Very Common |
| Hypotension | Common | Very Common | Very Common |
| Lymphocele | Uncommon | Uncommon | Uncommon |
| Venous thrombosis | Common | Common | Common |
| Vasodilatation | Common | Common | Very Common |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchiectasis | Uncommon | Uncommon | Uncommon |
| Cough | Very Common | Very Common | Very Common |
| Dyspnoea | Very Common | Very Common | Very Common |
| Interstitial lung disease | Uncommon | Very Rare | Very Rare |
| Pleural effusion | Common | Very Common | Very Common |
| Pulmonary fibrosis | Very Rare | Uncommon | Uncommon |
| Gastrointestinal disorders | | | |
| Abdominal distension | Common | Very Common | Common |
| Abdominal pain | Very Common | Very Common | Very Common |
| Colitis | Common | Common | Common |
| Constipation | Very Common | Very Common | Very Common |
| Decreased appetite | Common | Very Common | Very Common |
| Diarrhoea | Very Common | Very Common | Very Common |
| Dyspepsia | Very Common | Very Common | Very Common |
| Esophagitis | Common | Common | Common |
| Eructation | Uncommon | Uncommon | Common |
| Flatulence | Common | Very Common | Very Common |
| Gastritis | Common | Common | Common |
| Gastrointestinal haemorrhage | Common | Common | Common |
| Gastrointestinal ulcer | Common | Common | Common |
| Gingival hyperplasia | Common | Common | Common |
| Ileus | Common | Common | Common |

| Adverse reaction (MedDRA) System Organ Class | Renal transplant | Hepatic transplant | Cardiac transplant |
|---|-----------------------------|-------------------------------|-------------------------------|
| Mouth ulceration | Common | Common | Common |
| Nausea | Very Common | Very Common | Very Common |
| Pancreatitis | Uncommon | Common | Uncommon |
| Stomatitis | Common | Common | Common |
| Vomiting | Very Common | Very Common | Very Common |
| Immune system disorders | | | |
| Hypersensitivity | Uncommon | Common | Common |
| Hypogammaglobulinaemia | Uncommon | Very Rare | Very Rare |
| Hepatobiliary disorders | | | |
| Blood alkaline phosphatase increased | Common | Common | Common |
| Blood lactate dehydrogenase increased | Common | Uncommon | Very Common |
| Hepatic enzyme increased | Common | Very Common | Very Common |
| Hepatitis | Common | Very Common | Uncommon |
| Hyperbilirubinaemia | Common | Very Common | Very Common |
| Jaundice | Uncommon | Common | Common |
| Skin and subcutaneous tissue disorders | | | |
| Acne | Common | Common | Very Common |
| Alopecia | Common | Common | Common |
| Rash | Common | Very Common | Very Common |
| Skin hypertrophy | Common | Common | Very Common |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | Common | Common | Very Common |
| Muscular weakness | Common | Common | Very Common |
| Renal and urinary disorders | | | |
| Blood creatinine increased | Common | Very Common | Very Common |
| Blood urea increased | Uncommon | Very Common | Very Common |
| Haematuria | Very Common | Common | Common |
| Renal impairment | Common | Very Common | Very Common |

| Adverse reaction (MedDRA) System Organ Class | Renal transplant | Hepatic transplant | Cardiac transplant |
|--|-----------------------------|-------------------------------|-------------------------------|
| General disorders and administration site conditions | | | |
| Asthenia | Very Common | Very Common | Very Common |
| Chills | Common | Very Common | Very Common |
| Oedema | Very Common | Very Common | Very Common |
| Hernia | Common | Very Common | Very Common |
| Malaise | Common | Common | Common |
| Pain | Common | Very Common | Very Common |
| Pyrexia | Very Common | Very Common | Very Common |
| De novo purine synthesis inhibitors associated acute inflammatory syndrome | Uncommon | Uncommon | Uncommon |

Description of selected adverse reactions

Malignancies

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including mycophenolate mofetil, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.4). Three-year safety data in renal and cardiac transplant patients did not reveal any unexpected changes in incidence of malignancy compared to the 1-year data. Hepatic transplant patients were followed for at least 1 year, but less than 3 years.

Infections

All patients treated with immunosuppressants are at increased risk of bacterial, viral and fungal infections (some of which may lead to a fatal outcome), including those caused by opportunistic agents and latent viral reactivation. The risk increases with total immunosuppressive load (see section 4.4). The most serious infections were sepsis, peritonitis, meningitis, endocarditis, tuberculosis and atypical mycobacterial infection. The most common opportunistic infections in patients receiving mycophenolate mofetil (2 g or 3 g daily) with other immunosuppressants in controlled clinical trials in renal, cardiac and hepatic transplant patients followed for at least 1 year were candida mucocutaneous, CMV viraemia/syndrome and Herpes simplex. The proportion of patients with CMV viraemia/syndrome was 13.5%. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including mycophenolate mofetil.

Blood and lymphatic disorders

Cytopenias, including leukopenia, anaemia, thrombocytopenia and pancytopenia, are known risks associated with mycophenolate mofetil and may lead or contribute to the occurrence of infections and haemorrhages (see section 4.4). Agranulocytosis and neutropenia have been reported; therefore, regular monitoring of patients taking mycophenolate mofetil is advised (see section 4.4). There have been reports of aplastic anaemia and bone marrow failure in patients treated with mycophenolate mofetil, some of which have been fatal.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil (see section 4.4).

Isolated cases of abnormal neutrophil morphology, including the acquired Pelger-Huet anomaly, have been observed in patients treated with mycophenolate mofetil. These changes are not associated with impaired neutrophil function. These changes may suggest a 'left shift' in the maturity of neutrophils in haematological investigations, which may be mistakenly interpreted as a sign of infection in immunosuppressed patients such as those that receive mycophenolate mofetil.

Gastrointestinal disorders

The most serious gastrointestinal disorders were ulceration and haemorrhage which are known risks associated with mycophenolate mofetil. Mouth, oesophageal, gastric, duodenal, and intestinal ulcers often complicated by haemorrhage, as well as haematemesis, melena, and haemorrhagic forms of gastritis and colitis were commonly reported during the pivotal clinical trials. The most common gastrointestinal disorders, however, were diarrhoea, nausea and vomiting. Endoscopic investigation of patients with mycophenolate mofetil-related diarrhoea have revealed isolated cases of intestinal villous atrophy (see section 4.4).

Hypersensitivity

Hypersensitivity reactions, including angioneurotic oedema and anaphylactic reaction, have been reported.

Pregnancy, puerperium and perinatal conditions

Cases of spontaneous abortion have been reported in patients exposed to mycophenolate mofetil, mainly in the first trimester, see section 4.6.

Congenital disorders

Congenital malformations have been observed post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants, see section 4.6.

Respiratory, thoracic and mediastinal disorders

There have been isolated reports of interstitial lung disease and pulmonary fibrosis in patients treated with mycophenolate mofetil in combination with other immunosuppressants, some of which have been fatal. There have also been reports of bronchiectasis in children and adults.

Immune system disorders

Hypogammaglobulinaemia has been reported in patients receiving mycophenolate mofetil in combination with other immunosuppressants.

General disorders and administration site conditions

Oedema, including peripheral, face and scrotal oedema, was reported very commonly during the pivotal trials. Musculoskeletal pain such as myalgia, and neck and back pain were also very commonly reported.

De novo purine synthesis inhibitors associated acute inflammatory syndrome has been described from post-marketing experience as a paradoxical proinflammatory reaction associated with mycophenolate mofetil and mycophenolic acid, characterised by fever, arthralgia, arthritis, muscle pain and elevated inflammatory markers. Literature case reports showed rapid improvement following discontinuation of the medicinal product.

Special populations

Paediatric population

The type and frequency of adverse reactions were assessed in a long-term clinical trial, which recruited 33 paediatric renal transplant patients, aged 3 years to 18 years, who were given 23 mg/kg of mycophenolate mofetil orally, twice daily. Overall, the safety profile in these 33 children and adolescents was similar to that observed in adult recipients of solid organ allografts.

Similar observations were made in another clinical trial, which recruited 100 paediatric renal transplant patients aged 1 to 18 years. The type and frequency of adverse reactions in patients who were given 600 mg/m², up to 1 g/m² of mycophenolate mofetil orally, twice daily, were comparable to those observed in adult patients given 1 g mycophenolate mofetil twice daily. A summary of the more frequently occurring adverse reactions is shown in table 2 below:

Table 2 Summary of adverse reactions observed more frequently in a trial investigating mycophenolate mofetil in 100 paediatric renal transplant patients (age/surface area-based dosing [600 mg/m², up to 1 g/m² BID.]

| Adverse reaction (MedDRA) | <6 years (n=33) | 6-11 years (n=34) | 12-18 years (n=33) |
|---|------------------------|------------------------|------------------------|
| System Organ Class | | | |
| Infections and infestations | Very common (48.5%) | Very common (44.1%) | Very common (51.5%) |
| Blood and lymphatic system disorders | | | |
| Leukopenia | Very common (30.3%) | Very common (29.4%) | Very common (12.1%) |
| Anaemia | Very common (51.5%) | Very common (32.4%) | Very common (27.3%) |
| Gastrointestinal disorders | | | |
| Diarrhoea | Very common (87.9%) | Very common (67.6%) | Very common (30.3%) |
| Vomiting | Very common (69.7%) | Very common (44.1%) | Very common (36.4%) |

Based on limited sub-set data (i.e. 33 of the 100 patients) there was a higher frequency of severe diarrhoea (common, 9.1%), and candida mucocutaneous (very common, 21.2%) in children under 6 years of age, compared to the older paediatric cohort in which no cases of severe diarrhoea were reported (0.0%) and candida mucocutaneous was common (7.5%).

Review of the available medical literature on paediatric hepatic and cardiac transplant patients shows the type and frequency of the reported adverse reactions are consistent with those observed in paediatric and adult patients following renal transplant.

Very limited post-marketing data indicates a higher frequency of the following adverse reactions in patients under 6 years of age compared to older patients (see section 4.4):

- lymphomas and other malignancies particularly of post-transplant lymphoproliferative disorder in cardiac transplant patients
- blood and lymphatic system disorders including anaemia and neutropenia in cardiac transplant patients under 6 years of age compared to older patients, and compared to paediatric hepatic/renal transplant recipients
- gastrointestinal disorders including diarrhoea and vomiting.

Renal transplant patients under 2 years of age might be at a higher risk of infections and respiratory events compared to older patients. However, these data should be interpreted with caution due to a very limited number of post-marketing reports concerning the same patients suffering from multiple infections.

In case of undesirable effects, temporary dose reduction or interruption may be considered as deemed clinically necessary.

Elderly

Elderly patients (≥ 65 years) may generally be at increased risk of adverse reactions due to immunosuppression. Elderly patients receiving mycophenolate mofetil as part of a combination

immunosuppressive regimen may be at increased risk of certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared to younger individuals.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Reports of overdoses with mycophenolate mofetil have been received from clinical trials and during post-marketing experience. In the vast majority of these cases, either no adverse events were reported or they were in line with the known safety profile of the medicinal product and had a favourable outcome. However, isolated serious adverse events including a fatal case were observed during post-marketing experience.

It is expected that an overdose of mycophenolate mofetil could possibly result in oversuppression of the immune system and increase susceptibility to infections and bone marrow suppression (see section 4.4). If neutropenia develops, dosing with mycophenolate mofetil should be interrupted or the dose reduced (see section 4.4).

Haemodialysis would not be expected to remove clinically significant amounts of MPA or MPAG. Bile acid sequestrants, such as cholestyramine, can remove MPA by decreasing the enterohepatic recirculation of the drug (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressive agents ATC code L04AA06

Mechanism of action

Mycophenolate mofetil is the 2-morpholinoethyl ester of MPA. MPA is a selective, uncompetitive and reversible inhibitor of IMPDH, and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines whereas other cell types can utilise salvage pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells. In addition to its inhibition of IMPDH and the resulting deprivation of lymphocytes, MPA also influences cellular checkpoints responsible for metabolic programming of lymphocytes. It has been shown, using human CD4+ T-cells, that MPA shifts transcriptional activities in lymphocytes from a proliferative state to catabolic processes relevant to metabolism and survival leading to an anergic state of T-cells, whereby the cells become unresponsive to their specific antigen.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, MPA. As evidenced by suppression of acute rejection following renal transplantation, the immunosuppressant activity of mycophenolate mofetil is correlated with MPA concentration. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94% relative to intravenous mycophenolate mofetil. Food had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g BID to renal transplant patients. However, MPA C_{\max} was decreased by 40% in the presence of food. Mycophenolate mofetil is not measurable systemically in plasma following oral administration.

Distribution

As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed at approximately 6 - 12 hours post-dose. A reduction in the AUC of MPA of approximately 40% is associated with the co-administration of cholestyramine (4 g TID), indicating that there is a significant amount of enterohepatic recirculation. MPA at clinically relevant concentrations is 97% bound to plasma albumin.

In the early post-transplant period (< 40 days post-transplant), renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30% lower and C_{\max} approximately 40% lower compared to the late post-transplant period (3 - 6 months post-transplant).

Biotransformation

MPA is metabolised principally by glucuronyl transferase (isoform UGT1A9) to form the 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 mycophenolate mofetil's side effects (diarrhoea, leucopenia).

Elimination

A negligible amount of substance is excreted as MPA (< 1% of the dose) in the urine. Oral administration of radiolabelled mycophenolate mofetil results in complete recovery of the administered dose with 93% of the administered dose recovered in the urine and 6% recovered in the faeces. Most (about 87%) of the administered dose is excreted in the urine as MPAG.

At clinically encountered concentrations, MPA and MPAG are not removed by haemodialysis. However, at high MPAG plasma concentrations (> 100 µg/ml), small amounts of MPAG are removed. By interfering with enterohepatic recirculation of the drug, bile acid sequestrants such as cholestyramine reduce MPA AUC (see section 4.9).

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 potentially interact with renal organic anion transporters.

Enterohepatic recirculation interferes with accurate determination of MPA's disposition parameters; only apparent values can be indicated. In healthy volunteers and patients with autoimmune disease approximate clearance values of 10.6 L/h and 8.27 L/h respectively and half-life values of 17 h were observed. In transplant patients mean clearance values were higher (range 11.9-34.9 L/h) and mean half-life values shorter (5-11 h) with little difference between renal, hepatic or cardiac transplant

patients. In the individual patients, these elimination parameters vary based on type of co-treatment with other immunosuppressants, time post-transplantation, plasma albumin concentration and renal function. These factors explain why reduced exposure to mycophenolate is seen when mycophenolate mofetil is co-administered with ciclosporin (see section 4.5) and why plasma concentrations tend to increase over time compared to what is observed immediately after transplantation.

Special populations

Renal impairment

In a single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate < 25 ml/min/1.73 m²) were 28 – 75% higher relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. The mean single dose MPAG AUC was 3 – 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. Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Delayed renal graft function

In patients with delayed renal graft function post-transplant, mean MPA AUC_{0-12h} was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC_{0-12h} was 2 – 3-fold higher than in post-transplant patients without delayed graft function. There may be a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of mycophenolate mofetil does not appear to be necessary.

Hepatic impairment

In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were 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.

Paediatric population

In 33 paediatric renal allograft recipients it was established that the dose predicted to provide an MPA AUC_{0-12h} closest to the target exposure of 27.2 h·mg/l was 600 mg/m², and that doses calculated based on estimated BSA reduced interindividual variability (coefficient of variation, (CV)) by about 10%. Therefore, dosing based on BSA is preferred rather than dosing based on body weight.

Pharmacokinetic parameters were evaluated in up to 55 paediatric renal transplant patients (aged 1 to 18 years) given 600 mg/m², up to 1 g/m² of mycophenolate mofetil orally twice daily. This dose achieved MPA AUC values similar to those seen in adult renal transplant patients receiving mycophenolate mofetil at a dose of 1 g BID in the early and late post-transplant period as per Table 3 below. MPA AUC values across paediatric age groups were similar in the early and late post-transplant period.

For paediatric hepatic transplant recipients an open-label study of the safety, tolerability and pharmacokinetics of oral mycophenolate mofetil included 7 evaluable patients on concomitant ciclosporin and corticosteroid treatment. The dose predicted to achieve an exposure of 58 h·mg/l in the stable post-transplant period was estimated. The mean \pm SD AUC₀₋₁₂ (adjusted to a dose of 600 mg/m²) was 47.0 \pm 21.8 h·mg/l, adjusted C_{max} was 14.5 \pm 4.21 mg/l, with a median time to maximum concentration of 0.75 h. To achieve the target AUC₀₋₁₂ of 58 h·mg/l in the late post-transplant period, a dose in the range of 740-806 mg/m² BID would therefore have been required in the study population.

A comparison of dose-normalised (to 600 mg/m²) MPA AUC values in 12 paediatric renal transplant patients less than 6 years of age at 9 months post-transplant with those values in 7 paediatric hepatic transplant patients [median age 17 months (range: 10-60 months at enrolment)] at 6 months and beyond post-transplant revealed that, at the same dose, the AUC values were on average 23% lower in the paediatric hepatic patients compared to paediatric renal patients. This is consistent with the need

for higher dosing in adult hepatic transplant patients compared to adult renal transplant patients to achieve the same exposure.

In adult transplant patients administered the same dosage of mycophenolate mofetil, there is similar MPA exposure among renal transplant and cardiac transplant patients. In line with the established similarity in MPA exposure between paediatric renal transplant and adult renal transplant patients at their respective approved doses, existing data allows to conclude that MPA exposure at the recommended dosage will be similar in paediatric cardiac transplant, and adult cardiac transplant patients.

Table 3 Mean computed MPA PK parameters by age and time post-transplant (renal)

| Age group (n) | | Adjusted C_{\max} mg/l ^A mean \pm SD | Adjusted AUC_{0-12} h·mg/l mean \pm SD (CI) ^A |
|----------------------|-------------------|--|---|
| Day 7 | | | |
| <6 y | (17) | 13.2 \pm 7.16 | 27.4 \pm 9.54 (22.8-31.9) |
| 6 - <12 y | (16) | 13.1 \pm 6.30 | 33.2 \pm 12.1 (27.3-39.2) |
| 12-18 y | (21) | 11.7 \pm 10.7 | 26.3 \pm 9.14 (22.3-30.3) ^D |
| p-value ^B | | - | - |
| <2 y ^C | (6) | 10.3 \pm 5.80 | 22.5 \pm 6.68 (17.2-27.8) |
| >18 y | (141) | | 27.2 \pm 11.6 |
| Month 3 | | | |
| <6 y | (15) | 22.7 \pm 10.1 | 49.7 \pm 18.2 |
| 6 - <12 y | (14) ^E | 27.8 \pm 14.3 | 61.9 \pm 19.6 |
| 12-18 y | (17) | 17.9 \pm 9.57 | 53.6 \pm 20.2 ^F |
| p-value ^B | | - | - |
| <2 y ^C | (4) | 23.8 \pm 13.4 | 47.4 \pm 14.7 |
| >18 y | (104) | | 50.3 \pm 23.1 |
| Month 9 | | | |
| <6 y | (12) | 30.4 \pm 9.16 | 60.9 \pm 10.7 |
| 6 - <12 y | (11) | 29.2 \pm 12.6 | 66.8 \pm 21.2 |
| 12-18 y | (14) | 18.1 \pm 7.29 | 56.7 \pm 14.0 |
| p-value ^B | | 0.004 | - |
| <2 y ^C | (4) | 25.6 \pm 4.25 | 55.8 \pm 11.6 |
| >18 y | (70) | | 53.5 \pm 18.3 |

AUC_{0-12h} =area under the plasma concentration-time curve from time 0 h to time 12 h; CI=confidence interval; C_{\max} =maximum concentration; MPA=mycophenolic acid; SD=standard deviation; n=number of patients; y=year.

^A In the paediatric age groups C_{\max} and AUC_{0-12h} are adjusted to a dose of 600 mg/m² (95% confidence intervals (CIs) for AUC_{0-12h} Day 7 only); in the adult group AUC_{0-12h} is adjusted to a dose of 1 g.

^B p-value represents the combined p-values for the three major paediatric age groups, and is noted only if significant (p <0.05).

^C The <2-year group is a subset of the <6-year group: no statistical comparisons were made.

^D n=20.

^E Data for one patient was unavailable due to sampling error.

^F n=16.

Elderly

The pharmacokinetics of mycophenolate mofetil and its metabolites have not been found to be altered in the elderly patients (≥ 65 years) when compared to younger transplant patients.

Patients taking oral contraceptives

A study of the co-administration of mycophenolate mofetil (1 g BID) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) conducted in 18 non-transplant women (not taking other immunosuppressants) over 3 consecutive menstrual cycles showed no clinically relevant influence of mycophenolate mofetil on the ovulation-suppressing action of the oral contraceptives. Serum levels of LH, FSH and progesterone were not significantly affected. The pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by co-administration of mycophenolate mofetil (see also section 4.5).

5.3 Preclinical safety data

In experimental models, mycophenolate mofetil was not tumourigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2 – 3 times the systemic exposure (AUC or C_{max}) observed in renal transplant patients at the recommended clinical dose of 2 g/day and 1.3 – 2 times the systemic exposure (AUC or C_{max}) observed in cardiac transplant patients at the recommended clinical dose of 3 g/day.

Two genotoxicity assays (*in vitro* mouse lymphoma assay and *in vivo* mouse bone marrow micronucleus test) showed a potential of mycophenolate mofetil to cause chromosomal aberrations. These effects can be related to the pharmacodynamic mode of action, i.e. inhibition of nucleotide synthesis in sensitive cells. Other *in vitro* tests for detection of gene mutation did not demonstrate genotoxic activity.

In teratology studies in rats and rabbits, foetal resorptions and malformations occurred in rats at 6 mg/kg/day (including anophthalmia, agnathia, and hydrocephaly) and in rabbits at 90 mg/kg/day (including cardiovascular and renal anomalies, such as ectopia cordis and ectopic kidneys, and diaphragmatic and umbilical hernia), in the absence of maternal toxicity. The systemic exposure at these levels is approximately equivalent to or less than 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients (see section 4.6).

The haematopoietic and lymphoid systems were the primary organs affected in toxicology studies conducted with mycophenolate mofetil in the rat, mouse, dog and monkey. These effects occurred at systemic exposure levels that are equivalent to or less than the clinical exposure at the recommended dose of 2 g/day for renal transplant recipients. Gastrointestinal effects were observed in the dog at systemic exposure levels equivalent to or less than the clinical exposure at the recommended dose. Gastrointestinal and renal effects consistent with dehydration were also observed in the monkey at the highest dose (systemic exposure levels equivalent to or greater than clinical exposure). The non-clinical toxicity profile of mycophenolate mofetil appears to be consistent with adverse events observed in human clinical trials, which now provide safety data of more relevance to the patient population (see section 4.8).

Environmental Risk Assessment (ERA)

Environmental risk assessment studies have shown that the active substance, MPA may pose a risk for groundwater via bank filtration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

CellCept capsules

pregelatinised maize starch
croscarmellose sodium
polyvidone (K-90)
magnesium stearate

Capsule shells

gelatin
indigo carmine (E132)
yellow iron oxide (E172)
red iron oxide (E172)
titanium dioxide (E171)
black iron oxide (E172)
potassium hydroxide
shellac.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/aluminium foil blister strips

| | |
|---------------------------|---|
| CellCept 250 mg capsules: | 1 carton contains 100 capsules (in blister packs of 10) |
| | 1 carton contains 300 capsules (in blister packs of 10) |
| | multipacks containing 300 (3 packs of 100) capsules |

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/005/001 CellCept (100 capsules)
EU/1/96/005/003 CellCept (300 capsules)
EU/1/96/005/007 CellCept (300 (3x100) capsules multipack)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 February 1996

Date of latest renewal: 13 March 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

CellCept 500 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg mycophenolate mofetil (as hydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion

White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CellCept 500 mg powder for concentrate for solution for infusion is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adult patients receiving allogeneic renal or hepatic transplants.

4.2 Posology and method of administration

Treatment should be initiated and maintained by appropriately qualified transplant specialists.

CAUTION: CELLCEPT INTRAVENOUS SOLUTION MUST NOT BE ADMINISTERED BY RAPID OR BOLUS INTRAVENOUS INJECTION.

Posology

CellCept 500 mg powder for concentrate for solution for infusion is an alternative dosage form to CellCept oral forms (capsules, tablets and powder for oral suspension) that may be administered for up to 14 days. The initial dose of CellCept (mycophenolate mofetil) 500 mg powder for concentrate for solution for infusion should be given within 24 hours following transplantation.

Adults

Renal transplant

The recommended dose of mycophenolate mofetil for infusion in renal transplant patients is 1 g administered twice daily (2 g daily dose).

Hepatic transplant

The recommended dose of mycophenolate mofetil for infusion in hepatic transplant patients is 1 g administered twice daily (2 g daily dose). Intravenous mycophenolate mofetil should continue for the first 4 days following hepatic transplant, with oral mycophenolate mofetil initiated as soon after this as it can be tolerated. The recommended oral dose in hepatic transplant patients is 1.5 g administered twice daily (3 g daily dose).

Paediatric population

The safety and efficacy of mycophenolate mofetil for infusion in paediatric patients have not been established. No pharmacokinetic data with mycophenolate mofetil for infusion are available for renal and hepatic transplant patients. Paediatric indications are therefore only covered by the oral formulations of the mycophenolate mofetil product range.

Use in special populations

Elderly

The recommended dose of 1 g administered twice a day for renal or hepatic transplant patients is appropriate for the elderly.

Renal impairment

In renal transplant patients with severe chronic renal impairment (glomerular filtration rate $< 25 \text{ ml/min/1.73 m}^2$), outside the immediate post-transplant period, doses greater than 1 g administered twice a day should be avoided. These patients should also be carefully observed. No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively (see section 5.2). No data are available for hepatic transplant patients with severe chronic renal impairment.

Severe hepatic impairment

No dose adjustments are needed for renal transplant patients with severe hepatic parenchymal disease.

Treatment during rejection episodes

Adults

Mycophenolic acid (MPA) is the active metabolite of mycophenolate mofetil. Renal transplant rejection does not lead to changes in MPA pharmacokinetics; dose reduction or interruption of treatment is not required. No pharmacokinetic data are available during hepatic transplant rejection.

Paediatric population

No data are available for treatment of first or refractory rejection in paediatric transplant patients.

Method of administration

Following reconstitution to a concentration of 6 mg/ml, mycophenolate mofetil 500 mg powder for concentrate for solution for infusion must be administered by slow intravenous infusion over a period of 2 hours by either a peripheral or a central vein (see section 6.6).

Precautions to be taken before handling or administering the medicinal product

Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits, avoid direct contact of the dry powder or prepared solutions of mycophenolate mofetil 500 mg powder for concentrate for solution for infusion with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- CellCept should not be given to patients with hypersensitivity to mycophenolate mofetil, mycophenolic acid or to any of the excipients listed in section 6.1. Hypersensitivity reactions to this medicinal product have been observed (see section 4.8).
- Treatment should not be given to patients who are allergic to polysorbate 80.
- Treatment should not be given to women of childbearing potential who are not using highly effective contraception (see section 4.6).

- Treatment should not be initiated in women of childbearing potential without providing a pregnancy test result to rule out unintended use in pregnancy (see section 4.6).
- Treatment should not be used in pregnancy unless there is no suitable alternative treatment to prevent transplant rejection (see section 4.6).
- Treatment should not be given to women who are breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

Neoplasms

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including CellCept, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.8). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

As general advice to minimise the risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Infections

Patients treated with immunosuppressants, including mycophenolate mofetil, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis (see section 4.8). Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation and infections caused by polyomaviruses (BK virus-associated nephropathy, JC virus-associated progressive multifocal leukoencephalopathy PML). Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. Mycophenolic acid has a cytostatic effect on B- and T-lymphocytes, therefore an increased severity of COVID-19 may occur, and appropriate clinical action should be considered.

There have been reports of hypogammaglobulinaemia in association with recurrent infections in patients receiving mycophenolate mofetil in combination with other immunosuppressants. In some of these cases, switching mycophenolate mofetil to an alternative immunosuppressant resulted in serum IgG levels returning to normal. Patients on mycophenolate mofetil who develop recurrent infections should have their serum immunoglobulins measured. In cases of sustained, clinically relevant hypogammaglobulinaemia, appropriate clinical action should be considered taking into account the potent cytostatic effects that mycophenolic acid has on T- and B-lymphocytes.

There have been published reports of bronchiectasis in adults and children who received mycophenolate mofetil in combination with other immunosuppressants. In some of these cases, switching mycophenolate mofetil to another immunosuppressant resulted in improvement in respiratory symptoms. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect on the lung. There have also been isolated reports of interstitial lung disease and pulmonary fibrosis, some of which were fatal (see section 4.8). It is recommended that patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, are investigated.

Blood and immune system

Patients receiving mycophenolate mofetil should be monitored for neutropenia, which may be related to the treatment itself, concomitant medications, viral infections, or some combination of these causes. Patients taking mycophenolate mofetil should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first

year. If neutropenia develops (absolute neutrophil count $< 1.3 \times 10^3/\mu\text{l}$) it may be appropriate to interrupt or discontinue mycophenolate mofetil.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil in combination with other immunosuppressants. The mechanism for mycophenolate mofetil induced PRCA is unknown. PRCA may resolve with dose reduction or cessation of mycophenolate mofetil therapy. Changes to mycophenolate mofetil therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimise the risk of graft rejection (see section 4.8).

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

Patients should be advised that, during treatment with mycophenolate mofetil, vaccinations may be less effective, and the use of live attenuated vaccines should be avoided (see section 4.5). Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

Gastrointestinal

Mycophenolate mofetil has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, haemorrhage and perforation. Treatment should be administered with caution in patients with active serious digestive system disease.

Mycophenolate is an IMPDH (inosine monophosphate dehydrogenase) inhibitor. Therefore, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyltransferase (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 of mycophenolate and its efficacy (see also section 4.5). Some degree of enterohepatic recirculation is anticipated following intravenous administration of mycophenolate mofetil.

It is recommended that mycophenolate mofetil should not be administered concomitantly with azathioprine because such concomitant administration has not been studied.

The risk/benefit ratio of mycophenolate mofetil in combination with sirolimus has not been established (see also section 4.5).

Therapeutic drug monitoring

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).

Special populations

Elderly patients may be at an increased risk of adverse events such as certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared with younger individuals (see section 4.8).

Teratogenic effects

Mycophenolate is a powerful human teratogen. Spontaneous abortion (rate of 45% to 49%) and congenital malformations (estimated rate of 23% to 27%) have been reported following mycophenolate mofetil exposure during pregnancy. Therefore, treatment is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejection. Female patients of childbearing potential should be made aware of the risks and follow the recommendations provided in section 4.6 (e.g. contraceptive methods, pregnancy testing) prior to, during, and after therapy with mycophenolate mofetil. Physicians should ensure that women taking mycophenolate mofetil understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult their physician if there is a possibility of pregnancy.

Contraception (see section 4.6)

Because of robust clinical evidence showing a high risk of abortion and congenital malformations when mycophenolate mofetil is used in pregnancy, every effort to avoid pregnancy during treatment should be taken. Therefore, women with childbearing potential must use at least one form of reliable contraception (see section 4.3) before starting mycophenolate mofetil therapy, during therapy, and for six weeks after stopping the therapy, unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred to minimise the potential for contraceptive failure and unintended pregnancy.

For contraception advice for men see section 4.6.

Educational materials

In order to assist patients in avoiding foetal exposure to mycophenolate and to provide additional important safety information, the Marketing Authorisation Holder will provide educational materials to healthcare professionals. The educational materials will reinforce the warnings about the teratogenicity of mycophenolate, provide advice on contraception before therapy is started and guidance on the need for pregnancy testing. Full patient information about the teratogenic risk and the pregnancy prevention measures should be given by the physician to women of childbearing potential and, as appropriate, to male patients.

Additional precautions

Patients should not donate blood during therapy or for at least 6 weeks following discontinuation of mycophenolate mofetil. Men should not donate semen during therapy or for 90 days following discontinuation of mycophenolate mofetil.

Polysorbate contents

This medicinal product contains 25 mg of polysorbate 80 in each vial. Polysorbates may cause allergic reactions.

Sodium contents

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Aciclovir

Higher aciclovir plasma concentrations were observed when mycophenolate mofetil was administered with aciclovir in comparison to the administration of aciclovir alone. The changes in MPAG (the

phenolic glucuronide of MPA) pharmacokinetics (MPAG increased by 8%) were minimal and are not considered clinically significant. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are aciclovir concentrations, the potential exists for mycophenolate mofetil and aciclovir, or its prodrugs, e.g. valaciclovir, to compete for tubular secretion, and further increases in concentrations of both substances may occur.

Medicinal products that interfere with enterohepatic recirculation (e.g. cholestyramine, ciclosporin A, antibiotics)

Caution should be used with medicinal products that interfere with enterohepatic recirculation because of their potential to reduce the efficacy of mycophenolate mofetil.

Cholestyramine

Following single dose, oral administration of 1.5 g of mycophenolate mofetil to normal healthy subjects pre-treated with 4 g TID of cholestyramine for 4 days, there was a 40% reduction in the AUC of MPA (see section 4.4, and section 5.2). Caution should be used during concomitant administration because of the potential to reduce efficacy of mycophenolate mofetil.

Ciclosporin A

Ciclosporin A (CsA) pharmacokinetics are unaffected by mycophenolate mofetil.

In contrast, if concomitant CsA treatment is stopped, an increase in MPA AUC of around 30% should be expected. CsA interferes with MPA enterohepatic recycling, resulting in reduced MPA exposures by 30 - 50% in renal transplant patients treated with mycophenolate mofetil and CsA compared with patients receiving sirolimus or belatacept and similar doses of mycophenolate mofetil (see also section 4.4). Conversely, changes of MPA exposure should be expected when switching patients from CsA to one of the immunosuppressants which does not interfere with MPA's enterohepatic cycle.

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 about 50% have been reported in renal transplant recipients in the days immediately following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. This effect tended to diminish with continued antibiotic use and to cease within a few days of antibiotic discontinuation. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

Norfloxacin and metronidazole

In healthy volunteers, no significant interaction was observed when mycophenolate mofetil was concomitantly administered with norfloxacin or metronidazole separately. However, norfloxacin and metronidazole combined reduced the MPA exposure by approximately 30% following a single dose of mycophenolate mofetil.

Trimethoprim/sulfamethoxazole

No effect on the bioavailability of MPA was observed.

Medicinal products that affect glucuronidation (e.g. isavuconazole, telmisartan)

Concomitant administration of drugs affecting glucuronidation of MPA may change MPA exposure. Caution is therefore recommended when administering these drugs concomitantly with mycophenolate mofetil.

Isavuconazole

An increase of MPA exposure ($AUC_{0-\infty}$) by 35% was observed with concomitant administration of isavuconazole.

Telmisartan

Concomitant administration of telmisartan and mycophenolate mofetil resulted in an approximately 30% decrease of MPA concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression, which in turn results in an enhanced uridine diphosphate glucuronyltransferase isoform 1A9 (UGT1A9) expression and activity. When comparing rates of transplant rejection, rates of graft loss or adverse event profiles between patients on mycophenolate mofetil with and without concomitant telmisartan medication, no clinical consequences of the pharmacokinetic drug-drug interaction were seen.

Ganciclovir

Based on the results of a single dose administration study of recommended doses of oral mycophenolate mofetil and intravenous ganciclovir and the known effects of renal impairment on the pharmacokinetics of mycophenolate mofetil (see section 4.2) and ganciclovir, it is anticipated that co-administration of these agents (which compete for mechanisms of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics is anticipated and mycophenolate mofetil dose adjustment is not required. In patients with renal impairment in whom mycophenolate mofetil and ganciclovir or its prodrugs, e.g. valganciclovir, are co-administered, the dose recommendations for ganciclovir should be observed and patients should be monitored carefully.

Oral contraceptives

The pharmacodynamics and pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by co-administration of mycophenolate mofetil (see also section 5.2).

Rifampicin

In patients not also taking ciclosporin, concomitant administration of mycophenolate mofetil and rifampicin resulted in a decrease in MPA exposure (AUC_{0-12h}) of 18% to 70%. It is recommended to monitor MPA exposure levels and to adjust mycophenolate mofetil doses accordingly to maintain clinical efficacy when rifampicin is administered concomitantly.

Sevelamer

Decrease in MPA C_{max} and AUC_{0-12h} by 30% and 25%, respectively, were observed when mycophenolate mofetil was concomitantly administered with sevelamer without any clinical consequences (i.e. graft rejection). It is recommended, however, to administer mycophenolate mofetil at least one hour before or three hours after sevelamer intake to minimise the impact on the absorption of MPA. There are no data on mycophenolate mofetil with phosphate binders other than sevelamer.

Tacrolimus

In hepatic transplant patients initiated on mycophenolate mofetil and tacrolimus, the AUC and C_{max} of MPA, the active metabolite of mycophenolate mofetil, were not significantly affected by co-administration with tacrolimus. In contrast, there was an increase of approximately 20% in tacrolimus AUC when multiple doses of mycophenolate mofetil (1.5 g BID) were administered to hepatic transplant patients taking tacrolimus. However, in renal transplant patients, tacrolimus concentration did not appear to be altered by mycophenolate mofetil (see also section 4.4).

Live vaccines

Live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished (see also section 4.4).

Paediatric population

Interaction studies have only been performed in adults.

Potential interaction

Co-administration of probenecid with mycophenolate mofetil in monkeys raises plasma AUC of MPAG by 3-fold. Thus, other substances known to undergo renal tubular secretion may compete with MPAG, and thereby raise plasma concentrations of MPAG or the other substance undergoing tubular secretion.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Pregnancy whilst taking mycophenolate mofetil must be avoided. Therefore, women of childbearing potential must use at least one form of reliable contraception (see section 4.3) before starting the therapy, during therapy, and for six weeks after stopping the therapy, unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred.

Pregnancy

Mycophenolate mofetil is contraindicated during pregnancy unless there is no suitable alternative treatment to prevent transplant rejection. Treatment should not be initiated without providing a negative pregnancy test result to rule out unintended use in pregnancy (see section 4.3).

Female patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations at the beginning of the treatment and must be counselled regarding pregnancy prevention, and planning.

Before starting treatment, women of childbearing potential should have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/ml in order to exclude unintended exposure of an embryo to mycophenolate. It is recommended that the second test should be performed 8-10 days after the first test. For transplants from deceased donors, if it is not possible to perform two tests 8-10 days apart before treatment starts (because of the timing of transplant organ availability), a pregnancy test must be performed immediately before starting treatment and a further test 8-10 days later. Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported). Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.

Mycophenolate is a powerful human teratogen, with an increased risk of spontaneous abortions and congenital malformations in case of exposure during pregnancy;

- Spontaneous abortions have been reported in 45 to 49% of pregnant women exposed to mycophenolate mofetil, compared to a reported rate of between 12 and 33% in solid organ transplant patients treated with immunosuppressants other than mycophenolate mofetil.
- Based on literature reports, malformations occurred in 23 to 27% of live births in women exposed to mycophenolate mofetil during pregnancy (compared to 2 to 3% of live births in the overall population and approximately 4 to 5% of live births in solid organ transplant recipients treated with immunosuppressants other than mycophenolate mofetil).

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

- Abnormalities of the ear (e.g. abnormally formed or absent external ear), external auditory canal atresia (middle ear);
- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;
- Abnormalities of the eye (e.g. coloboma);
- Congenital heart disease such as atrial and ventricular septal defects;
- Malformations of the fingers (e.g. polydactyly, syndactyly);
- Tracheo-oesophageal malformations (e.g. oesophageal atresia);
- Nervous system malformations such as spina bifida;
- Renal abnormalities.

In addition, there have been isolated reports of the following malformations:

- Microphthalmia;
- Congenital choroid plexus cyst;
- Septum pellucidum agenesis;
- Olfactory nerve agenesis.

Studies in animals have shown reproductive toxicity (see section 5.3).

Breast-feeding

Limited data shows that mycophenolic acid is excreted in human milk. Because of the potential for serious adverse reactions to mycophenolic acid in breast-fed infants, treatment is contraindicated in nursing mothers (see section 4.3).

Men

The limited clinical evidence available does not indicate an increased risk of malformations or miscarriage following paternal exposure to mycophenolate mofetil.

MPA is a powerful teratogen. It is not known if MPA is present in semen. Calculations based on animal data show that the maximum amount of MPA that could potentially be transferred to woman is so low that it would be unlikely to have an effect. Mycophenolate has been shown to be genotoxic in animal studies at concentrations exceeding the human therapeutic exposures only by small margins such that the risk of genotoxic effects on sperm cells cannot completely be excluded.

Therefore, the following precautionary measures are recommended: sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 90 days after cessation of mycophenolate mofetil. Male patients of reproductive potential should be made aware of and discuss with a qualified healthcare professional the potential risks of fathering a child.

Fertility

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. The systemic exposure at this dose represents 2 – 3 times the clinical exposure at the recommended clinical dose of 2 g/day. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (including anophthalmia, agnathia, and hydrocephaly) in the first generation offspring in the absence of maternal toxicity. The systemic exposure at this dose was approximately 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

4.7 Effects on ability to drive and use machines

Mycophenolate mofetil has a moderate influence on the ability to drive and use machines. Treatment may cause somnolence, confusion, dizziness, tremor or hypotension, and therefore patients are advised to use caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

Diarrhoea (up to 52.6%), leukopenia (up to 45.8%), bacterial infections (up to 39.9%) and vomiting (up to 39.1%) were among the most common and/or serious adverse reactions associated with the administration of mycophenolate mofetil in combination with ciclosporin and corticosteroids. There is also evidence of a higher frequency of certain types of infections (see section 4.4).

Tabulated list of adverse reactions

The adverse reactions from clinical trials and post-marketing experience are listed in Table 1, by MedDRA system organ class (SOC) along with their frequencies. The corresponding frequency category for each adverse reaction is based on the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\,000$ to $< 1/100$), rare ($\geq 1/10\,000$ to $< 1/1\,000$) and very rare ($< 1/10\,000$). Due to the large differences observed in the frequency of certain adverse reactions across the different transplant indications, the frequency is presented separately for renal and hepatic transplant patients.

Table 1 Adverse reactions in studies investigating mycophenolate mofetil treatment in adults and adolescents, or through post-marketing surveillance

| Adverse reaction (MedDRA) System Organ Class | Renal transplant | Hepatic transplant |
|---|---------------------|-----------------------|
| | Frequency | Frequency |
| Infections and infestations | | |
| Bacterial infections | Very Common | Very Common |
| Fungal infections | Common | Very Common |
| Protozoal infections | Uncommon | Uncommon |
| Viral infections | Very Common | Very Common |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | | |
| Benign neoplasm of skin | Common | Common |
| Lymphoma | Uncommon | Uncommon |
| Lymphoproliferative disorder | Uncommon | Uncommon |
| Neoplasm | Common | Common |
| Skin cancer | Common | Uncommon |
| Blood and lymphatic system disorders | | |
| Anaemia | Very Common | Very Common |
| Aplasia pure red cell | Uncommon | Uncommon |
| Bone marrow failure | Uncommon | Uncommon |
| Ecchymosis | Common | Common |
| Leukocytosis | Common | Very Common |
| Leukopenia | Very Common | Very Common |
| Pancytopenia | Common | Common |

| Adverse reaction (MedDRA) | Renal transplant | Hepatic transplant |
|--|-----------------------------|-------------------------------|
| System Organ Class | | |
| Pseudolymphoma | Uncommon | Uncommon |
| Thrombocytopenia | Common | Very Common |
| Metabolism and nutrition disorders | | |
| Acidosis | Common | Common |
| Hypercholesterolaemia | Very Common | Common |
| Hyperglycaemia | Common | Very Common |
| Hyperkalaemia | Common | Very Common |
| Hyperlipidaemia | Common | Common |
| Hypocalcaemia | Common | Very Common |
| Hypokalaemia | Common | Very Common |
| Hypomagnesaemia | Common | Very Common |
| Hypophosphataemia | Very Common | Very Common |
| Hyperuricaemia | Common | Common |
| Gout | Common | Common |
| Weight decreased | Common | Common |
| Psychiatric disorders | | |
| Confusional state | Common | Very Common |
| Depression | Common | Very Common |
| Insomnia | Common | Very Common |
| Agitation | Uncommon | Common |
| Anxiety | Common | Very Common |
| Thinking abnormal | Uncommon | Common |
| Nervous system disorders | | |
| Dizziness | Common | Very Common |
| Headache | Very Common | Very Common |
| Hypertonia | Common | Common |
| Paresthesia | Common | Very Common |
| Somnolence | Common | Common |
| Tremor | Common | Very Common |
| Convulsion | Common | Common |
| Dysgeusia | Uncommon | Uncommon |
| Cardiac disorders | | |
| Tachycardia | Common | Very Common |
| Vascular disorders | | |
| Hypertension | Very Common | Very Common |
| Hypotension | Common | Very Common |
| Lymphocele | Uncommon | Uncommon |
| Venous thrombosis | Common | Common |
| Vasodilatation | Common | Common |
| Respiratory, thoracic and mediastinal disorders | | |
| Bronchiectasis | Uncommon | Uncommon |
| Cough | Very Common | Very Common |

| Adverse reaction (MedDRA) System Organ Class | Renal transplant | Hepatic transplant |
|---|-----------------------------|-------------------------------|
| Dyspnoea | Very Common | Very Common |
| Interstitial lung disease | Uncommon | Very Rare |
| Pleural effusion | Common | Very Common |
| Pulmonary fibrosis | Very Rare | Uncommon |
| Gastrointestinal disorders | | |
| Abdominal distension | Common | Very Common |
| Abdominal pain | Very Common | Very Common |
| Colitis | Common | Common |
| Constipation | Very Common | Very Common |
| Decreased appetite | Common | Very Common |
| Diarrhoea | Very Common | Very Common |
| Dyspepsia | Very Common | Very Common |
| Esophagitis | Common | Common |
| Eructation | Uncommon | Uncommon |
| Flatulence | Common | Very Common |
| Gastritis | Common | Common |
| Gastrointestinal haemorrhage | Common | Common |
| Gastrointestinal ulcer | Common | Common |
| Gingival hyperplasia | Common | Common |
| Ileus | Common | Common |
| Mouth ulceration | Common | Common |
| Nausea | Very Common | Very Common |
| Pancreatitis | Uncommon | Common |
| Stomatitis | Common | Common |
| Vomiting | Very Common | Very Common |
| Immune system disorders | | |
| Hypersensitivity | Uncommon | Common |
| Hypogammaglobulinaemia | Uncommon | Very Rare |
| Hepatobiliary disorders | | |
| Blood alkaline phosphatase increased | Common | Common |
| Blood lactate dehydrogenase increased | Common | Uncommon |
| Hepatic enzyme increased | Common | Very Common |
| Hepatitis | Common | Very Common |
| Hyperbilirubinaemia | Common | Very Common |
| Jaundice | Uncommon | Common |
| Skin and subcutaneous tissue disorders | | |
| Acne | Common | Common |
| Alopecia | Common | Common |
| Rash | Common | Very Common |
| Skin hypertrophy | Common | Common |
| Musculoskeletal and connective tissue disorders | | |
| Arthralgia | Common | Common |
| Muscular weakness | Common | Common |

| Adverse reaction (MedDRA) | Renal transplant | Hepatic transplant |
|--|-----------------------------|-------------------------------|
| System Organ Class | | |
| Renal and urinary disorders | | |
| Blood creatinine increased | Common | Very Common |
| Blood urea increased | Uncommon | Very Common |
| Haematuria | Very Common | Common |
| Renal impairment | Common | Very Common |
| General disorders and administration site conditions | | |
| Asthenia | Very Common | Very Common |
| Chills | Common | Very Common |
| Oedema | Very Common | Very Common |
| Hernia | Common | Very Common |
| Malaise | Common | Common |
| Pain | Common | Very Common |
| Pyrexia | Very Common | Very Common |
| De novo purine synthesis inhibitors associated acute inflammatory syndrome | Uncommon | Uncommon |

Adverse reactions attributable to peripheral venous infusion were phlebitis and thrombosis, both observed at 4% in patients treated with CellCept 500 mg powder for concentrate for solution for infusion.

Description of selected adverse reactions

Malignancies

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including mycophenolate mofetil, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.4). Three-year safety data in renal transplant patients did not reveal any unexpected changes in incidence of malignancy compared to the 1-year data. Hepatic transplant patients were followed for at least 1 year, but less than 3 years.

Infections

All patients treated with immunosuppressants are at increased risk of bacterial, viral and fungal infections (some of which may lead to a fatal outcome), including those caused by opportunistic agents and latent viral reactivation. The risk increases with total immunosuppressive load (see section 4.4). The most serious infections were sepsis, peritonitis, meningitis, endocarditis tuberculosis and atypical mycobacterial infection. The most common opportunistic infections in patients receiving mycophenolate mofetil (2 g or 3 g daily) with other immunosuppressants in controlled clinical trials in renal and hepatic transplant patients followed for at least 1 year were candida mucocutaneous, CMV viraemia/syndrome and Herpes simplex. The proportion of patients with CMV viraemia/syndrome was 13.5%. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including mycophenolate mofetil.

Blood and lymphatic disorders

Cytopenias, including leukopenia, anaemia, thrombocytopenia and pancytopenia, are known risks associated with mycophenolate mofetil and may lead or contribute to the occurrence of infections and haemorrhages (see section 4.4). Agranulocytosis and neutropenia have been reported; therefore, regular monitoring of patients taking mycophenolate mofetil is advised (see section 4.4). There have been reports of aplastic anaemia and bone marrow failure in patients treated with mycophenolate mofetil, some of which have been fatal.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil (see section 4.4).

Isolated cases of abnormal neutrophil morphology, including the acquired Pelger-Huet anomaly, have been observed in patients treated with mycophenolate mofetil. These changes are not associated with impaired neutrophil function. These changes may suggest a 'left shift' in the maturity of neutrophils in haematological investigations, which may be mistakenly interpreted as a sign of infection in immunosuppressed patients such as those that receive mycophenolate mofetil.

Gastrointestinal disorders

The most serious gastrointestinal disorders were ulceration and haemorrhage which are known risks associated with mycophenolate mofetil. Mouth, oesophageal, gastric, duodenal, and intestinal ulcers often complicated by haemorrhage, as well as haematemesis, melena, and haemorrhagic forms of gastritis and colitis were commonly reported during the pivotal clinical trials. The most common gastrointestinal disorders, however, were diarrhoea, nausea and vomiting. Endoscopic investigation of patients with mycophenolate mofetil-related diarrhoea have revealed isolated cases of intestinal villous atrophy (see section 4.4).

Hypersensitivity

Hypersensitivity reactions, including angioneurotic oedema and anaphylactic reaction, have been reported.

Pregnancy, puerperium and perinatal conditions

Cases of spontaneous abortion have been reported in patients exposed to mycophenolate mofetil, mainly in the first trimester, see section 4.6.

Congenital disorders

Congenital malformations have been observed post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants, see section 4.6.

Respiratory, thoracic and mediastinal disorders

There have been isolated reports of interstitial lung disease and pulmonary fibrosis in patients treated with mycophenolate mofetil in combination with other immunosuppressants, some of which have been fatal. There have also been reports of bronchiectasis in children and adults.

Immune system disorders

Hypogammaglobulinaemia has been reported in patients receiving mycophenolate mofetil in combination with other immunosuppressants.

General disorders and administration site conditions

Oedema, including peripheral, face and scrotal oedema, was reported very commonly during the pivotal trials. Musculoskeletal pain such as myalgia, and neck and back pain were also very commonly reported.

De novo purine synthesis inhibitors associated acute inflammatory syndrome has been described from post-marketing experience as a paradoxical proinflammatory reaction associated with mycophenolate mofetil and mycophenolic acid, characterised by fever, arthralgia, arthritis, muscle pain and elevated inflammatory markers. Literature case reports showed rapid improvement following discontinuation of the medicinal product.

Special populations

Elderly

Elderly patients (≥ 65 years) may generally be at increased risk of adverse reactions due to immunosuppression. Elderly patients receiving mycophenolate mofetil as part of a combination immunosuppressive regimen may be at increased risk of certain infections (including cytomegalovirus

tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared to younger individuals.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Reports of overdoses with mycophenolate mofetil 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 medicinal product.

It is expected that an overdose of mycophenolate mofetil could possibly result in oversuppression of the immune system and increase susceptibility to infections and bone marrow suppression (see section 4.4). If neutropenia develops, dosing with mycophenolate mofetil should be interrupted or the dose reduced (see section 4.4).

Haemodialysis would not be expected to remove clinically significant amounts of MPA or MPAG. Bile acid sequestrants, such as cholestyramine, can remove MPA by decreasing the enterohepatic recirculation of the drug (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressive agents ATC code: L04AA06

Mechanism of action

Mycophenolate mofetil is the 2-morpholinoethyl ester of MPA. MPA is a selective, uncompetitive and reversible inhibitor of IMPDH, and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines whereas other cell types can utilise salvage pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells.

In addition to its inhibition of IMPDH and the resulting deprivation of lymphocytes, MPA also influences cellular checkpoints responsible for metabolic programming of lymphocytes. It has been shown, using human CD4+ T-cells, that MPA shifts transcriptional activities in lymphocytes from a proliferative state to catabolic processes relevant to metabolism and survival leading to an anergic state of T-cells, whereby the cells become unresponsive to their specific antigen.

5.2 Pharmacokinetic properties

Distribution

Following intravenous administration, mycophenolate mofetil undergoes rapid and complete metabolism to the active metabolite, MPA. The parent substance mycophenolate mofetil can be measured systemically during intravenous infusion. MPA at clinically relevant concentrations is 97% bound to plasma albumin.

As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed at approximately 6 – 12 hours post-dose. A reduction in the AUC of MPA of

approximately 40% is associated with the co-administration of cholestyramine (4 g TID), indicating that there is a significant amount of enterohepatic recirculation.

In the early post-transplant period (< 40 days post-transplant), renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30% lower and C_{\max} approximately 40% lower compared to the late post-transplant period (3 – 6 months post-transplant).

Biotransformation

MPA is metabolised principally by glucuronyl transferase (isoform UGT1A9) to form the 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 mycophenolate mofetil's side effects (diarrhoea, leukopenia).

Elimination

A negligible amount of substance is excreted as MPA (< 1% of the dose) in the urine. Oral administration of radiolabelled mycophenolate mofetil results in complete recovery of the administered dose, with 93% of the administered dose recovered in the urine and 6% recovered in faeces. Most (about 87%) of the administered dose is excreted in the urine as MPAG.

At clinically encountered concentrations, MPA and MPAG are not removed by haemodialysis. However, at high MPAG plasma concentrations (> 100 µg/ml), small amounts of MPAG are removed. By interfering with enterohepatic recirculation of the drug, bile acid sequestrants such as cholestyramine, reduce MPA AUC (see section 4.9).

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 potentially interact with renal organic anion transporters.

Enterohepatic recirculation interferes with accurate determination of MPA's disposition parameters; only apparent values can be indicated. In healthy volunteers and patients with autoimmune disease approximate clearance values of 10.6 L/h and 8.27 L/h respectively and half-life values of 17 h were observed. In transplant patients mean clearance values were higher (range 11.9-34.9 L/h) and mean half-life values shorter (5-11 h) with little difference between renal, hepatic or cardiac transplant patients. In the individual patients, these elimination parameters vary based on type of co-treatment with other immunosuppressants, time post-transplantation, plasma albumin concentration and renal function. These factors explain why reduced exposure to mycophenolate is seen when mycophenolate mofetil is co-administered with ciclosporin (see section 4.5) and why plasma concentrations tend to increase over time compared to what is observed immediately after transplantation.

Equivalence with oral dosage forms

MPA AUC values obtained following administration of 1 g BID intravenous mycophenolate mofetil to renal transplant patients in the early post-transplant phase are comparable to those observed following 1 g BID oral mycophenolate mofetil. In hepatic transplant patients, administration of 1 g BID intravenous mycophenolate mofetil followed by 1.5 g BID oral mycophenolate mofetil resulted in MPA AUC values similar to those found in renal transplant patients administered 1 g mycophenolate mofetil BID.

Special populations

Renal impairment

In a single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate < 25 ml/min/1.73 m²) were 28 – 75% higher

relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. The mean single dose MPAG AUC was 3 – 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. Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied. No data are available for hepatic transplant patients with severe chronic renal impairment.

Delayed renal graft function

In patients with delayed renal graft function post-transplant, mean MPA AUC_{0-12h} was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC_{0-12h} was 2 – 3-fold higher than in post-transplant patients without delayed graft function. There may be a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of mycophenolate mofetil does not appear to be necessary.

Hepatic impairment

In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were 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

The pharmacokinetics of mycophenolate mofetil and its metabolites have not been found to be altered in the elderly patients (≥ 65 years) when compared to younger transplant patients.

Patients taking oral contraceptives

A study of the co-administration of mycophenolate mofetil (1 g BID) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) conducted in 18 non-transplant women (not taking other immunosuppressants) over 3 consecutive menstrual cycles showed no clinically relevant influence of mycophenolate mofetil on the ovulation-suppressing action of the oral contraceptives. Serum levels of LH, FSH and progesterone were not significantly affected. The pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by co-administration of mycophenolate mofetil (see also section 4.5).

5.3 Preclinical safety data

In experimental models, mycophenolate mofetil was not tumourigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2 – 3 times the systemic exposure (AUC or C_{max}) observed in renal transplant patients at the recommended clinical dose of 2 g/day.

Two genotoxicity assays (*in vitro* mouse lymphoma assay and *in vivo* mouse bone marrow micronucleus test) showed a potential of mycophenolate mofetil to cause chromosomal aberrations. These effects can be related to the pharmacodynamic mode of action, i.e. inhibition of nucleotide synthesis in sensitive cells. Other *in vitro* tests for detection of gene mutation did not demonstrate genotoxic activity.

In teratology studies in rats and rabbits, foetal resorptions and malformations occurred in rats at 6 mg/kg/day (including anophthalmia, agnathia, and hydrocephaly) and in rabbits at 90 mg/kg/day (including cardiovascular and renal anomalies, such as ectopia cordis and ectopic kidneys, and diaphragmatic and umbilical hernia), in the absence of maternal toxicity. The systemic exposure at these levels is approximately equivalent to or less than 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day (see section 4.6).

The haematopoietic and lymphoid systems were the primary organs affected in toxicology studies conducted with mycophenolate mofetil in the rat, mouse, dog and monkey. These effects occurred at systemic exposure levels that are equivalent to or less than the clinical exposure at the recommended dose of 2 g/day. Gastrointestinal effects were observed in the dog at systemic exposure levels

equivalent to or less than the clinical exposure at the recommended dose. Gastrointestinal and renal effects consistent with dehydration were also observed in the monkey at the highest dose (systemic exposure levels equivalent to or greater than clinical exposure). The non-clinical toxicity profile of mycophenolate mofetil appears to be consistent with adverse events observed in human clinical trials, which now provide safety data of more relevance to the patient population (see section 4.8).

Environmental Risk Assessment (ERA)

Environmental risk assessment studies have shown that the active substance, MPA may pose a risk for groundwater via bank filtration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

CellCept 500 mg powder for concentrate for solution for infusion

polysorbate 80
citric acid
hydrochloric acid
sodium chloride

6.2 Incompatibilities

CellCept 500 mg powder for concentrate for solution for infusion solution should not be mixed or administered concurrently via the same catheter with other intravenous medicinal products or infusion admixtures.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf-life

Powder for concentrate for solution for infusion: 3 years.

Reconstituted solution and infusion solution: If the infusion solution is not prepared immediately prior to administration, the commencement of administration of the infusion solution should be within 3 hours from reconstitution and dilution of the medicinal product.

6.4 Special precautions for storage

Powder for concentrate for solution for infusion: Do not store above 30 °C.

Reconstituted solution and infusion solution: Store at 15 – 30 °C.

6.5 Nature and contents of container

20 ml type I clear glass vials with grey butyl rubber stopper and aluminium seals with plastic flip-off caps. CellCept 500 mg powder for concentrate for solution for infusion is available in packs containing 4 vials.

6.6 Special precautions for disposal and other handling

Preparation of Infusion Solution (6 mg/ml)

CellCept 500 mg powder for concentrate for solution for infusion does not contain an antibacterial preservative; therefore, reconstitution and dilution of the product must be performed under aseptic conditions.

CellCept 500 mg powder for concentrate for solution for infusion must be prepared in two steps: the first step is a reconstitution step with glucose intravenous infusion 5% and the second step is a dilution step with glucose intravenous infusion 5%. A detailed description of the preparation is given below:

Step 1

- a. Two vials of CellCept 500 mg powder for concentrate for solution for infusion are used for preparing each 1 g dose. Reconstitute the content of each vial by injecting 14 ml of glucose intravenous infusion 5%.
- b. Gently shake the vial to dissolve the medicinal product yielding a slightly yellow solution.
- c. Inspect the resulting solution for particulate matter and discolouration prior to further dilution. Discard the vial if particulate matter or discolouration is observed.

Step 2

- a. Further dilute the content of the two reconstituted vials (approx. 2 x 15 ml) into 140 ml of glucose intravenous infusion 5%. The final concentration of the solution is 6 mg/ml mycophenolate mofetil.
- b. Inspect the infusion solution for particulate matter or discolouration. Discard the infusion solution if particulate matter or discolouration is observed.

If the infusion solution is not prepared immediately prior to administration, the commencement of administration of the infusion solution should be within 3 hours from reconstitution and dilution of the medicinal product. Keep solutions at 15 – 30°C.

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/005/005 CellCept (4 vials)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 February 1996
Date of latest renewal: 13 March 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

CellCept 1 g/5 ml powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle contains 35 g mycophenolate mofetil in 110 g powder for oral suspension. 5 ml of the reconstituted suspension contains 1 g of mycophenolate mofetil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CellCept 1 g/5 ml powder for oral suspension is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adult and paediatric (1 to 18 years of age) patients receiving allogeneic renal, cardiac or hepatic transplants.

4.2 Posology and method of administration

Treatment should be initiated and maintained by appropriately qualified transplant specialists.

Posology

Adults

Renal transplant

Treatment with 1 g/5 ml powder for oral suspension should be initiated within 72 hours following transplantation. The recommended dose in renal transplant patients is 1 g administered twice daily (2 g daily dose), i.e. 5 ml oral suspension twice daily.

Cardiac transplant

Treatment should be initiated within 5 days following transplantation. The recommended dose in cardiac transplant patients is 1.5 g administered twice daily (3 g daily dose).

Hepatic transplant

Treatment of intravenous mycophenolate mofetil should be administered for the first 4 days following hepatic transplant, with oral mycophenolate mofetil initiated as soon after this as it can be tolerated. The recommended oral dose in hepatic transplant patients is 1.5 g administered twice daily (3 g daily dose).

Paediatric population (1 to 18 years)

The paediatric dosing information in this section applies to all oral formulations within the range of mycophenolate mofetil products, as appropriate. Different oral formulations should not be substituted without clinical supervision.

The recommended mycophenolate mofetil initial dose for paediatric renal, cardiac and hepatic transplant patients is 600 mg/m² (of body surface area (BSA)) administered orally, twice daily (initial total daily dose not to exceed 2 g, or 10 ml of the oral suspension).

The dose and product form should be individualised based on clinical assessment. If the recommended initial dose is well tolerated but does not achieve clinically adequate immunosuppression in paediatric cardiac and hepatic transplant patients, the dose can be increased to 900 mg/m² BSA twice daily (maximum total daily dose of 3 g, or 15 ml of the oral suspension). The recommended maintenance dose for paediatric renal transplant patients remains at 600 mg/m² twice daily (maximum total daily dose of 2 g or 10 ml of the oral suspension).

The mycophenolate mofetil powder for oral suspension should be used in those patients unable to swallow capsules and tablets and/or with a BSA lower than 1.25 m² due to the increased risk of choking. Patients with a BSA of 1.25 to 1.5 m² may be prescribed mycophenolate mofetil capsules at a dose of 750 mg twice daily (1.5 g daily dose). Patients with a BSA greater than 1.5 m² may be prescribed mycophenolate mofetil capsules or tablets at a dose of 1 g twice daily (2 g daily dose). As some adverse reactions occur with greater frequency in this age group (see section 4.8) compared with adults, temporary dose reduction or interruption may be required; these will need to take into account relevant clinical factors including severity of reaction.

The table below shows, for a range of BSA, the dose (mg) to volume (ml) conversion using the oral dispenser.

Table 1 Dose (mg) to volume (ml) conversion of suspension (1 g/ 5 ml) using the oral dispenser

| 600 mg/m ² dose level | | | 900 mg/m ² dose level | | |
|--|---|--------------------------|--|---|--------------------------|
| Child's Body Surface Area (m ²) ^A | Total dose to be administered twice a day | | Child's Body Surface Area (m ²) ^A | Total dose to be administered twice a day | |
| | mg | ml (with oral dispenser) | | mg | ml (with oral dispenser) |
| 0.5 | 300 | 1.5 | 0.5 | 450 | 2.25 |
| 0.58 | 350 | 1.75 | 0.56 | 500 | 2.5 |
| 0.67 | 400 | 2.0 | 0.61 | 550 | 2.75 |
| 0.75 | 450 | 2.25 | 0.67 | 600 | 3.0 |
| 0.83 | 500 | 2.5 | 0.72 | 650 | 3.25 |
| 0.92 | 550 | 2.75 | 0.78 | 700 | 3.5 |
| 1.0 | 600 | 3.0 | 0.89 | 800 | 4.0 |
| 1.08 | 650 | 3.25 | 1.0 | 900 | 4.5 |
| 1.17 | 700 | 3.5 | 1.11 | 1000 | 5.0 ^B |
| 1.25 | 750 | 3.75 | 1.22 | 1100 | 5.5 ^B |
| 1.33 | 800 | 4.0 | 1.33 | 1200 | 6.0 ^B |

The table lists doses and volumes as calculated theoretically for the two dosing regimens. As the oral dispenser has graduations of 0.25 ml only (corresponding to a 50 mg dose increment), the volume in ml has been rounded up to the nearest graduation mark.

^Abased on the Mosteller formula for body surface area (BSA) calculation:

$$BSA (m^2) = \sqrt{(Height (cm) \times Weight (kg))/3600}$$

^BDoses above 5 ml to be composed from two draws, of at least 1 ml each. If feasible, switch to the oral solid dosage form for those that are able to swallow.

Use in special populations

Elderly

The recommended dose of 1 g administered twice a day for renal transplant patients and 1.5 g twice a day for cardiac or hepatic transplant patients is appropriate for the elderly.

Renal impairment

In renal transplant patients with severe chronic renal impairment (glomerular filtration rate $< 25 \text{ ml/min/1.73 m}^2$), outside the immediate post-transplant period, doses greater than 1 g administered twice a day should be avoided. These patients should also be carefully observed. No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively. (see section 5.2). No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Severe hepatic impairment

No dose adjustments are needed for renal transplant patients with severe hepatic parenchymal disease. No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

Treatment during rejection episodes

Adults

Mycophenolic acid (MPA) is the active metabolite of mycophenolate mofetil. Renal transplant rejection does not lead to changes in MPA pharmacokinetics; dosage reduction or interruption of treatment is not required. There is no basis for dose adjustment following cardiac transplant rejection. No pharmacokinetic data are available during hepatic transplant rejection.

Paediatric population

No data are available for treatment of first or refractory rejection in paediatric transplant patients.

Method of administration

For oral use.

Note: If required, CellCept 1 g/5 ml powder for oral suspension can be administered via a nasogastric tube with a minimum size of 8 French (minimum 1.7 mm interior diameter).

Precautions to be taken before handling or administering the medicinal product.

Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits, avoid inhalation or direct contact with skin or mucous membranes of the dry powder as well as direct contact of the reconstituted suspension with the skin. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.

For instruction on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- CellCept should not be given to patients with hypersensitivity to mycophenolate mofetil, mycophenolic acid or to any of the excipients listed in section 6.1. Hypersensitivity reactions to this medicinal product have been observed (see section 4.8).
- Treatment should not be given to women of childbearing potential who are not using highly effective contraception (see section 4.6).
- Treatment should not be initiated in women of childbearing potential without providing a pregnancy test result to rule out unintended use in pregnancy (see section 4.6).
- Treatment should not be used in pregnancy unless there is no suitable alternative treatment to prevent transplant rejection (see section 4.6).

- Treatment should not be given to women who are breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

Neoplasms

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including CellCept, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.8). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As general advice to minimise the risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Infections

Patients treated with immunosuppressants, including mycophenolate mofetil, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis (see section 4.8). Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation and infections caused by polyomaviruses (BK virus-associated nephropathy, JC virus-associated progressive multifocal leukoencephalopathy PML). Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. Mycophenolic acid has a cytostatic effect on B- and T-lymphocytes, therefore an increased severity of COVID-19 may occur, and appropriate clinical action should be considered.

There have been reports of hypogammaglobulinaemia in association with recurrent infections in patients receiving mycophenolate mofetil in combination with other immunosuppressants. In some of these cases switching mycophenolate mofetil to an alternative immunosuppressant resulted in serum IgG levels returning to normal. Patients on mycophenolate mofetil who develop recurrent infections should have their serum immunoglobulins measured. In cases of sustained, clinically relevant hypogammaglobulinaemia, appropriate clinical action should be considered taking into account the potent cytostatic effects that mycophenolic acid has on T- and B-lymphocytes.

There have been published reports of bronchiectasis in adults and children who received mycophenolate mofetil in combination with other immunosuppressants. In some of these cases switching mycophenolate mofetil to another immunosuppressant resulted in improvement in respiratory symptoms. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect on the lung. There have also been isolated reports of interstitial lung disease and pulmonary fibrosis, some of which were fatal (see section 4.8). It is recommended that patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, are investigated.

Blood and immune system

Patients receiving mycophenolate mofetil should be monitored for neutropenia, which may be related to the treatment itself, concomitant medications, viral infections, or some combination of these causes. Patients taking mycophenolate mofetil should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If neutropenia develops (absolute neutrophil count $< 1.3 \times 10^3/\mu\text{l}$), it may be appropriate to interrupt or discontinue mycophenolate mofetil.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil in combination with other immunosuppressants. The mechanism for mycophenolate mofetil induced PRCA is unknown. PRCA may resolve with dose reduction or cessation of mycophenolate mofetil therapy. Changes to mycophenolate mofetil therapy should only be undertaken under

appropriate supervision in transplant recipients in order to minimise the risk of graft rejection (see section 4.8).

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

Patients should be advised, that during treatment with mycophenolate mofetil, vaccinations may be less effective, and the use of live attenuated vaccines should be avoided (see section 4.5). Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

Gastrointestinal

Mycophenolate mofetil has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, haemorrhage and perforation. Treatment should be administered with caution in patients with active serious digestive system disease.

Mycophenolate is an IMPDH (inosine monophosphate dehydrogenase) inhibitor. Therefore, 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 plasma levels of mycophenolate and its efficacy (see also section 4.5).

It is recommended that mycophenolate mofetil should not be administered concomitantly with azathioprine because such concomitant administration has not been studied.

CellCept 1 g/5 ml powder for oral suspension contains aspartame. Therefore, care should be taken if CellCept 1 g/5 ml powder for oral suspension is administered to patients with phenylketonuria (see section 6.1)

The risk/benefit ratio of mycophenolate mofetil in combination with sirolimus has not been established (see also section 4.5).

This medicinal product contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Therapeutic drug monitoring

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).

Special populations

Paediatric population

Very limited post-marketing information indicates a higher frequency of the following adverse events in patients under 6 years of age compared to older patients:

- lymphomas and other malignancies, particularly of post-transplant lymphoproliferative disorder in cardiac transplant patients.
- blood and lymphatic system disorders including anaemia and neutropenia in cardiac transplant patients. This applies for children under 6 years of age compared to older patients, and compared to paediatric hepatic/renal transplant recipients.

Patients taking mycophenolate mofetil should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If neutropenia develops, it may be appropriate to interrupt or discontinue mycophenolate mofetil.

- gastrointestinal disorders including diarrhoea and vomiting.

Treatment should be administered with caution in patients with active serious digestive system disease.

Elderly population

Elderly patients may be at an increased risk of adverse events such as certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared with younger individuals (see section 4.8).

Teratogenic effects

Mycophenolate is a powerful human teratogen. Spontaneous abortion (rate of 45% to 49%) and congenital malformations (estimated rate of 23% to 27%) have been reported following mycophenolate mofetil exposure during pregnancy. Therefore, treatment is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejection. Female patients of childbearing potential should be made aware of the risks and follow the recommendations provided in section 4.6 (e.g. contraceptive methods, pregnancy testing) prior to, during, and after therapy with mycophenolate mofetil. Physicians should ensure that women taking mycophenolate mofetil understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult their physician if there is a possibility of pregnancy.

Contraception (see section 4.6)

Because of robust clinical evidence showing a high risk of abortion and congenital malformations when mycophenolate mofetil is used in pregnancy, every effort to avoid pregnancy during treatment should be taken. Therefore, women with childbearing potential must use at least one form of reliable contraception (see section 4.3) before starting mycophenolate mofetil therapy, during therapy, and for six weeks after stopping the therapy, unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred to minimise the potential for contraceptive failure and unintended pregnancy.

For contraception advice for men see section 4.6.

Educational materials

In order to assist patients in avoiding foetal exposure to mycophenolate and to provide additional important safety information, the Marketing Authorisation Holder will provide educational materials to healthcare professionals. The educational materials will reinforce the warnings about the teratogenicity of mycophenolate, provide advice on contraception before therapy is started and guidance on the need for pregnancy testing. Full patient information about the teratogenic risk and the pregnancy prevention measures should be given by the physician to women of childbearing potential and, as appropriate, to male patients.

Additional precautions

Patients should not donate blood during therapy or for at least 6 weeks following discontinuation of mycophenolate mofetil. Men should not donate semen during therapy or for 90 days following discontinuation of mycophenolate mofetil.

Methyl Parahydroxybenzoate contents

This medicinal product contains methyl parahydroxybenzoate (E218) which may cause allergic reactions (possibly delayed).

Sodium contents

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Aciclovir

Higher aciclovir plasma concentrations were observed when mycophenolate mofetil was administered with aciclovir in comparison to the administration of aciclovir alone. The changes in MPAG (the phenolic glucuronide of MPA) pharmacokinetics (MPAG increased by 8%) were minimal and are not considered clinically significant. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are aciclovir concentrations, the potential exists for mycophenolate mofetil and aciclovir, or its prodrugs, e.g. valaciclovir, to compete for tubular secretion and further increases in concentrations of both substances may occur.

Antacids and proton pump inhibitors (PPIs)

Decreased MPA exposure has been observed when antacids, such as magnesium and aluminium hydroxides, and PPIs, including lansoprazole and pantoprazole, were administered with mycophenolate mofetil. When comparing rates of transplant rejection or rates of graft loss between mycophenolate mofetil patients taking PPIs vs. mycophenolate mofetil patients not taking PPIs, no significant differences were seen. These data support extrapolation of this finding to all antacids because the reduction in exposure when mycophenolate mofetil was co-administered with magnesium and aluminium hydroxides is considerably less than when mycophenolate mofetil was co-administered with PPIs.

Medicinal products that interfere with enterohepatic recirculation (e.g. cholestyramine, ciclosporin A, antibiotics)

Caution should be used with medicinal products that interfere with enterohepatic recirculation because of their potential to reduce the efficacy of mycophenolate mofetil.

Cholestyramine

Following single dose administration of 1.5 g of mycophenolate mofetil to normal healthy subjects pre-treated with 4 g TID of cholestyramine for 4 days, there was a 40% reduction in the AUC of MPA. (see section 4.4, and section 5.2). Caution should be used during concomitant administration because of the potential to reduce efficacy of mycophenolate mofetil.

Ciclosporin A

Ciclosporin A (CsA) pharmacokinetics are unaffected by mycophenolate mofetil.

In contrast, if concomitant CsA treatment is stopped, an increase in MPA AUC of around 30% should be expected. CsA interferes with MPA enterohepatic recycling, resulting in reduced MPA exposures by 30 - 50% in renal transplant patients treated with mycophenolate mofetil and CsA compared with patients receiving sirolimus or belatacept and similar doses of mycophenolate mofetil (see also section

4.4). Conversely, changes of MPA exposure should be expected when switching patients from CsA to one of the immunosuppressants which does not interfere with MPA's enterohepatic cycle.

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 about 50% have been reported in renal transplant recipients in the days immediately following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. This effect tended to diminish with continued antibiotic use and to cease within a few days of antibiotic discontinuation. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

Norfloxacin and metronidazole

In healthy volunteers, no significant interaction was observed when mycophenolate mofetil was concomitantly administered with norfloxacin or metronidazole separately. However, norfloxacin and metronidazole combined reduced the MPA exposure by approximately 30% following a single dose of mycophenolate mofetil.

Trimethoprim/sulfamethoxazole

No effect on the bioavailability of MPA was observed.

Medicinal products that affect glucuronidation (e.g. isavuconazole, telmisartan)

Concomitant administration of drugs affecting glucuronidation of MPA may change MPA exposure. Caution is therefore recommended when administering these drugs concomitantly with mycophenolate mofetil.

Isavuconazole

An increase of MPA exposure ($AUC_{0-\infty}$) by 35% was observed with concomitant administration of isavuconazole.

Telmisartan

Concomitant administration of telmisartan and mycophenolate mofetil resulted in an approximately 30% decrease of MPA concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression, which in turn results in an enhanced uridine diphosphate glucuronyltransferase isoform 1A9 (UGT1A9) expression and activity. When comparing rates of transplant rejection, rates of graft loss or adverse event profiles between patients on mycophenolate mofetil with and without concomitant telmisartan medication, no clinical consequences of the pharmacokinetic drug-drug interaction were seen.

Ganciclovir

Based on the results of a single dose administration study of recommended doses of oral mycophenolate mofetil and intravenous ganciclovir and the known effects of renal impairment on the pharmacokinetics of mycophenolate mofetil (see section 4.2) and ganciclovir, it is anticipated that co-administration of these agents (which compete for mechanisms of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics is anticipated and mycophenolate mofetil dose adjustment is not required. In patients with renal impairment in whom mycophenolate mofetil and ganciclovir or its prodrugs, e.g. valganciclovir, are co-administered, the dose recommendations for ganciclovir should be observed and patients should be monitored carefully.

Oral contraceptives

The pharmacodynamics and pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by co-administration of mycophenolate mofetil (see also section 5.2).

Rifampicin

In patients not also taking ciclosporin, concomitant administration of mycophenolate mofetil and rifampicin resulted in a decrease in MPA exposure (AUC_{0-12h}) of 18% to 70%. It is recommended to monitor MPA exposure levels and to adjust mycophenolate mofetil doses accordingly to maintain clinical efficacy when rifampicin is administered concomitantly.

Sevelamer

Decrease in MPA C_{max} and AUC_{0-12h} by 30% and 25%, respectively, were observed when mycophenolate mofetil was concomitantly administered with sevelamer without any clinical consequences (i.e. graft rejection). It is recommended, however, to administer mycophenolate mofetil at least one hour before or three hours after sevelamer intake to minimise the impact on the absorption of MPA. There are no data on mycophenolate mofetil with phosphate binders other than sevelamer.

Tacrolimus

In hepatic transplant patients initiated on mycophenolate mofetil and tacrolimus, the AUC and C_{max} of MPA, the active metabolite of mycophenolate mofetil, were not significantly affected by co-administration with tacrolimus. In contrast, there was an increase of approximately 20% in tacrolimus AUC when multiple doses of mycophenolate mofetil (1.5 g BID) were administered to hepatic transplant patients taking tacrolimus. However, in renal transplant patients, tacrolimus concentration did not appear to be altered by mycophenolate mofetil (see also section 4.4).

Live vaccines

Live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished (see also section 4.4).

Paediatric population

Interaction studies have only been performed in adults.

Potential interaction

Co-administration of probenecid with mycophenolate mofetil in monkeys raises plasma AUC of MPAG by 3-fold. Thus, other substances known to undergo renal tubular secretion may compete with MPAG, and thereby raise plasma concentrations of MPAG or the other substance undergoing tubular secretion.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Pregnancy whilst taking mycophenolate mofetil must be avoided. Therefore, women of childbearing potential must use at least one form of reliable contraception (see section 4.3) before starting the therapy, during therapy, and for six weeks after stopping the therapy, unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred.

Pregnancy

Mycophenolate mofetil is contraindicated during pregnancy unless there is no suitable alternative treatment to prevent transplant rejection. Treatment should not be initiated without providing a negative pregnancy test result to rule out unintended use in pregnancy (see section 4.3).

Female patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations at the beginning of the treatment and must be counselled regarding pregnancy prevention and planning.

Before starting treatment, women of childbearing potential should have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/ml in order to exclude unintended exposure of an embryo to mycophenolate. It is recommended that the second test should be performed 8-10 days after the first test. For transplants from deceased donors, if it is not possible to perform two tests 8-10 days apart before treatment starts (because of the timing of transplant organ availability), a pregnancy test must be performed immediately before starting treatment and a further test 8-10 days later. Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported). Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.

Mycophenolate is a powerful human teratogen, with an increased risk of spontaneous abortions and congenital malformations in case of exposure during pregnancy;

- Spontaneous abortions have been reported in 45 to 49% of pregnant women exposed to mycophenolate mofetil, compared to a reported rate of between 12 and 33% in solid organ transplant patients treated with immunosuppressants other than mycophenolate mofetil.
- Based on literature reports, malformations occurred in 23 to 27% of live births in women exposed to mycophenolate mofetil during pregnancy (compared to 2 to 3 % of live births in the overall population and approximately 4 to 5% of live births in solid organ transplant recipients treated with immunosuppressants other than mycophenolate mofetil).

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

- Abnormalities of the ear (e.g. abnormally formed or absent external ear), external auditory canal atresia (middle ear);
- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;
- Abnormalities of the eye (e.g. coloboma);
- Congenital heart disease such as atrial and ventricular septal defects;
- Malformations of the fingers (e.g. polydactyly, syndactyly);
- Tracheo-oesophageal malformations (e.g. oesophageal atresia);
- Nervous system malformations such as spina bifida;
- Renal abnormalities.

In addition, there have been isolated reports of the following malformations:

- Microphthalmia;
- Congenital choroid plexus cyst;
- Septum pellucidum agenesis;
- Olfactory nerve agenesis.

Studies in animals have shown reproductive toxicity (see section 5.3).

Breast-feeding

Limited data shows that mycophenolic acid is excreted in human milk. Because of the potential for serious adverse reactions to mycophenolic acid in breast-fed infants, treatment is contraindicated in nursing mothers (see section 4.3).

Men

The limited clinical evidence available does not indicate an increased risk of malformations or miscarriage following paternal exposure to mycophenolate mofetil.

MPA is a powerful teratogen. It is not known if MPA is present in semen. Calculations based on animal data show that the maximum amount of MPA that could potentially be transferred to woman is so low that it would be unlikely to have an effect. Mycophenolate has been shown to be genotoxic in animal studies at concentrations exceeding the human therapeutic exposures only by small margins such that the risk of genotoxic effects on sperm cells cannot completely be excluded.

Therefore, the following precautionary measures are recommended: sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 90 days after cessation of mycophenolate mofetil. Male patients of reproductive potential should be made aware of and discuss with a qualified healthcare professional the potential risks of fathering a child.

Fertility

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. The systemic exposure at this dose represents 2 – 3 times the clinical exposure at the recommended clinical dose of 2 g/day in renal transplant patients and 1.3 – 2 times the clinical exposure at the recommended clinical dose of 3 g/day in cardiac transplant patients. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (including anophthalmia, agnathia, and hydrocephaly) in the first generation offspring in the absence of maternal toxicity. The systemic exposure at this dose was approximately 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

4.7 Effects on ability to drive and use machines

Mycophenolate mofetil has moderate influence on the ability to drive and use machines. Treatment may cause somnolence, confusion, dizziness, tremor or hypotension, and therefore patients are advised to use caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

Diarrhoea (up to 52.6%), leukopenia (up to 45.8%), bacterial infections (up to 39.9%) and vomiting (up to 39.1%) were among the most common and/or serious adverse reactions associated with the administration of mycophenolate mofetil in combination with ciclosporin and corticosteroids. There is evidence of a higher frequency of certain types of infections (see section 4.4).

Tabulated list of adverse reactions

The adverse reactions from clinical trials and post-marketing experience are listed in Table 2, by MedDRA system organ class (SOC) along with their frequencies. The corresponding frequency category for each adverse reaction is based on the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\,000$ to $< 1/100$), rare ($\geq 1/10\,000$ to $< 1/1\,000$) and very rare ($< 1/10\,000$). Due to the large differences observed in the frequency of certain adverse reactions across the different transplant indications, the frequency is presented separately for renal, hepatic and cardiac transplant patients.

Table 2 Adverse reactions in studies investigating mycophenolate mofetil treatment in adults and adolescents, or through post-marketing surveillance

| Adverse reaction (MedDRA) System Organ Class | Renal transplant | Hepatic transplant | Cardiac transplant |
|---|---------------------|-----------------------|-----------------------|
| | Frequency | Frequency | Frequency |
| Infections and infestations | | | |
| Bacterial infections | Very Common | Very Common | Very Common |
| Fungal infections | Common | Very Common | Very Common |
| Protozoal infections | Uncommon | Uncommon | Uncommon |
| Viral infections | Very Common | Very Common | Very Common |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | | | |
| Benign neoplasm of skin | Common | Common | Common |
| Lymphoma | Uncommon | Uncommon | Uncommon |
| Lymphoproliferative disorder | Uncommon | Uncommon | Uncommon |
| Neoplasm | Common | Common | Common |
| Skin cancer | Common | Uncommon | Common |
| Blood and lymphatic system disorders | | | |
| Anaemia | Very Common | Very Common | Very Common |
| Aplasia pure red cell | Uncommon | Uncommon | Uncommon |
| Bone marrow failure | Uncommon | Uncommon | Uncommon |
| Ecchymosis | Common | Common | Very Common |
| Leukocytosis | Common | Very Common | Very Common |
| Leukopenia | Very Common | Very Common | Very Common |
| Pancytopenia | Common | Common | Uncommon |
| Pseudolymphoma | Uncommon | Uncommon | Common |
| Thrombocytopenia | Common | Very Common | Very Common |
| Metabolism and nutrition disorders | | | |
| Acidosis | Common | Common | Very Common |
| Hypercholesterolaemia | Very Common | Common | Very Common |
| Hyperglycaemia | Common | Very Common | Very Common |
| Hyperkalaemia | Common | Very Common | Very Common |
| Hyperlipidaemia | Common | Common | Very Common |
| Hypocalcaemia | Common | Very Common | Common |
| Hypokalaemia | Common | Very Common | Very Common |
| Hypomagnesaemia | Common | Very Common | Very Common |
| Hypophosphataemia | Very Common | Very Common | Common |
| Hyperuricaemia | Common | Common | Very Common |
| Gout | Common | Common | Very Common |
| Weight decreased | Common | Common | Common |
| Psychiatric disorders | | | |
| Confusional state | Common | Very Common | Very Common |
| Depression | Common | Very Common | Very Common |
| Insomnia | Common | Very Common | Very Common |
| Agitation | Uncommon | Common | Very Common |

| Adverse reaction (MedDRA) System Organ Class | Renal transplant | Hepatic transplant | Cardiac transplant |
|---|-----------------------------|-------------------------------|-------------------------------|
| Anxiety | Common | Very Common | Very Common |
| Thinking abnormal | Uncommon | Common | Common |
| Nervous system disorders | | | |
| Dizziness | Common | Very Common | Very Common |
| Headache | Very Common | Very Common | Very Common |
| Hypertonia | Common | Common | Very Common |
| Paresthesia | Common | Very Common | Very Common |
| Somnolence | Common | Common | Very Common |
| Tremor | Common | Very Common | Very Common |
| Convulsion | Common | Common | Common |
| Dysgeusia | Uncommon | Uncommon | Common |
| Cardiac disorders | | | |
| Tachycardia | Common | Very Common | Very Common |
| Vascular disorders | | | |
| Hypertension | Very Common | Very Common | Very Common |
| Hypotension | Common | Very Common | Very Common |
| Lymphocele | Uncommon | Uncommon | Uncommon |
| Venous thrombosis | Common | Common | Common |
| Vasodilatation | Common | Common | Very Common |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchiectasis | Uncommon | Uncommon | Uncommon |
| Cough | Very Common | Very Common | Very Common |
| Dyspnoea | Very Common | Very Common | Very Common |
| Interstitial lung disease | Uncommon | Very Rare | Very Rare |
| Pleural effusion | Common | Very Common | Very Common |
| Pulmonary fibrosis | Very Rare | Uncommon | Uncommon |
| Gastrointestinal disorders | | | |
| Abdominal distension | Common | Very Common | Common |
| Abdominal pain | Very Common | Very Common | Very Common |
| Colitis | Common | Common | Common |
| Constipation | Very Common | Very Common | Very Common |
| Decreased appetite | Common | Very Common | Very Common |
| Diarrhoea | Very Common | Very Common | Very Common |
| Dyspepsia | Very Common | Very Common | Very Common |
| Esophagitis | Common | Common | Common |
| Eructation | Uncommon | Uncommon | Common |
| Flatulence | Common | Very Common | Very Common |
| Gastritis | Common | Common | Common |
| Gastrointestinal haemorrhage | Common | Common | Common |
| Gastrointestinal ulcer | Common | Common | Common |
| Gingival hyperplasia | Common | Common | Common |
| Ileus | Common | Common | Common |

| Adverse reaction (MedDRA) System Organ Class | Renal transplant | Hepatic transplant | Cardiac transplant |
|--|-----------------------------|-------------------------------|-------------------------------|
| Mouth ulceration | Common | Common | Common |
| Nausea | Very Common | Very Common | Very Common |
| Pancreatitis | Uncommon | Common | Uncommon |
| Stomatitis | Common | Common | Common |
| Vomiting | Very Common | Very Common | Very Common |
| Immune system disorders | | | |
| Hypersensitivity | Uncommon | Common | Common |
| Hypogammaglobulinaemia | Uncommon | Very Rare | Very Rare |
| Hepatobiliary disorders | | | |
| Blood alkaline phosphatase increased | Common | Common | Common |
| Blood lactate dehydrogenase increased | Common | Uncommon | Very Common |
| Hepatic enzyme increased | Common | Very Common | Very Common |
| Hepatitis | Common | Very Common | Uncommon |
| Hyperbilirubinaemia | Common | Very Common | Very Common |
| Jaundice | Uncommon | Common | Common |
| Skin and subcutaneous tissue disorders | | | |
| Acne | Common | Common | Very Common |
| Alopecia | Common | Common | Common |
| Rash | Common | Very Common | Very Common |
| Skin hypertrophy | Common | Common | Very Common |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | Common | Common | Very Common |
| Muscular weakness | Common | Common | Very Common |
| Renal and urinary disorders | | | |
| Blood creatinine increased | Common | Very Common | Very Common |
| Blood urea increased | Uncommon | Very Common | Very Common |
| Haematuria | Very Common | Common | Common |
| Renal impairment | Common | Very Common | Very Common |
| General disorders and administration site conditions | | | |
| Asthenia | Very Common | Very Common | Very Common |
| Chills | Common | Very Common | Very Common |
| Oedema | Very Common | Very Common | Very Common |
| Hernia | Common | Very Common | Very Common |
| Malaise | Common | Common | Common |
| Pain | Common | Very Common | Very Common |
| Pyrexia | Very Common | Very Common | Very Common |
| De novo purine synthesis inhibitors associated acute inflammatory syndrome | Uncommon | Uncommon | Uncommon |

Description of selected adverse reactions

Malignancies

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including mycophenolate mofetil, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.4). Three-year safety data in renal and cardiac transplant patients did not reveal any unexpected changes in incidence of malignancy compared to the 1-year data. Hepatic transplant patients were followed for at least 1 year, but less than 3 years.

Infections

All patients treated with immunosuppressants are at increased risk of bacterial, viral and fungal infections (some of which may lead to a fatal outcome), including those caused by opportunistic agents and latent viral reactivation. The risk increases with total immunosuppressive load (see section 4.4). The most serious infections were sepsis, peritonitis, meningitis, endocarditis, tuberculosis and atypical mycobacterial infection. The most common opportunistic infections in patients receiving mycophenolate mofetil (2 g or 3 g daily) with other immunosuppressants in controlled clinical trials in renal, cardiac and hepatic transplant patients followed for at least 1 year were candida mucocutaneous, CMV viraemia/syndrome and Herpes simplex. The proportion of patients with CMV viraemia/syndrome was 13.5%. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including mycophenolate mofetil.

Blood and lymphatic disorders

Cytopenias, including leukopenia, anaemia, thrombocytopenia and pancytopenia, are known risks associated with mycophenolate mofetil and may lead or contribute to the occurrence of infections and haemorrhages (see section 4.4). Agranulocytosis and neutropenia have been reported; therefore, regular monitoring of patients taking mycophenolate mofetil is advised (see section 4.4). There have been reports of aplastic anaemia and bone marrow failure in patients treated with mycophenolate mofetil, some of which have been fatal.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil (see section 4.4).

Isolated cases of abnormal neutrophil morphology, including the acquired Pelger-Huet anomaly, have been observed in patients treated with mycophenolate mofetil. These changes are not associated with impaired neutrophil function. These changes may suggest a 'left shift' in the maturity of neutrophils in haematological investigations, which may be mistakenly interpreted as a sign of infection in immunosuppressed patients such as those that receive mycophenolate mofetil.

Gastrointestinal disorders

The most serious gastrointestinal disorders were ulceration and haemorrhage which are known risks associated with mycophenolate mofetil. Mouth, oesophageal, gastric, duodenal, and intestinal ulcers often complicated by haemorrhage, as well as haematemesis, melena, and haemorrhagic forms of gastritis and colitis were commonly reported during the pivotal clinical trials. The most common gastrointestinal disorders, however, were diarrhoea, nausea and vomiting. Endoscopic investigation of patients with mycophenolate mofetil-related diarrhoea have revealed isolated cases of intestinal villous atrophy (see section 4.4).

Hypersensitivity

Hypersensitivity reactions, including angioneurotic oedema and anaphylactic reaction have been reported.

Pregnancy, puerperium and perinatal conditions

Cases of spontaneous abortion have been reported in patients exposed to mycophenolate mofetil, mainly in the first trimester, see section 4.6.

Congenital disorders

Congenital malformations have been observed post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants, see section 4.6.

Respiratory, thoracic and mediastinal disorders

There have been isolated reports of interstitial lung disease and pulmonary fibrosis in patients treated with mycophenolate mofetil in combination with other immunosuppressants, some of which have been fatal. There have also been reports of bronchiectasis in children and adults.

Immune system disorders

Hypogammaglobulinaemia has been reported in patients receiving mycophenolate mofetil in combination with other immunosuppressants.

General disorders and administration site conditions

Oedema, including peripheral, face and scrotal oedema, was reported very commonly during the pivotal trials. Musculoskeletal pain such as myalgia, and neck and back pain were also very commonly reported.

De novo purine synthesis inhibitors associated acute inflammatory syndrome has been described from post-marketing experience as a paradoxical proinflammatory reaction associated with mycophenolate mofetil and mycophenolic acid, characterised by fever, arthralgia, arthritis, muscle pain and elevated inflammatory markers. Literature case reports showed rapid improvement following discontinuation of the medicinal product.

Special populations

Paediatric population

The type and frequency of adverse reactions were assessed in a long-term clinical trial, which recruited 33 paediatric renal transplant patients, aged 3 years to 18 years, who were given 23 mg/kg of mycophenolate mofetil orally, twice daily. Overall, the safety profile in these 33 children and adolescents was similar to that observed in adult recipients of solid organ allografts.

Similar observations were made in another clinical trial, which recruited 100 paediatric renal transplant patients aged 1 to 18 years. The type and frequency of adverse reactions in patients who were given 600 mg/m², up to 1 g/m² of mycophenolate mofetil orally, twice daily, were comparable to those observed in adult patients given 1 g mycophenolate mofetil twice daily. A summary of the more frequently occurring adverse reactions is shown in table 3 below:

Table 3 Summary of adverse reactions observed more frequently in a trial investigating mycophenolate mofetil in 100 paediatric renal transplant patients (age/surface area-based dosing [600 mg/m², up to 1 g/m² BID.]

| Adverse reaction (MedDRA) | <6 years (n=33) | 6-11 years (n=34) | 12-18 years (n=33) |
|---|------------------------|------------------------|------------------------|
| System Organ Class | | | |
| Infections and infestations | Very common (48.5%) | Very common (44.1%) | Very common (51.5%) |
| Blood and lymphatic system disorders | | | |
| Leukopenia | Very common (30.3%) | Very common (29.4%) | Very common (12.1%) |
| Anaemia | Very common (51.5%) | Very common (32.4%) | Very common (27.3%) |
| Gastrointestinal disorders | | | |
| Diarrhoea | Very common (87.9%) | Very common (67.6%) | Very common (30.3%) |
| Vomiting | Very common (69.7%) | Very common (44.1%) | Very common (36.4%) |

Based on limited sub-set data (i.e. 33 of the 100 patients) there was a higher frequency of severe diarrhoea (common, 9.1%), and candida mucocutaneous (very common, 21.2%) in children under 6 years of age, compared to the older paediatric cohort in which no cases of severe diarrhoea were reported (0.0%) and candida mucocutaneous was common (7.5%).

Review of the available medical literature on paediatric hepatic and cardiac transplant patients shows the type and frequency of the reported adverse reactions are consistent with those observed in paediatric and adult patients following renal transplant.

Very limited post-marketing data indicates a higher frequency of the following adverse reactions in patients under 6 years of age compared to older patients (see section 4.4):

- lymphomas and other malignancies particularly of post-transplant lymphoproliferative disorder in cardiac transplant patients
- blood and lymphatic system disorders including anaemia and neutropenia in cardiac transplant patients under 6 years of age compared to older patients, and compared to paediatric hepatic/renal transplant recipients
- gastrointestinal disorders including diarrhoea and vomiting.

Renal transplant patients under 2 years of age might be at a higher risk of infections and respiratory events compared to older patients. However, these data should be interpreted with caution due to a very limited number of post-marketing reports concerning the same patients suffering from multiple infections.

In case of undesirable effects, temporary dose reduction or interruption may be considered as deemed clinically necessary.

Elderly

Elderly patients (≥ 65 years) may generally be at increased risk of adverse reactions due to immunosuppression. Elderly patients receiving mycophenolate mofetil as part of a combination

immunosuppressive regimen may be at increased risk of certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared to younger individuals.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Reports of overdoses with mycophenolate mofetil have been received from clinical trials and during post-marketing experience. In the vast majority of these cases, either no adverse events were reported or they were in line with the known safety profile of the medicinal product and had a favourable outcome. However, isolated serious adverse events including a fatal case were observed during post-marketing experience.

It is expected that an overdose of mycophenolate mofetil could possibly result in oversuppression of the immune system and increase susceptibility to infections and bone marrow suppression (see section 4.4). If neutropenia develops, dosing with mycophenolate mofetil should be interrupted or the dose reduced (see section 4.4).

Haemodialysis would not be expected to remove clinically significant amounts of MPA or MPAG. Bile acid sequestrants, such as cholestyramine, can remove MPA by decreasing the enterohepatic recirculation of the drug (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressive agents ATC code L04AA06

Mechanism of action

Mycophenolate mofetil is the 2-morpholinoethyl ester of MPA. MPA is a selective, uncompetitive and reversible inhibitor of IMPDH, and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines whereas other cell types can utilise salvage pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells. In addition to its inhibition of IMPDH and the resulting deprivation of lymphocytes, MPA also influences cellular checkpoints responsible for metabolic programming of lymphocytes. It has been shown, using human CD4+ T-cells, that MPA shifts transcriptional activities in lymphocytes from a proliferative state to catabolic processes relevant to metabolism and survival leading to an anergic state of T-cells, whereby the cells become unresponsive to their specific antigen.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, MPA. As evidenced by suppression of acute rejection following renal transplantation, the immunosuppressant activity of mycophenolate mofetil is correlated with MPA concentration. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94% relative to intravenous mycophenolate mofetil. Food had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g BID to renal transplant patients. However, MPA C_{\max} was decreased by 40% in the presence of food. Mycophenolate mofetil is not measurable systemically in plasma following oral administration.

Distribution

As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed at approximately 6 – 12 hours post-dose. A reduction in the AUC of MPA of approximately 40% is associated with the co-administration of cholestyramine (4 g TID), indicating that there is a significant amount of enterohepatic recirculation.

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

In the early post-transplant period (< 40 days post-transplant), renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30% lower and C_{\max} approximately 40% lower compared to the late post-transplant period (3 – 6 months post-transplant).

Biotransformation

MPA is metabolised principally by glucuronyl transferase (isoform UGT1A9) to form the 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 mycophenolate mofetil's side effects (diarrhoea, leucopenia).

Elimination

A negligible amount of substance is excreted as MPA (< 1% of the dose) in the urine. Oral administration of radiolabelled mycophenolate mofetil results in complete recovery of the administered dose, with 93% of the administered dose recovered in the urine and 6% recovered in the faeces. Most (about 87%) of the administered dose is excreted in the urine as MPAG.

At clinically encountered concentrations, MPA and MPAG are not removed by haemodialysis. However, at high MPAG plasma concentrations (> 100 µg/ml), small amounts of MPAG are removed. By interfering with enterohepatic recirculation of the drug, bile acid sequestrants such as cholestyramine, reduce MPA AUC (see section 4.9).

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 potentially interact with renal organic anion transporters.

Enterohepatic recirculation interferes with accurate determination of MPA's disposition parameters; only apparent values can be indicated. In healthy volunteers and patients with autoimmune disease approximate clearance values of 10.6 L/h and 8.27 L/h respectively and half-life values of 17 h were observed. In transplant patients mean clearance values were higher (range 11.9-34.9 L/h) and mean half-life values shorter (5-11 h) with little difference between renal, hepatic or cardiac transplant

patients. In the individual patients, these elimination parameters vary based on type of co-treatment with other immunosuppressants, time post-transplantation, plasma albumin concentration and renal function. These factors explain why reduced exposure to mycophenolate is seen when mycophenolate mofetil is co-administered with ciclosporin (see section 4.5) and why plasma concentrations tend to increase over time compared to what is observed immediately after transplantation.

Special populations

Renal impairment

In a single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate < 25 ml/min/1.73 m²) were 28 – 75% higher relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. The mean single dose MPAG AUC was 3 – 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. Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Delayed renal graft function

In patients with delayed renal graft function post-transplant, mean MPA AUC_{0-12h} was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC_{0-12h} was 2 – 3-fold higher than in post-transplant patients without delayed graft function. There may be a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of mycophenolate mofetil does not appear to be necessary.

Hepatic impairment

In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were 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.

Paediatric population

In 33 paediatric renal allograft recipients it was established that the dose predicted to provide an MPA AUC_{0-12h} closest to the target exposure of 27.2 h·mg/l was 600 mg/m², and that doses calculated based on estimated BSA reduced interindividual variability (coefficient of variation, (CV)) by about 10%. Therefore, dosing based on BSA is preferred rather than dosing based on body weight.

Pharmacokinetic parameters were evaluated in up to 55 paediatric renal transplant patients (aged 1 to 18 years) given 600 mg/m², up to 1 g/m² of mycophenolate mofetil orally twice daily. This dose achieved MPA AUC values similar to those seen in adult renal transplant patients receiving mycophenolate mofetil at a dose of 1 g BID in the early and late post-transplant period as per Table 4 below. MPA AUC values across paediatric age groups were similar in the early and late post-transplant period.

For paediatric hepatic transplant recipients an open-label study of the safety, tolerability and pharmacokinetics of oral mycophenolate mofetil included 7 evaluable patients on concomitant ciclosporin and corticosteroid treatment. The dose predicted to achieve an exposure of 58 h·mg/l in the stable post-transplant period was estimated. The mean \pm SD AUC₀₋₁₂ (adjusted to a dose of 600 mg/m²) was 47.0 \pm 21.8 h·mg/l, adjusted C_{max} was 14.5 \pm 4.21 mg/l, with a median time to maximum concentration of 0.75 h. To achieve the target AUC₀₋₁₂ of 58 h·mg/l in the late post-transplant period, a dose in the range of 740-806 mg/m² BID would therefore have been required in the study population.

A comparison of dose-normalised (to 600 mg/m²) MPA AUC values in 12 paediatric renal transplant patients less than 6 years of age at 9 months post-transplant with those values in 7 paediatric hepatic transplant patients [median age 17 months (range: 10-60 months at enrolment)] at 6 months and beyond post-transplant revealed that, at the same dose, the AUC values were on average 23% lower in the paediatric hepatic patients compared to paediatric renal patients. This is consistent with the need

for higher dosing in adult hepatic transplant patients compared to adult renal transplant patients to achieve the same exposure.

In adult transplant patients administered the same dosage of mycophenolate mofetil, there is similar MPA exposure among renal transplant and cardiac transplant patients. In line with the established similarity in MPA exposure between paediatric renal transplant and adult renal transplant patients at their respective approved doses, existing data allows to conclude that MPA exposure at the recommended dosage will be similar in paediatric cardiac transplant, and adult cardiac transplant patients.

Table 4 Mean computed MPA PK parameters by age and time post-transplant (renal)

| Age group (n) | | Adjusted C_{\max} mg/l ^A mean \pm SD | Adjusted AUC_{0-12} h·mg/l mean \pm SD (CI) ^A |
|----------------------|-------------------|--|---|
| Day 7 | | | |
| <6 y | (17) | 13.2 \pm 7.16 | 27.4 \pm 9.54 (22.8-31.9) |
| 6 - <12 y | (16) | 13.1 \pm 6.30 | 33.2 \pm 12.1 (27.3-39.2) |
| 12-18 y | (21) | 11.7 \pm 10.7 | 26.3 \pm 9.14 (22.3-30.3) ^D |
| p-value ^B | | - | - |
| <2 y ^C | (6) | 10.3 \pm 5.80 | 22.5 \pm 6.68 (17.2-27.8) |
| >18 y | (141) | | 27.2 \pm 11.6 |
| Month 3 | | | |
| <6 y | (15) | 22.7 \pm 10.1 | 49.7 \pm 18.2 |
| 6 - <12 y | (14) ^E | 27.8 \pm 14.3 | 61.9 \pm 19.6 |
| 12-18 y | (17) | 17.9 \pm 9.57 | 53.6 \pm 20.2 ^F |
| p-value ^B | | - | - |
| <2 y ^C | (4) | 23.8 \pm 13.4 | 47.4 \pm 14.7 |
| >18 y | (104) | | 50.3 \pm 23.1 |
| Month 9 | | | |
| <6 y | (12) | 30.4 \pm 9.16 | 60.9 \pm 10.7 |
| 6 - <12 y | (11) | 29.2 \pm 12.6 | 66.8 \pm 21.2 |
| 12-18 y | (14) | 18.1 \pm 7.29 | 56.7 \pm 14.0 |
| p-value ^B | | 0.004 | - |
| <2 y ^C | (4) | 25.6 \pm 4.25 | 55.8 \pm 11.6 |
| >18 y | (70) | | 53.5 \pm 18.3 |

AUC_{0-12h} =area under the plasma concentration-time curve from time 0 h to time 12 h; CI=confidence interval; C_{\max} =maximum concentration; MPA=mycophenolic acid; SD=standard deviation; n=number of patients; y=year.

^A In the paediatric age groups C_{\max} and AUC_{0-12h} are adjusted to a dose of 600 mg/m² (95% confidence intervals (CIs) for AUC_{0-12h} Day 7 only); in the adult group AUC_{0-12h} is adjusted to a dose of 1 g.

^B p-value represents the combined p-value for the three major paediatric age groups, and is noted only if significant (p <0.05).

^C The <2-year group is a subset of the <6-year group: no statistical comparisons were made.

^D n=20.

^E Data for one patient was unavailable due to sampling error.

^F n=16.

Elderly

The pharmacokinetics of mycophenolate mofetil and its metabolites have not been found to be altered in the elderly patients (≥ 65 years) when compared to younger patients.

Patients taking oral contraceptives

A study of the co-administration of mycophenolate mofetil (1 g BID) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) conducted in 18 non-transplant women (not taking other immunosuppressants) over 3 consecutive menstrual cycles showed no clinically relevant influence of mycophenolate mofetil on the ovulation-suppressing action of the oral contraceptives. Serum levels of LH, FSH and progesterone were not significantly affected. The pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by co-administration of mycophenolate mofetil (see also section 4.5).

5.3 Preclinical safety data

In experimental models, mycophenolate mofetil was not tumourigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2 – 3 times the systemic exposure (AUC or C_{max}) observed in renal transplant patients at the recommended clinical dose of 2 g/day and 1.3 – 2 times the systemic exposure (AUC or C_{max}) observed in cardiac transplant patients at the recommended clinical dose of 3 g/day.

Two genotoxicity assays (*in vitro* mouse lymphoma assay and *in vivo* mouse bone marrow micronucleus test) showed a potential of mycophenolate mofetil to cause chromosomal aberrations. These effects can be related to the pharmacodynamic mode of action, i.e. inhibition of nucleotide synthesis in sensitive cells. Other *in vitro* tests for detection of gene mutation did not demonstrate genotoxic activity.

In teratology studies in rats and rabbits, foetal resorptions and malformations occurred in rats at 6 mg/kg/day (including anophthalmia, agnathia, and hydrocephaly) and in rabbits at 90 mg/kg/day (including cardiovascular and renal anomalies, such as ectopia cordis and ectopic kidneys, and diaphragmatic and umbilical hernia), in the absence of maternal toxicity. The systemic exposure at these levels is approximately equivalent to or less than 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients (see section 4.6).

The haematopoietic and lymphoid systems were the primary organs affected in toxicology studies conducted with mycophenolate mofetil in the rat, mouse, dog and monkey. These effects occurred at systemic exposure levels that are equivalent to or less than the clinical exposure at the recommended dose of 2 g/day for renal transplant recipients. Gastrointestinal effects were observed in the dog at systemic exposure levels equivalent to or less than the clinical exposure at the recommended dose. Gastrointestinal and renal effects consistent with dehydration were also observed in the monkey at the highest dose (systemic exposure levels equivalent to or greater than clinical exposure). The non-clinical toxicity profile of mycophenolate mofetil appears to be consistent with adverse events observed in human clinical trials, which now provide safety data of more relevance to the patient population (see section 4.8).

Environmental Risk Assessment (ERA)

Environmental risk assessment studies have shown that the active substance, MPA may pose a risk for groundwater via bank filtration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

CellCept 1 g/5 ml powder for oral suspension

sorbitol

silica, colloidal anhydrous

sodium citrate

soybean lecithin
mixed fruit flavour
xanthan gum
aspartame* (E951)
methyl parahydroxybenzoate (E218)
citric acid anhydrous

* contains phenylalanine equivalent to 2.78 mg/5 ml of suspension.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf-life

The shelf-life of the powder for oral suspension is 2 years.
The shelf-life of the reconstituted suspension is 2 months.

6.4 Special precautions for storage

Powder for oral suspension and reconstituted suspension: Do not store above 30 °C.

6.5 Nature and contents of container

Each bottle contains 35 g mycophenolate mofetil in 110 g powder for oral suspension. When reconstituted, the volume of the suspension is 175 ml, providing a usable volume of 160 – 165 ml. 5 ml of the reconstituted suspension contains 1 g of mycophenolate mofetil. A bottle adapter and 2 oral dispensers are also provided.

6.6 Special precautions for disposal and other handling

It is recommended that CellCept 1 g/5 ml powder for oral 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.

Preparation of suspension

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 the closed bottle well for about 1 minute.
4. Add the remainder of water and shake the closed bottle well for about 1 minute.
5. Remove child-resistant cap and push bottle adapter into neck of bottle.
6. Close bottle with child-resistant cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child-resistant status of the cap.
7. Write the date of expiration of the reconstituted suspension on the bottle label. (The shelf-life of the reconstituted suspension is two months.)

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1

79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/005/006 CellCept (1 bottle 110 g)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 February 1996

Date of latest renewal: 13 March 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

CellCept 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg mycophenolate mofetil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets (tablets)

Lavender-coloured caplet-shaped tablet, engraved with "CellCept 500" on one side and "Roche" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CellCept is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adult and paediatric (1 to 18 years of age) patients receiving allogeneic renal, cardiac or hepatic transplants.

4.2 Posology and method of administration

Treatment should be initiated and maintained by appropriately qualified transplant specialists.

Posology

Adults

Renal transplant

Treatment should be initiated within 72 hours following transplantation. The recommended dose in renal transplant patients is 1 g administered twice daily (2 g daily dose).

Cardiac transplant

Treatment should be initiated within 5 days following transplantation. The recommended dose in cardiac transplant patients is 1.5 g administered twice daily (3 g daily dose).

Hepatic transplant

Treatment of intravenous mycophenolate mofetil should be administered for the first 4 days following hepatic transplant, with oral mycophenolate mofetil initiated as soon after this as it can be tolerated. The recommended oral dose in hepatic transplant patients is 1.5 g administered twice daily (3 g daily dose).

Paediatric population (1 to 18 years)

The paediatric dosing information in this section applies to all oral formulations within the range of mycophenolate mofetil products, as appropriate. Different oral formulations should not be substituted without clinical supervision.

The recommended mycophenolate mofetil initial dose for paediatric renal, cardiac and hepatic transplant patients is 600 mg/m² (of body surface area (BSA)), administered orally, twice daily (initial total daily dose not to exceed 2 g, or 10 ml of the oral suspension).

The dose and product form should be individualised based on clinical assessment. If the recommended initial dose is well tolerated but does not achieve clinically adequate immunosuppression in paediatric cardiac and hepatic transplant patients, the dose can be increased to 900 mg/m² BSA twice daily (maximum total daily dose of 3 g, or 15 ml of the oral suspension). The recommended maintenance dose for paediatric renal transplant patients remains at 600 mg/m² twice daily (maximum total daily dose of 2 g or 10 ml of the oral suspension).

The mycophenolate mofetil powder for oral suspension should be used in those patients unable to swallow capsules and tablets and/or with BSA lower than 1.25 m² due to the increased risk of choking. Patients with a BSA of 1.25 to 1.5 m² may be prescribed mycophenolate mofetil capsules at a dose of 750 mg twice daily (1.5 g daily dose). Patients with a BSA greater than 1.5 m² may be prescribed mycophenolate mofetil capsules or tablets at a dose of 1 g twice daily (2 g daily dose). As some adverse reactions occur with greater frequency in this age group (see section 4.8) compared with adults, temporary dose reduction or interruption may be required; these will need to take into account relevant clinical factors including severity of reaction.

Use in special populations

Elderly

The recommended dose of 1 g administered twice a day for renal transplant patients and 1.5 g twice a day for cardiac or hepatic transplant patients is appropriate for the elderly.

Renal impairment

In renal transplant patients with severe chronic renal impairment (glomerular filtration rate < 25 ml/min/1.73 m²), outside the immediate post-transplant period, doses greater than 1 g administered twice a day should be avoided. These patients should also be carefully observed. No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively (see section 5.2). No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Severe hepatic impairment

No dose adjustments are needed for renal transplant patients with severe hepatic parenchymal disease. No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

Treatment during rejection episodes

Adults

Mycophenolic acid (MPA) is the active metabolite of mycophenolate mofetil. Renal transplant rejection does not lead to changes in MPA pharmacokinetics; dose reduction or interruption of treatment is not required. There is no basis for dose adjustment following cardiac transplant rejection. No pharmacokinetic data are available during hepatic transplant rejection.

Paediatric population

No data are available for treatment of first or refractory rejection in paediatric transplant patients.

Method of administration

For oral use.

Precautions to be taken before handling or administering the medicinal product.

Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits, tablets should not be crushed to avoid inhalation or direct contact with skin or mucous membranes with powder. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.

4.3 Contraindications

- CellCept should not be given to patients with hypersensitivity to mycophenolate mofetil, mycophenolic acid or to any of the excipients listed in section 6.1. Hypersensitivity reactions to this medicinal product have been observed (see section 4.8).
- Treatment should not be given to women of childbearing potential who are not using highly effective contraception (see section 4.6).
- Treatment should not be initiated in women of childbearing potential without providing a pregnancy test result to rule out unintended use in pregnancy (see section 4.6).
- Treatment should not be used during pregnancy unless there is no suitable alternative treatment to prevent transplant rejection (see section 4.6).
- Treatment should not be given to women who are breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

Neoplasms

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including CellCept, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.8). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As general advice to minimise the risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Infections

Patients treated with immunosuppressants, including mycophenolate mofetil, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis (see section 4.8). Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation and infections caused by polyomaviruses (BK virus-associated nephropathy, JC virus-associated progressive multifocal leukoencephalopathy PML). Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. Mycophenolic acid has a cytostatic effect on B- and T-lymphocytes, therefore an increased severity of COVID-19 may occur, and appropriate clinical action should be considered.

There have been reports of hypogammaglobulinaemia in association with recurrent infections in patients receiving mycophenolate mofetil in combination with other immunosuppressants. In some of these cases switching mycophenolate mofetil to an alternative immunosuppressant resulted in serum IgG levels returning to normal. Patients on mycophenolate mofetil who develop recurrent infections should have their serum immunoglobulins measured. In cases of sustained, clinically relevant hypogammaglobulinaemia, appropriate clinical action should be considered taking into account the potent cytostatic effects that mycophenolic acid has on T- and B-lymphocytes.

There have been published reports of bronchiectasis in adults and children who received mycophenolate mofetil in combination with other immunosuppressants. In some of these cases switching mycophenolate mofetil to another immunosuppressant resulted in improvement in respiratory symptoms. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect on the lung. There have also been isolated reports of interstitial lung disease and pulmonary fibrosis, some of which were fatal (see section 4.8). It is recommended that patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, are investigated.

Blood and immune system

Patients receiving mycophenolate mofetil should be monitored for neutropenia, which may be related to the treatment itself, concomitant medications, viral infections, or some combination of these causes. Patients taking mycophenolate mofetil should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If neutropenia develops (absolute neutrophil count $< 1.3 \times 10^3/\mu\text{l}$), it may be appropriate to interrupt or discontinue mycophenolate mofetil.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil in combination with other immunosuppressants. The mechanism for mycophenolate mofetil induced PRCA is unknown. PRCA may resolve with dose reduction or cessation of mycophenolate mofetil therapy. Changes to mycophenolate mofetil therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimise the risk of graft rejection (see section 4.8).

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

Patients should be advised that, during treatment with mycophenolate mofetil, vaccinations may be less effective, and the use of live attenuated vaccines should be avoided (see section 4.5). Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

Gastrointestinal

Mycophenolate mofetil has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, haemorrhage and perforation. Treatment should be administered with caution in patients with active serious digestive system disease.

Mycophenolate is an IMPDH (inosine monophosphate dehydrogenase) inhibitor. Therefore, 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 level of mycophenolate and its efficacy (see also section 4.5).

It is recommended that mycophenolate mofetil should not be administered concomitantly with azathioprine because such concomitant administration has not been studied.

The risk/benefit ratio of mycophenolate mofetil in combination with sirolimus has not been established (see also section 4.5).

Therapeutic drug monitoring

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).

Special populations

Paediatric population

Very limited post-marketing information indicates a higher frequency of the following adverse events in patients under 6 years of age compared to older patients:

- lymphomas and other malignancies, particularly of post-transplant lymphoproliferative disorder in cardiac transplant patients.
- blood and lymphatic system disorders including anaemia and neutropenia in cardiac transplant patients. This applies for children under 6 years of age compared to older patients, and compared to paediatric hepatic/renal transplant recipients.
Patients taking mycophenolate mofetil should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If neutropenia develops, it may be appropriate to interrupt or discontinue mycophenolate mofetil.
- gastrointestinal disorders including diarrhoea and vomiting.
Treatment should be administered with caution in patients with active serious digestive system disease.

Elderly population

Elderly patients may be at an increased risk of adverse events such as certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared with younger individuals (see section 4.8).

Teratogenic effects

Mycophenolate is a powerful human teratogen. Spontaneous abortion (rate of 45% to 49%) and congenital malformations (estimated rate of 23% to 27%) have been reported following mycophenolate mofetil exposure during pregnancy. Therefore, treatment is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejection. Female patients of childbearing potential should be made aware of the risks and follow the recommendations provided in section 4.6 (e.g. contraceptive methods, pregnancy testing) prior to, during, and after therapy with mycophenolate mofetil. Physicians should ensure that women taking mycophenolate mofetil understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult their physician if there is a possibility of pregnancy.

Contraception (see section 4.6)

Because of robust clinical evidence showing a high risk of abortion and congenital malformations when mycophenolate mofetil is used in pregnancy, every effort to avoid pregnancy during treatment should be taken. Therefore, women with childbearing potential must use at least one form of reliable contraception (see section 4.3) before starting mycophenolate mofetil therapy, during therapy, and for six weeks after stopping the therapy, unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred to minimise the potential for contraceptive failure and unintended pregnancy.

For contraception advice for men see section 4.6.

Educational materials

In order to assist patients in avoiding foetal exposure to mycophenolate and to provide additional important safety information, the Marketing Authorisation Holder will provide educational materials to healthcare professionals. The educational materials will reinforce the warnings about the teratogenicity of mycophenolate, provide advice on contraception before therapy is started and guidance on the need for pregnancy testing. Full patient information about the teratogenic risk and the pregnancy prevention measures should be given by the physician to women of childbearing potential and, as appropriate, to male patients.

Additional precautions

Patients should not donate blood during therapy or for at least 6 weeks following discontinuation of mycophenolate mofetil. Men should not donate semen during therapy or for 90 days following discontinuation of mycophenolate mofetil.

Sodium contents

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Aciclovir

Higher aciclovir plasma concentrations were observed when mycophenolate mofetil was administered with aciclovir in comparison to the administration of aciclovir alone. The changes in MPAG (the phenolic glucuronide of MPA) pharmacokinetics (MPAG increased by 8%) were minimal and are not considered clinically significant. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are aciclovir concentrations, the potential exists for mycophenolate mofetil and aciclovir, or its prodrugs, e.g. valaciclovir, to compete for tubular secretion and further increases in concentrations of both substances may occur.

Antacids and proton pump inhibitors (PPIs)

Decreased MPA exposure has been observed when antacids, such as magnesium and aluminium hydroxides, and PPIs, including lansoprazole and pantoprazole, were administered with mycophenolate mofetil. When comparing rates of transplant rejection or rates of graft loss between mycophenolate mofetil patients taking PPIs vs. mycophenolate mofetil patients not taking PPIs, no significant differences were seen. These data support extrapolation of this finding to all antacids because the reduction in exposure when mycophenolate mofetil was co-administered with magnesium and aluminium hydroxides is considerably less than when mycophenolate mofetil was co-administered with PPIs.

Medicinal products that interfere with enterohepatic recirculation (e.g. cholestyramine, ciclosporin A, antibiotics)

Caution should be used with medicinal products that interfere with enterohepatic recirculation because of their potential to reduce the efficacy of mycophenolate mofetil.

Cholestyramine

Following single dose administration of 1.5 g of mycophenolate mofetil to normal healthy subjects pre-treated with 4 g TID of cholestyramine for 4 days, there was a 40% reduction in the AUC of MPA (see section 4.4 and section 5.2). Caution should be used during concomitant administration because of the potential to reduce efficacy of mycophenolate mofetil.

Ciclosporin A

Ciclosporin A (CsA) pharmacokinetics are unaffected by mycophenolate mofetil.

In contrast, if concomitant CsA treatment is stopped, an increase in MPA AUC of around 30% should be expected. CsA interferes with MPA enterohepatic recycling, resulting in reduced MPA exposures by 30 - 50% in renal transplant patients treated with mycophenolate mofetil and CsA compared with patients receiving sirolimus or belatacept and similar doses of mycophenolate mofetil (see also section 4.4). Conversely, changes of MPA exposure should be expected when switching patients from CsA to one of the immunosuppressants which does not interfere with MPA's enterohepatic cycle.

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 about 50% have been reported in renal transplant recipients in the days immediately following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. This effect tended to diminish with continued antibiotic use and to cease within a few days of antibiotic discontinuation. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

Norfloxacin and metronidazole

In healthy volunteers, no significant interaction was observed when mycophenolate mofetil was concomitantly administered with norfloxacin or metronidazole separately. However, norfloxacin and metronidazole combined reduced the MPA exposure by approximately 30% following a single dose of mycophenolate mofetil.

Trimethoprim/sulfamethoxazole

No effect on the bioavailability of MPA was observed.

Medicinal products that affect glucuronidation (e.g. isavuconazole, telmisartan)

Concomitant administration of drugs affecting glucuronidation of MPA may change MPA exposure. Caution is therefore recommended when administering these drugs concomitantly with mycophenolate mofetil.

Isavuconazole

An increase of MPA exposure ($AUC_{0-\infty}$) by 35% was observed with concomitant administration of isavuconazole.

Telmisartan

Concomitant administration of telmisartan and mycophenolate mofetil resulted in an approximately 30% decrease of MPA concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression, which in turn results in an enhanced uridine diphosphate glucuronyltransferase isoform 1A9 (UGT1A9) expression and activity. When comparing rates of transplant rejection, rates of graft loss or adverse event profiles between patients on mycophenolate mofetil with and without concomitant telmisartan medication, no clinical consequences of the pharmacokinetic drug-drug interaction were seen.

Ganciclovir

Based on the results of a single dose administration study of recommended doses of oral mycophenolate mofetil and intravenous ganciclovir and the known effects of renal impairment on the pharmacokinetics of mycophenolate mofetil (see section 4.2) and ganciclovir, it is anticipated that co-administration of these agents (which compete for mechanisms of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics is anticipated and mycophenolate mofetil dose adjustment is not required. In patients with renal impairment in whom mycophenolate mofetil and ganciclovir or its prodrugs, e.g. valganciclovir, are co-administered, the dose recommendations for ganciclovir should be observed and patients should be monitored carefully.

Oral contraceptives

The pharmacodynamics and pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by co-administration of mycophenolate mofetil (see also section 5.2).

Rifampicin

In patients not also taking ciclosporin, concomitant administration of mycophenolate mofetil and rifampicin resulted in a decrease in MPA exposure (AUC_{0-12h}) of 18% to 70%. It is recommended to monitor MPA exposure levels and to adjust mycophenolate mofetil doses accordingly to maintain clinical efficacy when rifampicin is administered concomitantly.

Sevelamer

Decrease in MPA C_{max} and AUC_{0-12h} by 30% and 25%, respectively, were observed when mycophenolate mofetil was concomitantly administered with sevelamer without any clinical consequences (i.e. graft rejection). It is recommended, however, to administer mycophenolate mofetil at least one hour before or three hours after sevelamer intake to minimise the impact on the absorption of MPA. There are no data on mycophenolate mofetil with phosphate binders other than sevelamer.

Tacrolimus

In hepatic transplant patients initiated on mycophenolate mofetil and tacrolimus, the AUC and C_{max} of MPA, the active metabolite of mycophenolate mofetil, were not significantly affected by co-administration with tacrolimus. In contrast, there was an increase of approximately 20% in tacrolimus AUC when multiple doses of mycophenolate mofetil (1.5 g BID) were administered to hepatic transplant patients taking tacrolimus. However, in renal transplant patients, tacrolimus concentration did not appear to be altered by mycophenolate mofetil (see also section 4.4).

Live vaccines

Live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished (see also 4.4).

Paediatric population

Interaction studies have only been performed in adults.

Potential interaction

Co-administration of probenecid with mycophenolate mofetil in monkeys raises plasma AUC of MPAG by 3-fold. Thus, other substances known to undergo renal tubular secretion may compete with MPAG, and thereby raise plasma concentrations of MPAG or the other substance undergoing tubular secretion.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Pregnancy whilst taking mycophenolate mofetil must be avoided. Therefore, women of childbearing potential must use at least one form of reliable contraception (see section 4.3) before starting the therapy, during therapy, and for six weeks after stopping the therapy, unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred.

Pregnancy

Mycophenolate mofetil is contraindicated during pregnancy unless there is no suitable alternative treatment to prevent transplant rejection. Treatment should not be initiated without providing a negative pregnancy test result to rule out unintended use in pregnancy (see section 4.3).

Female patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations at the beginning of the treatment and must be counselled regarding pregnancy prevention and planning.

Before starting treatment, women of childbearing potential should have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/ml in order to exclude unintended exposure of an embryo to mycophenolate. It is recommended that the second test should be performed 8-10 days after the first test. For transplants from deceased donors, if it is not possible to perform two tests 8-10 days apart before treatment starts (because of the timing of transplant organ availability), a pregnancy test must be performed immediately before starting treatment and a further test 8-10 days later. Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported. Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.

Mycophenolate is a powerful human teratogen, with an increased risk of spontaneous abortions and congenital malformations in case of exposure during pregnancy;

- Spontaneous abortions have been reported in 45 to 49% of pregnant women exposed to mycophenolate mofetil, compared to a reported rate of between 12 and 33% in solid organ transplant patients treated with immunosuppressants other than mycophenolate mofetil.
- Based on literature reports, malformations occurred in 23 to 27% of live births in women exposed to mycophenolate mofetil during pregnancy (compared to 2 to 3% of live births in the overall population and approximately 4 to 5% of live births in solid organ transplant recipients treated with immunosuppressants other than mycophenolate mofetil).

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

- Abnormalities of the ear (e.g. abnormally formed or absent external ear), external auditory canal atresia (middle ear);
- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;
- Abnormalities of the eye (e.g. coloboma);
- Congenital heart disease such as atrial and ventricular septal defects;
- Malformations of the fingers (e.g. polydactyly, syndactyly);
- Tracheo-oesophageal malformations (e.g. oesophageal atresia);
- Nervous system malformations such as spina bifida;
- Renal abnormalities.

In addition, there have been isolated reports of the following malformations:

- Microphthalmia;
- Congenital choroid plexus cyst;
- Septum pellucidum agenesis;
- Olfactory nerve agenesis.

Studies in animals have shown reproductive toxicity (see section 5.3).

Breast-feeding

Limited data shows that mycophenolic acid is excreted in human milk. Because of the potential for serious adverse reactions to mycophenolic acid in breast-fed infants, treatment is contraindicated in nursing mothers (see section 4.3).

Men

The limited clinical evidence available does not indicate an increased risk of malformations or miscarriage following paternal exposure to mycophenolate mofetil.

MPA is a powerful teratogen. It is not known if MPA is present in semen. Calculations based on animal data show that the maximum amount of MPA that could potentially be transferred to woman is so low that it would be unlikely to have an effect. Mycophenolate has been shown to be genotoxic in

animal studies at concentrations exceeding the human therapeutic exposures only by small margins such that the risk of genotoxic effects on sperm cells cannot completely be excluded.

Therefore, the following precautionary measures are recommended: sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 90 days after cessation of mycophenolate mofetil. Male patients of reproductive potential should be made aware of and discuss with a qualified healthcare professional the potential risks of fathering a child.

Fertility

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. The systemic exposure at this dose represents 2 – 3 times the clinical exposure at the recommended clinical dose of 2 g/day in renal transplant patients and 1.3 – 2 times the clinical exposure at the recommended clinical dose of 3 g/day in cardiac transplant patients. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (including anophthalmia, agnathia, and hydrocephaly) in the first generation offspring in the absence of maternal toxicity. The systemic exposure at this dose was approximately 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

4.7 Effects on ability to drive and use machines

Mycophenolate mofetil has a moderate influence on the ability to drive and use machines. Treatment may cause somnolence, confusion, dizziness, tremor or hypotension, and therefore patients are advised to use caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

Diarrhoea (up to 52.6%), leukopenia (up to 45.8%), bacterial infections (up to 39.9%) and vomiting (up to 39.1%) were among the most common and/or serious adverse reactions associated with the administration of mycophenolate mofetil in combination with ciclosporin and corticosteroids. There is evidence of a higher frequency of certain types of infections (see section 4.4).

Tabulated list of adverse reactions

The adverse reactions from clinical trials and post-marketing experience are listed in Table 1, by MedDRA system organ class (SOC) along with their frequencies. The corresponding frequency category for each adverse reaction is based on the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ to $< 1/1\ 000$) and very rare ($< 1/10\ 000$). Due to the large differences observed in the frequency of certain adverse reactions across the different transplant indications, the frequency is presented separately for renal, hepatic and cardiac transplant patients.

Table 1 Adverse reactions in studies investigating mycophenolate mofetil treatment in adults and adolescents, or through post-marketing surveillance

| Adverse reaction (MedDRA) System Organ Class | Renal transplant | Hepatic transplant | Cardiac transplant |
|---|-------------------------|---------------------------|-------------------------------|
| | Frequency | Frequency | Frequency |
| Infections and infestations | | | |

| Adverse reaction (MedDRA) | | | |
|---|-------------------------|---------------------------|---------------------------|
| System Organ Class | Renal transplant | Hepatic transplant | Cardiac transplant |
| Bacterial infections | Very Common | Very Common | Very Common |
| Fungal infections | Common | Very Common | Very Common |
| Protozoal infections | Uncommon | Uncommon | Uncommon |
| Viral infections | Very Common | Very Common | Very Common |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | | | |
| Benign neoplasm of skin | Common | Common | Common |
| Lymphoma | Uncommon | Uncommon | Uncommon |
| Lymphoproliferative disorder | Uncommon | Uncommon | Uncommon |
| Neoplasm | Common | Common | Common |
| Skin cancer | Common | Uncommon | Common |
| Blood and lymphatic system disorders | | | |
| Anaemia | Very Common | Very Common | Very Common |
| Aplasia pure red cell | Uncommon | Uncommon | Uncommon |
| Bone marrow failure | Uncommon | Uncommon | Uncommon |
| Ecchymosis | Common | Common | Very Common |
| Leukocytosis | Common | Very Common | Very Common |
| Leukopenia | Very Common | Very Common | Very Common |
| Pancytopenia | Common | Common | Uncommon |
| Pseudolymphoma | Uncommon | Uncommon | Common |
| Thrombocytopenia | Common | Very Common | Very Common |
| Metabolism and nutrition disorders | | | |
| Acidosis | Common | Common | Very Common |
| Hypercholesterolaemia | Very Common | Common | Very Common |
| Hyperglycaemia | Common | Very Common | Very Common |
| Hyperkalaemia | Common | Very Common | Very Common |
| Hyperlipidaemia | Common | Common | Very Common |
| Hypocalcaemia | Common | Very Common | Common |
| Hypokalaemia | Common | Very Common | Very Common |
| Hypomagnesaemia | Common | Very Common | Very Common |
| Hypophosphataemia | Very Common | Very Common | Common |
| Hyperuricaemia | Common | Common | Very Common |
| Gout | Common | Common | Very Common |
| Weight decreased | Common | Common | Common |
| Psychiatric disorders | | | |
| Confusional state | Common | Very Common | Very Common |
| Depression | Common | Very Common | Very Common |
| Insomnia | Common | Very Common | Very Common |
| Agitation | Uncommon | Common | Very Common |
| Anxiety | Common | Very Common | Very Common |
| Thinking abnormal | Uncommon | Common | Common |
| Nervous system disorders | | | |
| Dizziness | Common | Very Common | Very Common |

| Adverse reaction (MedDRA) | | | |
|--|-------------------------|---------------------------|---------------------------|
| System Organ Class | Renal transplant | Hepatic transplant | Cardiac transplant |
| Headache | Very Common | Very Common | Very Common |
| Hypertonia | Common | Common | Very Common |
| Paresthesia | Common | Very Common | Very Common |
| Somnolence | Common | Common | Very Common |
| Tremor | Common | Very Common | Very Common |
| Convulsion | Common | Common | Common |
| Dysgeusia | Uncommon | Uncommon | Common |
| Cardiac disorders | | | |
| Tachycardia | Common | Very Common | Very Common |
| Vascular disorders | | | |
| Hypertension | Very Common | Very Common | Very Common |
| Hypotension | Common | Very Common | Very Common |
| Lymphocele | Uncommon | Uncommon | Uncommon |
| Venous thrombosis | Common | Common | Common |
| Vasodilatation | Common | Common | Very Common |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchiectasis | Uncommon | Uncommon | Uncommon |
| Cough | Very Common | Very Common | Very Common |
| Dyspnoea | Very Common | Very Common | Very Common |
| Interstitial lung disease | Uncommon | Very Rare | Very Rare |
| Pleural effusion | Common | Very Common | Very Common |
| Pulmonary fibrosis | Very Rare | Uncommon | Uncommon |
| Gastrointestinal disorders | | | |
| Abdominal distension | Common | Very Common | Common |
| Abdominal pain | Very Common | Very Common | Very Common |
| Colitis | Common | Common | Common |
| Constipation | Very Common | Very Common | Very Common |
| Decreased appetite | Common | Very Common | Very Common |
| Diarrhoea | Very Common | Very Common | Very Common |
| Dyspepsia | Very Common | Very Common | Very Common |
| Esophagitis | Common | Common | Common |
| Eructation | Uncommon | Uncommon | Common |
| Flatulence | Common | Very Common | Very Common |
| Gastritis | Common | Common | Common |
| Gastrointestinal haemorrhage | Common | Common | Common |
| Gastrointestinal ulcer | Common | Common | Common |
| Gingival hyperplasia | Common | Common | Common |
| Ileus | Common | Common | Common |
| Mouth ulceration | Common | Common | Common |
| Nausea | Very Common | Very Common | Very Common |
| Pancreatitis | Uncommon | Common | Uncommon |
| Stomatitis | Common | Common | Common |

| Adverse reaction (MedDRA) | | | |
|--|-------------------------|---------------------------|---------------------------|
| System Organ Class | Renal transplant | Hepatic transplant | Cardiac transplant |
| Vomiting | Very Common | Very Common | Very Common |
| Immune system disorders | | | |
| Hypersensitivity | Uncommon | Common | Common |
| Hypogammaglobulinaemia | Uncommon | Very Rare | Very Rare |
| Hepatobiliary disorders | | | |
| Blood alkaline phosphatase increased | Common | Common | Common |
| Blood lactate dehydrogenase increased | Common | Uncommon | Very Common |
| Hepatic enzyme increased | Common | Very Common | Very Common |
| Hepatitis | Common | Very Common | Uncommon |
| Hyperbilirubinaemia | Common | Very Common | Very Common |
| Jaundice | Uncommon | Common | Common |
| Skin and subcutaneous tissue disorders | | | |
| Acne | Common | Common | Very Common |
| Alopecia | Common | Common | Common |
| Rash | Common | Very Common | Very Common |
| Skin hypertrophy | Common | Common | Very Common |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | Common | Common | Very Common |
| Muscular weakness | Common | Common | Very Common |
| Renal and urinary disorders | | | |
| Blood creatinine increased | Common | Very Common | Very Common |
| Blood urea increased | Uncommon | Very Common | Very Common |
| Haematuria | Very Common | Common | Common |
| Renal impairment | Common | Very Common | Very Common |
| General disorders and administration site conditions | | | |
| Asthenia | Very Common | Very Common | Very Common |
| Chills | Common | Very Common | Very Common |
| Oedema | Very Common | Very Common | Very Common |
| Hernia | Common | Very Common | Very Common |
| Malaise | Common | Common | Common |
| Pain | Common | Very Common | Very Common |
| Pyrexia | Very Common | Very Common | Very Common |
| De novo purine synthesis inhibitors associated acute inflammatory syndrome | Uncommon | Uncommon | Uncommon |

Description of selected adverse reactions

Malignancies

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including mycophenolate mofetil, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.4). Three-year safety data in renal and cardiac

transplant patients did not reveal any unexpected changes in incidence of malignancy compared to the 1-year data. Hepatic transplant patients were followed for at least 1 year, but less than 3 years.

Infections

All patients treated with immunosuppressants are at increased risk of bacterial, viral and fungal infections (some of which may lead to a fatal outcome), including those caused by opportunistic agents and latent viral reactivation. The risk increases with total immunosuppressive load (see section 4.4). The most serious infections were sepsis, peritonitis, meningitis, endocarditis, tuberculosis and atypical mycobacterial infection. The most common opportunistic infections in patients receiving mycophenolate mofetil (2 g or 3 g daily) with other immunosuppressants in controlled clinical trials in renal, cardiac and hepatic transplant patients followed for at least 1 year were candida mucocutaneous, CMV viraemia/syndrome and Herpes simplex. The proportion of patients with CMV viraemia/syndrome was 13.5%. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including mycophenolate mofetil.

Blood and lymphatic disorders

Cytopenias, including leukopenia, anaemia, thrombocytopenia and pancytopenia, are known risks associated with mycophenolate mofetil and may lead or contribute to the occurrence of infections and haemorrhages (see section 4.4). Agranulocytosis and neutropenia have been reported; therefore, regular monitoring of patients taking mycophenolate mofetil is advised (see section 4.4). There have been reports of aplastic anaemia and bone marrow failure in patients treated with mycophenolate mofetil, some of which have been fatal.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil (see section 4.4).

Isolated cases of abnormal neutrophil morphology, including the acquired Pelger-Huet anomaly, have been observed in patients treated with mycophenolate mofetil. These changes are not associated with impaired neutrophil function. These changes may suggest a 'left shift' in the maturity of neutrophils in haematological investigations, which may be mistakenly interpreted as a sign of infection in immunosuppressed patients such as those that receive mycophenolate mofetil.

Gastrointestinal disorders

The most serious gastrointestinal disorders were ulceration and haemorrhage which are known risks associated with mycophenolate mofetil. Mouth, oesophageal, gastric, duodenal, and intestinal ulcers often complicated by haemorrhage, as well as haematemesis, melena, and haemorrhagic forms of gastritis and colitis were commonly reported during the pivotal clinical trials. The most common gastrointestinal disorders, however, were diarrhoea, nausea and vomiting. Endoscopic investigation of patients with mycophenolate mofetil-related diarrhoea have revealed isolated cases of intestinal villous atrophy (see section 4.4).

Hypersensitivity

Hypersensitivity reactions, including angioneurotic oedema and anaphylactic reaction have been reported.

Pregnancy, puerperium and perinatal conditions

Cases of spontaneous abortion have been reported in patients exposed to mycophenolate mofetil, mainly in the first trimester, see section 4.6.

Congenital disorders

Congenital malformations have been observed post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants, see section 4.6.

Respiratory, thoracic and mediastinal disorders

There have been isolated reports of interstitial lung disease and pulmonary fibrosis in patients treated with mycophenolate mofetil in combination with other immunosuppressants, some of which have been fatal. There have also been reports of bronchiectasis in children and adults.

Immune system disorders

Hypogammaglobulinaemia has been reported in patients receiving mycophenolate mofetil in combination with other immunosuppressants.

General disorders and administration site conditions

Oedema, including peripheral, face and scrotal oedema, was reported very commonly during the pivotal trials. Musculoskeletal pain such as myalgia, and neck and back pain were also very commonly reported.

De novo purine synthesis inhibitors associated acute inflammatory syndrome has been described from post-marketing experience as a paradoxical proinflammatory reaction associated with mycophenolate mofetil and mycophenolic acid, characterised by fever, arthralgia, arthritis, muscle pain and elevated inflammatory markers. Literature case reports showed rapid improvement following discontinuation of the medicinal product.

Special populations

Paediatric population

The type and frequency of adverse reactions were assessed in a long-term clinical trial, which recruited 33 paediatric renal transplant patients, aged 3 years to 18 years, who were given 23 mg/kg of mycophenolate mofetil orally, twice daily. Overall, the safety profile in these 33 children and adolescents was similar to that observed in adult recipients of solid organ allografts.

Similar observations were made in another clinical trial, which recruited 100 paediatric renal transplant patients aged 1 to 18 years. The type and frequency of adverse reactions in patients who were given 600 mg/m², up to 1 g/m² of mycophenolate mofetil orally, twice daily, were comparable to those observed in adult patients given 1 g mycophenolate mofetil twice daily. A summary of the more frequently occurring adverse reactions is shown in table 2 below:

Table 2 Summary of adverse reactions observed more frequently in a trial investigating mycophenolate mofetil in 100 paediatric renal transplant patients (age/surface area-based dosing [600 mg/m², up to 1 g/m² BID.]

| Adverse reaction (MedDRA) | <6 years (n=33) | 6-11 years (n=34) | 12-18 years (n=33) |
|---|------------------------|------------------------|------------------------|
| System Organ Class | | | |
| Infections and infestations | Very common (48.5%) | Very common (44.1%) | Very common (51.5%) |
| Blood and lymphatic system disorders | | | |
| Leukopenia | Very common (30.3%) | Very common (29.4%) | Very common (12.1%) |
| Anaemia | Very common (51.5%) | Very common (32.4%) | Very common (27.3%) |
| Gastrointestinal disorders | | | |
| Diarrhoea | Very common (87.9%) | Very common (67.6%) | Very common (30.3%) |
| Vomiting | Very common (69.7%) | Very common (44.1%) | Very common (36.4%) |

Based on limited sub-set data (i.e. 33 of the 100 patients) there was a higher frequency of severe diarrhoea (common, 9.1%), and candida mucocutaneous (very common, 21.2%) in children under 6 years of age, compared to the older paediatric cohort in which no cases of severe diarrhoea were reported (0.0%) and candida mucocutaneous was common (7.5%).

Review of the available medical literature on paediatric hepatic and cardiac transplant patients shows the type and frequency of the reported adverse reactions are consistent with those observed in paediatric and adult patients following renal transplant.

Very limited post-marketing data indicates a higher frequency of the following adverse reactions in patients under 6 years of age compared to older patients (see section 4.4):

- lymphomas and other malignancies particularly of post-transplant lymphoproliferative disorder in cardiac transplant patients
- blood and lymphatic system disorders including anaemia and neutropenia in cardiac transplant patients under 6 years of age compared to older patients, and compared to paediatric hepatic/renal transplant recipients
- gastrointestinal disorders including diarrhoea and vomiting.

Renal transplant patients under 2 years of age might be at a higher risk of infections and respiratory events compared to older patients. However, these data should be interpreted with caution due to a very limited number of post-marketing reports concerning the same patients suffering from multiple infections.

In case of undesirable effects, temporary dose reduction or interruption may be considered as deemed clinically necessary.

Elderly

Elderly patients (≥ 65 years) may generally be at increased risk of adverse reactions due to immunosuppression. Elderly patients receiving mycophenolate mofetil as part of a combination immunosuppressive regimen, may be at increased risk of certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared to younger individuals.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via **the national reporting system** listed in [Appendix V](#).

4.9 Overdose

Reports of overdoses with mycophenolate mofetil have been received from clinical trials and during post-marketing experience. In the vast majority of these cases, either no adverse events were reported or they were in line with the known safety profile of the medicinal product and had a favourable outcome. However, isolated serious adverse events including a fatal case were observed during post-marketing experience.

It is expected that an overdose of mycophenolate mofetil could possibly result in oversuppression of the immune system and increase susceptibility to infections and bone marrow suppression (see section 4.4). If neutropenia develops, dosing with mycophenolate mofetil should be interrupted or the dose reduced (see section 4.4).

Haemodialysis would not be expected to remove clinically significant amounts of MPA or MPAG. Bile acid sequestrants, such as cholestyramine, can remove MPA by decreasing the enterohepatic recirculation of the drug (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressive agents ATC code: L04AA06

Mechanism of action

Mycophenolate mofetil is the 2-morpholinoethyl ester of MPA. MPA is a selective, uncompetitive and reversible inhibitor of IMPDH, and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines whereas other cell types can utilise salvage pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells.

In addition to its inhibition of IMPDH and the resulting deprivation of lymphocytes, MPA also influences cellular checkpoints responsible for metabolic programming of lymphocytes. It has been shown, using human CD4+ T-cells, that MPA shifts transcriptional activities in lymphocytes from a proliferative state to catabolic processes relevant to metabolism and survival leading to an anergic state of T-cells, whereby the cells become unresponsive to their specific antigen.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, MPA. As evidenced by suppression of acute rejection following renal transplantation, the immunosuppressant activity of mycophenolate mofetil is correlated with MPA concentration. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94% relative to intravenous mycophenolate mofetil. Food had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g BID to renal transplant patients. However, MPA C_{max} was decreased by 40% in the presence of food. Mycophenolate mofetil is not measurable systemically in plasma following oral administration.

Distribution

As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed at approximately 6 – 12 hours post-dose. A reduction in the AUC of MPA of approximately 40% is associated with the co-administration of cholestyramine (4 g TID), indicating that there is a significant amount of enterohepatic recirculation.

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

In the early post-transplant period (< 40 days post-transplant), renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30% lower and C_{max} approximately 40% lower compared to the late post-transplant period (3 - 6 months post-transplant).

Biotransformation

MPA is metabolised principally by glucuronyl transferase (isoform UGT1A9) to form the 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 mycophenolate mofetil's side effects (diarrhoea, leukopenia).

Elimination

A negligible amount of substance is excreted as MPA (< 1% of the dose) in the urine. Oral administration of radiolabelled mycophenolate mofetil results in complete recovery of the

administered dose with 93% of the administered dose recovered in the urine and 6% recovered in the faeces. Most (about 87%) of the administered dose is excreted in the urine as MPAG.

At clinically encountered concentrations, MPA and MPAG are not removed by haemodialysis. However, at high MPAG plasma concentrations ($> 100 \mu\text{g/ml}$), small amounts of MPAG are removed. By interfering with enterohepatic recirculation of the drug, bile acid sequestrants such as cholestyramine, reduce MPA AUC (see section 4.9).

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 potentially interact with renal organic anion transporters.

Enterohepatic recirculation interferes with accurate determination of MPA's disposition parameters; only apparent values can be indicated. In healthy volunteers and patients with autoimmune disease approximate clearance values of 10.6 L/h and 8.27 L/h respectively and half-life values of 17 h were observed. In transplant patients mean clearance values were higher (range 11.9-34.9 L/h) and mean half-life values shorter (5-11 h) with little difference between renal, hepatic or cardiac transplant patients. In the individual patients, these elimination parameters vary based on type of co-treatment with other immunosuppressants, time post-transplantation, plasma albumin concentration and renal function. These factors explain why reduced exposure to mycophenolate is seen when mycophenolate mofetil is co-administered with ciclosporin (see section 4.5) and why plasma concentrations tend to increase over time compared to what is observed immediately after transplantation.

Special populations

Renal impairment

In a single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate $< 25 \text{ ml/min/1.73 m}^2$) were 28 – 75% higher relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. The mean single dose MPAG AUC was 3 – 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. Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Delayed renal graft function

In patients with delayed renal graft function post-transplant, mean MPA AUC_{0-12h} was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC_{0-12h} was 2 – 3-fold higher than in post-transplant patients without delayed graft function. There may be a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of mycophenolate mofetil does not appear to be necessary.

Hepatic impairment

In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were 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.

Paediatric population

In 33 paediatric renal allograft recipients it was established that the dose predicted to provide an MPA AUC_{0-12h} closest to the target exposure of 27.2 h·mg/l was 600 mg/m², and that doses calculated based on estimated BSA reduced interindividual variability (coefficient of variation, (CV)) by about 10%. Therefore, dosing based on BSA is preferred rather than dosing based on body weight.

Pharmacokinetic parameters were evaluated in up to 55 paediatric renal transplant patients (aged 1 to 18 years) given 600 mg/m², up to 1 g/m² of mycophenolate mofetil orally twice daily. This dose achieved MPA AUC values similar to those seen in adult renal transplant patients receiving mycophenolate mofetil at a dose of 1 g BID in the early and late post-transplant period as per Table 3 below. MPA AUC values across paediatric age groups were similar in the early and late post-transplant period.

For paediatric hepatic transplant recipients an open-label study of the safety, tolerability and pharmacokinetics of oral mycophenolate mofetil included 7 evaluable patients on concomitant ciclosporin and corticosteroid treatment. The dose predicted to achieve an exposure of 58 h-mg/l in the stable post-transplant period was estimated. The mean \pm SD AUC₀₋₁₂ (adjusted to a dose of 600 mg/m²) was 47.0 \pm 21.8 h-mg/l, adjusted C_{max} was 14.5 \pm 4.21 mg/l, with a median time to maximum concentration of 0.75 h. To achieve the target AUC₀₋₁₂ of 58 h-mg/l in the late post-transplant period, a dose in the range of 740-806 mg/m² BID would therefore have been required in the study population.

A comparison of dose-normalised (to 600 mg/m²) MPA AUC values in 12 paediatric renal transplant patients less than 6 years of age at 9 months post-transplant with those values in 7 paediatric hepatic transplant patients [median age 17 months (range: 10-60 months at enrolment)] at 6 months and beyond post-transplant revealed that, at the same dose, the AUC values were on average 23% lower in the paediatric hepatic patients compared to paediatric renal patients. This is consistent with the need for higher dosing in adult hepatic transplant patients compared to adult renal transplant patients to achieve the same exposure.

In adult transplant patients administered the same dosage of mycophenolate mofetil, there is similar MPA exposure among renal transplant and cardiac transplant patients. In line with the established similarity in MPA exposure between paediatric renal transplant and adult renal transplant patients at their respective approved doses, existing data allows to conclude that MPA exposure at the recommended dosage will be similar in paediatric cardiac transplant and adult cardiac transplant patients.

Table 3 Mean computed MPA PK parameters by age and time post-transplant (renal)

| Age group (n) | | Adjusted C _{max} mg/l ^A mean \pm SD | Adjusted AUC ₀₋₁₂ h-mg/l mean \pm SD (CI) ^A |
|----------------------|-------------------|--|--|
| Day 7 | | | |
| <6 y | (17) | 13.2 \pm 7.16 | 27.4 \pm 9.54 (22.8-31.9) |
| 6 - <12 y | (16) | 13.1 \pm 6.30 | 33.2 \pm 12.1 (27.3-39.2) |
| 12-18 y | (21) | 11.7 \pm 10.7 | 26.3 \pm 9.14 (22.3-30.3) ^D |
| p-value ^B | | - | - |
| <2 y ^C | (6) | 10.3 \pm 5.80 | 22.5 \pm 6.68 (17.2-27.8) |
| >18 y | (141) | | 27.2 \pm 11.6 |
| Month 3 | | | |
| <6 y | (15) | 22.7 \pm 10.1 | 49.7 \pm 18.2 |
| 6 - <12 y | (14) ^E | 27.8 \pm 14.3 | 61.9 \pm 19.6 |
| 12-18 y | (17) | 17.9 \pm 9.57 | 53.6 \pm 20.2 ^F |
| p-value ^B | | - | - |
| <2 y ^C | (4) | 23.8 \pm 13.4 | 47.4 \pm 14.7 |
| >18 y | (104) | | 50.3 \pm 23.1 |
| Month 9 | | | |
| <6 y | (12) | 30.4 \pm 9.16 | 60.9 \pm 10.7 |
| 6 - <12 y | (11) | 29.2 \pm 12.6 | 66.8 \pm 21.2 |

| Age group (n) | | Adjusted C _{max} mg/l ^A mean ± SD | Adjusted AUC ₀₋₁₂ h·mg/l mean ± SD (CI) ^A |
|----------------------|------|--|--|
| 12-18 y | (14) | 18.1±7.29 | 56.7±14.0 |
| p-value ^B | | 0.004 | - |
| <2 y ^C | (4) | 25.6±4.25 | 55.8±11.6 |
| >18 y | (70) | | 53.5±18.3 |

AUC_{0-12h}=area under the plasma concentration-time curve from time 0 h to time 12 h; CI=confidence interval; C_{max}=maximum concentration; MPA=mycophenolic acid; SD=standard deviation; n=number of patients; y=year.

^A In the paediatric age groups C_{max} and AUC_{0-12h} are adjusted to a dose of 600 mg/m² (95% confidence intervals (CIs) for AUC_{0-12h} Day 7 only); in the adult group AUC_{0-12h} is adjusted to a dose of 1 g.

^B p-value represents the combined p-value for the three major paediatric age groups, and is noted only if significant (p <0.05).

^C The <2-year group is a subset of the <6-year group: no statistical comparisons were made.

^D n=20.

^E Data for one patient was unavailable due to sampling error.

^F n=16.

Elderly

The pharmacokinetics of mycophenolate mofetil and its metabolites have not been found to be altered in the elderly patients (≥ 65 years) when compared to younger transplant patients.

Patients taking oral contraceptives

A study of the co-administration of mycophenolate mofetil (1 g BID) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) conducted in 18 non-transplant women (not taking other immunosuppressants) over 3 consecutive menstrual cycles showed no clinically relevant influence of mycophenolate mofetil on the ovulation-suppressing action of the oral contraceptives. Serum levels of LH, FSH and progesterone were not significantly affected. The pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by co-administration of mycophenolate mofetil (see also section 4.5).

5.3 Preclinical safety data

In experimental models, mycophenolate mofetil was not tumourigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2 – 3 times the systemic exposure (AUC or C_{max}) observed in renal transplant patients at the recommended clinical dose of 2 g/day and 1.3 – 2 times the systemic exposure (AUC or C_{max}) observed in cardiac transplant patients at the recommended clinical dose of 3 g/day.

Two genotoxicity assays (*in vitro* mouse lymphoma assay and *in vivo* mouse bone marrow micronucleus test) showed a potential of mycophenolate mofetil to cause chromosomal aberrations. These effects can be related to the pharmacodynamic mode of action, i.e. inhibition of nucleotide synthesis in sensitive cells. Other *in vitro* tests for detection of gene mutation did not demonstrate genotoxic activity.

In teratology studies in rats and rabbits, foetal resorptions and malformations occurred in rats at 6 mg/kg/day (including anophthalmia, agnathia, and hydrocephaly) and in rabbits at 90 mg/kg/day (including cardiovascular and renal anomalies, such as ectopia cordis and ectopic kidneys, and diaphragmatic and umbilical hernia), in the absence of maternal toxicity. The systemic exposure at these levels is approximately equivalent to or less than 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients (see section 4.6).

The haematopoietic and lymphoid systems were the primary organs affected in toxicology studies conducted with mycophenolate mofetil in the rat, mouse, dog and monkey. These effects occurred at

systemic exposure levels that are equivalent to or less than the clinical exposure at the recommended dose of 2 g/day for renal transplant recipients. Gastrointestinal effects were observed in the dog at systemic exposure levels equivalent to or less than the clinical exposure at the recommended dose. Gastrointestinal and renal effects consistent with dehydration were also observed in the monkey at the highest dose (systemic exposure levels equivalent to or greater than clinical exposure). The non-clinical toxicity profile of mycophenolate mofetil appears to be consistent with adverse events observed in human clinical trials, which now provide safety data of more relevance to the patient population (see section 4.8).

Environmental Risk Assessment (ERA)

Environmental risk assessment studies have shown that the active substance, MPA may pose a risk for groundwater via bank filtration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

CellCept tablets

microcrystalline cellulose
polyvidone (K-90)
croscarmellose sodium
magnesium stearate

Tablet coating

hydroxypropyl methylcellulose
hydroxypropyl cellulose
titanium dioxide (E171)
polyethylene glycol 400
indigo carmine aluminium lake (E132)
red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

Do not store above 30 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/aluminium foil blister strips

CellCept 500 mg film-coated tablets: 1 carton contains 50 tablets (in blister packs of 10)
multipacks containing 150 (3 packs of 50) tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/005/002 CellCept (50 tablets)
EU/1/96/005/004 CellCept (150 (3x50) tablets multipack)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 February 1996
Date of latest renewal: 13 March 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

- CellCept 500 mg powder for concentrate for solution for infusion
- CellCept 1 g/5 ml powder for oral suspension:

Roche Pharma AG, Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany.

Name and address of the manufacturer(s) responsible for batch release

- CellCept 250 mg capsules
- CellCept 500 mg film-coated tablets

Roche Pharma AG, Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic safety update reports (PSURs)

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

• Additional risk minimisation measures

The Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme and a follow-up pregnancy questionnaire, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at ensuring that the health professionals and patients are aware of the teratogenicity and mutagenicity, the need for pregnancy tests before starting therapy with CellCept,

the contraceptive requirements for both male and female patients and what to do in case of pregnancy during treatment with CellCept.

The MAH shall ensure that in each MS where CellCept is marketed, all healthcare professionals and patients who are expected to prescribe, dispense or use CellCept are provided with the following educational package:

- Physician educational material
- Patient information pack

The health professional educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals

The patient information pack should contain:

- The Package Leaflet
- Guide for patients

The educational materials shall contain the following key elements:

Separate guides for healthcare professionals and patients should be provided. For patients, the text should be appropriately separated for men and women. The following areas should be covered in these guides:

- An introduction in each guide will inform the reader that the purpose of the guide is to tell them that a foetal exposure must be avoided and how to minimise the risk of birth defects and miscarriage associated with mycophenolate mofetil. It will explain that although this guide is very important it does not provide full information on mycophenolate mofetil and that the SmPC (healthcare professionals) and package leaflet (patients) supplied with the medicine must also be read carefully.
- Background information on mycophenolate mofetil teratogenicity and mutagenicity in humans. This section will provide important background information concerning the teratogenicity and mutagenicity of mycophenolate mofetil. It will provide details about the nature and magnitude of the risk, in line with the information provided in the SmPC. The information provided in this section will facilitate a correct understanding of the risk and explain the rationale for the following pregnancy prevention measures. Guides should also mention that patients should not give this drug to any other person.
- Counselling of patients: This section will emphasise the importance of a thorough, informative and ongoing dialogue between patient and healthcare professional about the pregnancy risks associated with mycophenolate mofetil and the relevant minimisation strategies including alternative treatment choices, if applicable. The need to plan a pregnancy will be highlighted.
- The need to avoid foetal exposure: Contraceptive requirements for patients of reproductive potential prior to, during and after treatment with mycophenolate mofetil. Contraceptive requirements for sexually active male patients (including vasectomised men) and female patients of childbearing potential will be explained. The need for contraception prior to, during and after treatment with mycophenolate mofetil, including details of the duration of time for which contraception must be continued after cessation of therapy, will be clearly stated.

In addition, the text relating to women should explain the pregnancy test requirements prior to and during therapy with mycophenolate mofetil; including the advice for two negative pregnancy tests prior to starting therapy and the importance of the timing of these tests. The need for subsequent pregnancy tests during treatment will also be explained.

- Advice that patients should not donate blood during therapy or for at least 6 weeks following discontinuation of mycophenolate mofetil. Furthermore, men should not donate semen during therapy or for 90 days following discontinuation of mycophenolate mofetil.

- Advice on action if a pregnancy occurs or is suspected during or shortly after being treated with mycophenolate mofetil. Patients will be informed that they should not stop taking mycophenolate mofetil but must contact their doctor immediately. It will be explained that the correct course of action, based on an assessment of the individual benefit-risk, will be determined on a case-by-case basis through a discussion between the treating physician and the patient.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

CellCept 250 mg hard capsules
mycophenolate mofetil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 250 mg mycophenolate mofetil.

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

100 hard capsules
300 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Capsules should be handled with caution
Do not open or crush the capsules and breathe the powder inside the capsules or allow it to touch your skin

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C
Store in the original package in order to protect from moisture

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| 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE |
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|---|
| 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER |
|---|

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

| |
|--|
| 12. MARKETING AUTHORISATION NUMBER(S) |
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EU/1/96/005/001 100 hard capsules
EU/1/96/005/003 300 hard capsules

| |
|-------------------------|
| 13. BATCH NUMBER |
|-------------------------|

Lot

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| 14. GENERAL CLASSIFICATION FOR SUPPLY |
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|--------------------------------|
| 15. INSTRUCTIONS ON USE |
|--------------------------------|

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|-----------------------------------|
| 16. INFORMATION IN BRAILLE |
|-----------------------------------|

cellcept 250 mg

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| 17. UNIQUE IDENTIFIER – 2D BARCODE |
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2D barcode carrying the unique identifier included.

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| 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA |
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PC
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NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON FOR THE MULTIPACK (INCLUDING BLUE BOX)****1. NAME OF THE MEDICINAL PRODUCT**

CellCept 250 mg hard capsules
mycophenolate mofetil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 250 mg mycophenolate mofetil.

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Multipack: 300 (3 packs of 100) hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Capsules should be handled with caution
Do not open or crush the capsules and breathe the powder inside the capsules or allow it to touch your skin

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C
Store in the original package in order to protect from moisture

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|--|
| 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE |
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|---|
| 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER |
|---|

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

| |
|--|
| 12. MARKETING AUTHORISATION NUMBER(S) |
|--|

EU/1/96/005/007

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| 13. BATCH NUMBER |
|-------------------------|

Lot

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| 14. GENERAL CLASSIFICATION FOR SUPPLY |
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| 15. INSTRUCTIONS ON USE |
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|-----------------------------------|
| 16. INFORMATION IN BRAILLE |
|-----------------------------------|

cellcept 250 mg

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|---|
| 17. UNIQUE IDENTIFIER – 2D BARCODE |
|---|

2D barcode carrying the unique identifier included.

| |
|--|
| 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA |
|--|

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)****1. NAME OF THE MEDICINAL PRODUCT**

CellCept 250 mg hard capsules
mycophenolate mofetil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 250 mg mycophenolate mofetil.

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

100 hard capsules. Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Capsules should be handled with caution
Do not open or crush the capsules and breathe the powder inside the capsules or allow it to touch your skin

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C
Store in the original package in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/005/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

cellcept 250 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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| MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS |
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| BLISTER FOIL |
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| |
|---|
| 1. NAME OF THE MEDICINAL PRODUCT |
|---|

CellCept 250 mg capsules
mycophenolate mofetil

| |
|--|
| 2. NAME OF THE MARKETING AUTHORISATION HOLDER |
|--|

Roche Registration GmbH

| |
|-----------------------|
| 3. EXPIRY DATE |
|-----------------------|

EXP

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| 4. BATCH NUMBER |
|------------------------|

Lot

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|-----------------|
| 5. OTHER |
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PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

CellCept 500 mg powder for concentrate for solution for infusion
mycophenolate mofetil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 500 mg mycophenolate mofetil (as hydrochloride).

3. LIST OF EXCIPIENTS

Also contains polysorbate 80, citric acid, hydrochloric acid and sodium chloride.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
4 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For intravenous infusion only
Reconstitute and dilute before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Avoid skin contact with infusion solution

8. EXPIRY DATE

EXP
Shelf life after reconstitution: 3 hours

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C

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| 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE |
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| 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER |
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Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

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| 12. MARKETING AUTHORISATION NUMBER(S) |
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EU/1/96/005/005

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| 13. BATCH NUMBER |
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| 14. GENERAL CLASSIFICATION FOR SUPPLY |
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| 15. INSTRUCTIONS ON USE |
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| 16. INFORMATION IN BRAILLE |
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| 17. UNIQUE IDENTIFIER – 2D BARCODE |
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2D barcode carrying the unique identifier included.

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| 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA |
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| MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS |
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| VIAL LABEL |
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| 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION |
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CellCept 500 mg powder for concentrate for solution for infusion
mycophenolate mofetil
For intravenous infusion only

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| 2. METHOD OF ADMINISTRATION |
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Read the package leaflet before use

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| 3. EXPIRY DATE |
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| 4. BATCH NUMBER |
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| 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT |
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| 6. OTHER |
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PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

CellCept 1 g/5 ml powder for oral suspension
mycophenolate mofetil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each bottle contains 35 g mycophenolate mofetil in 110 g powder for oral suspension
5 ml suspension contains 1 g mycophenolate mofetil when reconstituted.
The usable volume of the reconstituted suspension is 160 - 165 ml.

3. LIST OF EXCIPIENTS

Also contains aspartame (E951) and methyl parahydroxybenzoate (E218).

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension
1 bottle, 1 bottle adapter and 2 oral dispensers

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For oral use after reconstitution

Shake bottle well before use

It is recommended that the suspension be reconstituted by the pharmacist prior to dispensing to the patient

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not breathe the powder before reconstitution or allow it to touch your skin
Avoid skin contact with the reconstituted suspension

8. EXPIRY DATE

EXP
Shelf life after reconstitution: 2 months

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| 9. SPECIAL STORAGE CONDITIONS |
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Do not store above 30 °C

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| 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE |
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| 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER |
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Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

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| 12. MARKETING AUTHORISATION NUMBER(S) |
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EU/1/96/005/006

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| 13. BATCH NUMBER |
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| 14. GENERAL CLASSIFICATION FOR SUPPLY |
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| 15. INSTRUCTIONS ON USE |
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| 16. INFORMATION IN BRAILLE |
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cellcept 1 g/5 ml

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| 17. UNIQUE IDENTIFIER – 2D BARCODE |
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2D barcode carrying the unique identifier included.

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| 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA |
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PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**BOTTLE LABEL****1. NAME OF THE MEDICINAL PRODUCT**

CellCept 1 g/5 ml powder for oral suspension
mycophenolate mofetil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each bottle contains 35 g mycophenolate mofetil in 110 g powder for oral suspension
5 ml suspension contains 1 g mycophenolate mofetil when reconstituted.

3. LIST OF EXCIPIENTS

Also contains aspartame (E951) and methyl parahydroxybenzoate (E218).

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For oral use after reconstitution

Shake bottle well before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not breathe the powder before reconstitution or allow it to touch your skin
Avoid skin contact with the reconstituted suspension

8. EXPIRY DATE

EXP
Shelf life after reconstitution: 2 months
Use before

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| 9. SPECIAL STORAGE CONDITIONS |
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Do not store above 30 °C

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| 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE |
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| 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER |
|---|

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Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

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| 12. MARKETING AUTHORISATION NUMBER(S) |
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| 13. BATCH NUMBER |
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| 14. GENERAL CLASSIFICATION FOR SUPPLY |
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| 15. INSTRUCTIONS ON USE |
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| 16. INFORMATION IN BRAILLE |
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| 17. UNIQUE IDENTIFIER – 2D BARCODE |
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| 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA |
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PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

CellCept 500 mg film-coated tablets
mycophenolate mofetil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 500 mg mycophenolate mofetil.

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

50 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For oral use
Do not crush the tablets

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Tablets should be handled with caution

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C
Store in the original package in order to protect from moisture

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| 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE |
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| 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER |
|---|

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

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| 12. MARKETING AUTHORISATION NUMBER(S) |
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| 13. BATCH NUMBER |
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| 14. GENERAL CLASSIFICATION FOR SUPPLY |
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| 15. INSTRUCTIONS ON USE |
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| 16. INFORMATION IN BRAILLE |
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cellcept 500 mg

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| 17. UNIQUE IDENTIFIER – 2D BARCODE |
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2D barcode carrying the unique identifier included.

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| 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA |
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PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON FOR MULTIPACK (INCLUDING BLUE BOX)****1. NAME OF THE MEDICINAL PRODUCT**

CellCept 500 mg film-coated tablets
mycophenolate mofetil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 500 mg mycophenolate mofetil.

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

Multipack: 150 (3 packs of 50) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For oral use
Do not crush the tablets

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Tablets should be handled with caution

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C
Store in the original package in order to protect from moisture

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| 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE |
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| 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER |
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Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

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| 12. MARKETING AUTHORISATION NUMBER(S) |
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EU/1/96/005/004

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| 13. BATCH NUMBER |
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| 14. GENERAL CLASSIFICATION FOR SUPPLY |
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| 15. INSTRUCTIONS ON USE |
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| 16. INFORMATION IN BRAILLE |
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cellcept 500 mg

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| 17. UNIQUE IDENTIFIER – 2D BARCODE |
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2D barcode carrying the unique identifier included.

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| 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA |
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PARTICULARS TO APPEAR ON THE OUTER PACKAGING**INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)****1. NAME OF THE MEDICINAL PRODUCT**

CellCept 500 mg film-coated tablets
mycophenolate mofetil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 500 mg mycophenolate mofetil.

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

50 film-coated tablets. Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For oral use
Do not crush the tablets

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Tablets should be handled with caution

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C
Store in the original package in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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| 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER |
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Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

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| 12. MARKETING AUTHORISATION NUMBER(S) |
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EU/1/96/005/004

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| 13. BATCH NUMBER |
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| 14. GENERAL CLASSIFICATION FOR SUPPLY |
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| 15. INSTRUCTIONS ON USE |
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| 16. INFORMATION IN BRAILLE |
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cellcept 500 mg

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| 17. UNIQUE IDENTIFIER – 2D BARCODE |
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| 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA |
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| MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS |
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| 1. NAME OF THE MEDICINAL PRODUCT |
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CellCept 500 mg tablets
mycophenolate mofetil

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| 2. NAME OF THE MARKETING AUTHORISATION HOLDER |
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Roche Registration GmbH

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| 3. EXPIRY DATE |
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| 4. BATCH NUMBER |
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| 5. OTHER |
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B. PACKAGE LEAFLET

Package Leaflet: Information for the patient

CellCept 250 mg hard capsules mycophenolate mofetil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What CellCept is and what it is used for
2. What you need to know before you take CellCept
3. How to take CellCept
4. Possible side effects
5. How to store CellCept
6. Contents of the pack and other information

1. What CellCept is and what it is used for

CellCept contains mycophenolate mofetil:

- This belongs to a group of medicines called “immunosuppressants”.

CellCept is used to prevent the body rejecting a transplanted organ in adults and children:

- A kidney, heart or liver.

CellCept should be used together with other medicines:

- Ciclosporin and corticosteroids.

2. What you need to know before you take CellCept

WARNING

Mycophenolate causes birth defects and miscarriage. If you are a woman who could become pregnant, you must provide a negative pregnancy test before starting treatment and must follow the contraception advice given to you by your doctor.

Your doctor will speak to you and give you written information, particularly on the effects of mycophenolate on unborn babies. Read the information carefully and follow the instructions. If you do not fully understand these instructions, please ask your doctor to explain them again before you take mycophenolate. See also further information in this section under “Warnings and precautions” and “Pregnancy and breast-feeding”.

Do not take CellCept:

- If you are allergic to mycophenolate mofetil, mycophenolic acid or any of the other ingredients of this medicine (listed in section 6).
- If you are a woman who could be pregnant and you have not provided a negative pregnancy test before your first prescription, as mycophenolate causes birth defects and miscarriage.
- If you are pregnant or planning to become pregnant or think you may be pregnant
- If you are not using effective contraception (see Contraception, pregnancy and breast-feeding).
- If you are breast-feeding.

Do not take this medicine if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking CellCept.

Warnings and precautions

Talk to your doctor straight away before starting treatment with CellCept:

- If you are older than 65 years as you may have an increased risk of developing adverse events such as certain viral infections, gastrointestinal bleeding and pulmonary oedema when compared to younger patients
- If you have a sign of infection such as a fever or sore throat
- If you have any unexpected bruising or bleeding
- If you have ever had a problem with your digestive system such as a stomach ulcer
- If you are planning to become pregnant or if you get pregnant while you or your partner are taking CellCept
- If you have a hereditary enzyme deficiency such as Lesch-Nyhan and Kelley-Seegmiller syndrome

If any of the above apply to you (or you are not sure), talk to your doctor straight away before starting treatment with CellCept.

The effect of sunlight

CellCept reduces your body's defences. As a result, there is an increased risk of skin cancer. Limit the amount of sunlight and UV light you get. Do this by:

- wearing protective clothing that also covers your head, neck, arms and legs
- using a sunscreen with a high protection factor.

Children

Children, especially those under 6 years old, may be more likely than adults to have some side effects, including diarrhoea, vomiting, infections, fewer red cells and fewer white cells in the blood, and possibly lymph or skin cancer.

Capsules are only appropriate for children who are capable of swallowing solid medication without the risk of choking. The medicine should therefore only be given in line with the doctor's prescription.

If you are not sure about anything for your child's treatment, talk to your doctor or pharmacist before use.

Other medicines and CellCept

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, such as herbal medicines. This is because CellCept can affect the way some other medicines work. Also, other medicines can affect the way CellCept works.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines before you start CellCept:

- azathioprine or other medicines that suppress your immune system – given after a transplant operation
- cholestyramine – used to treat high cholesterol
- rifampicin – an antibiotic used to prevent and treat infections such as tuberculosis (TB)
- antacids or proton pump inhibitors – used for acid problems in your stomach such as indigestion
- phosphate binders – used by people with chronic kidney failure to reduce how much phosphate gets absorbed into their blood
- antibiotics – used to treat bacterial infections
- isavuconazole – used to treat fungal infections
- telmisartan – used to treat high blood pressure

Vaccines

If you need to have a vaccination (a live vaccine) while taking CellCept, talk to your doctor or pharmacist first. Your doctor will have to advise you on what vaccines you can have.

You must not donate blood during treatment with CellCept and for at least 6 weeks after stopping treatment. Men must not donate semen during treatment with CellCept and for at least 90 days after stopping treatment.

CellCept with food and drink

Taking food and drink has no effect on your treatment with CellCept.

Contraception in women taking CellCept

If you are a woman who could become pregnant, you must use an effective method of contraception with CellCept. This includes:

- Before you start taking CellCept
- During your entire treatment with CellCept
- For 6 weeks after you stop taking CellCept.

Talk to your doctor about the most suitable contraception for you. This will depend on your individual situation. Two forms of contraception are preferable as this will reduce the risk of unintended pregnancy. **Contact your doctor as soon as possible, if you think your contraception may not have been effective or if you have forgotten to take your contraceptive pill.**

You cannot become pregnant if any of the following conditions applies to you:

- You are post-menopausal, i.e. at least 50 years old and your last period was more than a year ago (if your periods have stopped because you have had treatment for cancer, then there is still a chance you could become pregnant)
- Your fallopian tubes and both ovaries have been removed by surgery (bilateral salpingo-oophorectomy)
- Your womb (uterus) has been removed by surgery (hysterectomy)
- Your ovaries no longer work (premature ovarian failure, which has been confirmed by a specialist gynaecologist)
- You were born with one of the following rare conditions that make pregnancy impossible: the XY genotype, Turner's syndrome or uterine agenesis
- You are a child or teenager who has not started having periods.

Contraception in men taking CellCept

The available evidence does not indicate an increased risk of malformations or miscarriage if the father takes mycophenolate. However, a risk cannot be completely excluded. As a precaution you or your female partner are recommended to use reliable contraception during treatment and for 90 days after you stop taking CellCept.

If you are planning to have a child, talk to your doctor about the potential risks and alternative therapies.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will talk to you about the risks in case of pregnancy and the alternatives you can take to prevent rejection of your transplant organ if:

- You plan to become pregnant.
- You miss or think you have missed a period, or you have unusual menstrual bleeding, or suspect you are pregnant.
- You have sex without using effective methods of contraception.

If you do become pregnant during the treatment with mycophenolate, you must inform your doctor immediately. However, keep taking CellCept until you see him or her.

Pregnancy

Mycophenolate causes a very high frequency of miscarriage (50%) and of severe birth defects (23 - 27%) in the unborn baby. Birth defects that have been reported include anomalies of ears, of eyes, of face (cleft lip/palate), of development of fingers, of heart, oesophagus (tube that connects the throat with the stomach), kidneys and nervous system (for example spina bifida (where the bones of the spine are not properly developed)). Your baby may be affected by one or more of these.

If you are a woman who could become pregnant, you must provide a negative pregnancy test before starting treatment and must follow the contraception advice given to you by your doctor. Your doctor may request more than one test to ensure you are not pregnant before starting treatment.

Breast-feeding

Do not take CellCept if you are breast-feeding. This is because small amounts of the medicine can pass into the mother's milk.

Driving and using machines

CellCept has a moderate influence on your ability to drive or use any tools or machines. If you feel drowsy, numb or confused, talk to your doctor or nurse and do not drive or use any tools or machines until you feel better.

CellCept contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

3. How to take CellCept

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take

The amount you take depends on the type of transplant you have had. The usual doses are shown below. Treatment will continue for as long as you need to prevent rejection of your transplant organ.

Kidney transplant

Adults

- The first dose is given within 3 days of the transplant operation.
- The daily dose is 8 capsules (2 g of the medicine) taken as 2 separate doses.
- Take 4 capsules in the morning and then 4 capsules in the evening.

Children

- Capsules are only appropriate for children who are capable of swallowing solid medication without the risk of choking. The medicine should therefore only be given in line with the doctor's prescription. If you are not sure, talk to your doctor or pharmacist before use.
- The dose given will vary depending on the size of the child.
- Your child's doctor will decide the most appropriate dose based on your child's height and weight (body surface area – measured as square metres or "m²"). The recommended initial dose is 600 mg/m² taken twice a day. The recommended maintenance dose remains at 600 mg/m² twice a day (maximum total daily dose of 2 g). The dose should be individualised based on the doctor's clinical assessment.

Heart transplant

Adults

- The first dose is given within 5 days of the transplant operation.
- The daily dose is 12 capsules (3 g of the medicine) taken as 2 separate doses.
- Take 6 capsules in the morning and then 6 capsules in the evening.

Children

- Capsules are only appropriate for children who are capable of swallowing solid medication without the risk of choking. The medicine should therefore only be given in line with the doctor's prescription. If you are not sure, talk to your doctor or pharmacist before use.
- The dose given will vary depending on the size of the child.
- Your child's doctor will decide the most appropriate dose based on your child's height and weight (body surface area – measured as square metres or "m²"). The recommended initial dose is 600 mg/m² taken twice a day. The dose should be individualised based on the doctor's clinical assessment. If well tolerated, the dose can be increased to 900 mg/m² twice daily if required (maximum total daily dose of 3 g).

Liver transplant

Adults

- The first dose of oral CellCept will be given to you at least 4 days after the transplant operation and when you are able to swallow oral medicines.
- The daily dose is 12 capsules (3 g of the medicine) taken as 2 separate doses.
- Take 6 capsules in the morning and then 6 capsules in the evening.

Children

- Capsules are only appropriate for children who are capable of swallowing solid medication without the risk of choking. The medicine should therefore only be given in line with the doctor's prescription. If you are not sure, talk to your doctor or pharmacist before use.
- The dose given will vary depending on the size of the child.
- Your child's doctor will decide the most appropriate dose based on your child's height and weight (body surface area – measured as square metres or "m²"). The recommended initial dose is 600 mg/m² taken twice a day. The dose should be individualised based on the doctor's clinical assessment. If well tolerated, the dose can be increased to 900 mg/m² twice daily if required (maximum total daily dose of 3 g).

Taking the medicine

Swallow your capsules whole with a glass of water

- Do not break or crush them
- Do not take any capsules that have broken open or split.

Take care not to let any powder from inside a broken capsule get into your eyes or mouth.

- If this happens, rinse with plenty of plain water.

Take care not to let any powder from inside a broken capsule get onto your skin.

- If this happens, wash the area thoroughly with soap and water.

If you take more CellCept than you should

If you take more CellCept than you should, talk to a doctor or go to a hospital straight away. Also do this if someone else accidentally takes your medicine. Take the medicine pack with you.

If you forget to take CellCept

If you forget to take your medicine at any time, take it as soon as you remember. Then continue to take it at the usual times. Do not take a double dose to make up for a missed dose.

If you stop taking CellCept

Do not stop taking CellCept unless your doctor tells you to. If you stop your treatment you may increase the chance of rejection of your transplant organ.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, CellCept can cause side effects, although not everybody gets them.

Talk to a doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

- you have a sign of infection such as a fever or sore throat
- you have any unexpected bruising or bleeding
- you have a rash, swelling of your face, lips, tongue or throat, with difficulty breathing - you may be having a serious allergic reaction to the medicine (such as anaphylaxis, angioedema).

Usual problems

Some of the more usual problems are diarrhoea, fewer white cells or red cells in your blood, infection and vomiting. Your doctor will do regular blood tests to check for any changes in:

- the number of your blood cells or signs of infections

Fighting infections

CellCept reduces your body's defences. This is to stop you rejecting your transplant. As a result, your body will not be as good as normal at fighting infections. This means you may catch more infections than usual. This includes infections of the brain, skin, mouth, stomach and gut, lungs and urinary system.

Lymph and skin cancer

As can happen in patients taking this type of medicine (immune-suppressants), a very small number of patients on CellCept have developed cancer of the lymphoid tissues and skin.

General unwanted effects

You may get general side effects affecting your body as a whole. These include serious allergic reactions (such as anaphylaxis, angioedema), fever, feeling very tired, difficulty sleeping, pains (such as stomach, chest, joint or muscle), headache, flu symptoms and swelling.

Other unwanted effects may include:

Skin problems such as:

- acne, cold sores, shingles, skin growth, hair loss, rash, itching.

Urinary problems such as:

- blood in the urine.

Digestive system and mouth problems such as:

- swelling of the gums and mouth ulcers,
- inflammation of the pancreas, colon or stomach,
- gastrointestinal disorders including bleeding,
- liver disorder,
- diarrhoea, constipation, feeling sick (nausea), indigestion, loss of appetite, flatulence.

Nervous system problems such as:

- feeling dizzy, drowsy or numb,
- tremor, muscle spasms, convulsions,
- feeling anxious or depressed, changes in your mood or thoughts.

Heart and blood vessel problems such as:

- change in blood pressure, accelerated heartbeat widening of blood vessels.

Lung problems such as:

- pneumonia, bronchitis,
- shortness of breath, cough, which can be due to bronchiectasis (a condition in which the lung airways are abnormally dilated) or pulmonary fibrosis (scarring of the lung). Talk to your doctor if you develop a persistent cough or breathlessness.
- fluid on the lungs or inside the chest,
- sinus problems.

Other problems such as:

- weight loss, gout, high blood sugar, bleeding, bruising.

Additional side effects in children and adolescents

Children, especially those under 6 years old, may be more likely than adults to have some side effects, including diarrhoea, vomiting, infections, fewer red cells and fewer white cells in the blood, and possibly lymph or skin cancer.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store CellCept

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton after EXP.
- Do not store above 25 °C.
- Store in the original package in order to protect from moisture.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What CellCept contains

- The active substance is mycophenolate mofetil.

Each capsule contains 250 mg mycophenolate mofetil.

- The other ingredients are:

- CellCept capsules: pregelatinised maize starch, croscarmellose sodium, polyvidone (K-90), magnesium stearate (see section 2 “CellCept contains sodium”)
- Capsule shell: gelatin, indigo carmine (E132), yellow iron oxide (E172), red iron oxide (E172), titanium dioxide (E171), black iron oxide (E172), potassium hydroxide, shellac.

What CellCept looks like and contents of the pack

- CellCept capsules are oblong-shaped with one end blue and the other end brown. They have “CellCept 250” printed in black on the capsule cap and “Roche” printed in black on the capsule body.
- They are available as a carton of 100 or 300 capsules (both in blister packs of 10) or as a multipack containing 300 (3 packs of 100) capsules. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Roche Registration GmbH
Emil-Barell-Strasse 1
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Manufacturer

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>

Package leaflet: Information for the user

CellCept 500 mg powder for concentrate for solution for infusion mycophenolate mofetil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What CellCept is and what it is used for
2. What you need to know before you take CellCept
3. How to take CellCept
4. Possible side effects
5. How to store CellCept
6. Contents of the pack and other information
7. Making up the medicine

1. What CellCept is and what it is used for

CellCept contains mycophenolate mofetil:

- This belongs to a group of medicines called “immunosuppressants”.

CellCept is used to prevent the body rejecting a transplanted organ:

- A kidney or liver.

CellCept should be used together with other medicines:

- Ciclosporin and corticosteroids.

2. What you need to know before you take CellCept

WARNING

Mycophenolate causes birth defects and miscarriage. If you are a woman who could become pregnant, you must provide a negative pregnancy test before starting treatment and must follow the contraception advice given to you by your doctor.

Your doctor will speak to you and give you written information, particularly on the effects of mycophenolate on unborn babies. Read the information carefully and follow the instructions.

If you do not fully understand these instructions, please ask your doctor to explain them again before you take mycophenolate. See also further information in this section under “Warnings and precautions” and “Pregnancy and breast-feeding”.

Do not take CellCept:

- If you are allergic to mycophenolate mofetil, mycophenolic acid, polysorbate 80 or any of the other ingredients in this medicine (listed in section 6)
- If you are a woman who could be pregnant and you have not provided a negative pregnancy test before your first prescription, as mycophenolate causes birth defects and miscarriage.
- If you are pregnant or planning to become pregnant or think you may be pregnant
- If you are not using effective contraception (see Pregnancy, contraception and breast-feeding).
- If you are breast-feeding.

Do not have this medicine if any of the above applies to you. If you are not sure, talk to your doctor or nurse before having CellCept.

Warnings and precautions

Talk to your doctor or nurse straight away before starting treatment with CellCept:

- If you are older than 65 years as you may have an increased risk of developing adverse events such as certain viral infections, gastrointestinal bleeding and pulmonary oedema when compared to younger patients
- If you have a sign of infection such as a fever or sore throat
- If you have any unexpected bruising or bleeding
- If you have ever had a problem with your digestive system such as a stomach ulcer
- If you are planning to become pregnant or if you get pregnant while you or your partner are taking CellCept.
- If you have a hereditary enzyme deficiency such as Lesch-Nyhan and Kelley-Seegmiller syndrome

If any of the above apply to you (or you are not sure), talk to your doctor or nurse straight away before starting treatment with CellCept.

The effect of sunlight

CellCept reduces your body's defences. As a result, there is an increased risk of skin cancer. Limit the amount of sunlight and UV light you get. Do this by:

- wearing protective clothing that also covers your head, neck, arms and legs
- using a sunscreen with a high protection factor.

Children

Do not administer this medicine to children because safety and efficacy of infusions to paediatric patients have not been established.

Other medicines and CellCept

Tell your doctor or nurse if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, such as herbal medicines. This is because CellCept can affect the way some other medicines work. Also other medicines can affect the way CellCept works.

In particular, tell your doctor or nurse if you are taking any of the following medicines before you start CellCept:

- azathioprine or other medicines that suppress your immune system – given after a transplant operation
- cholestyramine – used to treat high cholesterol
- rifampicin – an antibiotic used to prevent and treat infections such as tuberculosis (TB)
- phosphate binders – used by people with chronic kidney failure to reduce how much phosphate gets absorbed into their blood.
- antibiotics – used to treat bacterial infections
- isavuconazole – used to treat fungal infections
- telmisartan – used to treat high blood pressure

Vaccines

If you need to have a vaccination (a live vaccine) while having CellCept, talk to your doctor or pharmacist first. Your doctor will have to advise you on what vaccines you can have.

You must not donate blood during treatment with CellCept and for at least 6 weeks after stopping treatment. Men must not donate semen during treatment with CellCept and for at least 90 days after stopping treatment.

Contraception in women taking CellCept

If you are a woman who could become pregnant, you must use an effective method of contraception with CellCept. This includes:

- Before you start taking CellCept

- During your entire treatment with CellCept
- For 6 weeks after you stop taking CellCept.

Talk to your doctor about the most suitable contraception for you. This will depend on your individual situation. Two forms of contraception are preferable as this will reduce the risk of unintended pregnancy. **Contact your doctor as soon as possible, if you think your contraception may not have been effective or if you have forgotten to take your contraceptive pill.**

You cannot become pregnant if any of the following conditions applies to you:

- You are post-menopausal, i.e. at least 50 years old and your last period was more than a year ago (if your periods have stopped because you have had treatment for cancer, then there is still a chance you could become pregnant)
- Your fallopian tubes and both ovaries have been removed by surgery (bilateral salpingo-oophorectomy)
- Your womb (uterus) has been removed by surgery (hysterectomy)
- Your ovaries no longer work (premature ovarian failure, which has been confirmed by a specialist gynaecologist)
- You were born with one of the following rare conditions that make pregnancy impossible: the XY genotype, Turner's syndrome or uterine agenesis
- You are a child or teenager who has not started having periods.

Contraception in men taking CellCept

The available evidence does not indicate an increased risk of malformations or miscarriage if the father takes mycophenolate. However, a risk cannot be completely excluded. As a precaution, you or your female partner are recommended to use reliable contraception during treatment and for 90 days after you stop taking CellCept.

If you are planning to have a child, talk to your doctor about the potential risks and alternative therapies.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will talk to you about the risks in case of pregnancy and the alternatives you can take to prevent rejection of your transplant organ if:

- You plan to become pregnant.
- You miss or think you have missed a period, or you have unusual menstrual bleeding, or suspect you are pregnant.
- You have sex without using effective methods of contraception.

If you do become pregnant during the treatment with mycophenolate, you must inform your doctor immediately. However, keep taking CellCept until you see him or her.

Pregnancy

Mycophenolate causes a very high frequency of miscarriage (50%) and of severe birth defects (23-27 %) in the unborn baby. Birth defects which have been reported include anomalies of ears, of eyes, of face (cleft lip/palate), of development of fingers, of heart, oesophagus (tube that connects the throat with the stomach), kidneys and nervous system (for example spina bifida (where the bones of the spine are not properly developed)). Your baby may be affected by one or more of these.

If you are a woman who could become pregnant, you must provide a negative pregnancy test before starting treatment and must follow the contraception advice given to you by your doctor. Your doctor may request more than one test to ensure you are not pregnant before starting treatment.

Breast-feeding

Do not take CellCept if you are breast-feeding. This is because small amounts of the medicine can pass into the mother's milk.

Driving and using machines

CellCept has a moderate influence on your ability to drive or use any tools or machines. If you feel drowsy, numb or confused, talk to your doctor or nurse and do not drive or use any tools or machines until you feel better.

CellCept contains polysorbate

This medicine contains 25 mg of polysorbate 80 in each vial. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

CellCept contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to take CellCept

CellCept is usually given by a doctor or nurse in hospital. It is given as a slow drip (infusion) into a vein.

How much to take

The amount you take depends on the type of transplant you have had. The usual doses are shown below. Treatment will continue for as long as you need to prevent rejection of your transplant organ.

Kidney transplant**Adults**

- The first dose is given within 24 hours of the transplant operation.
- The daily dose is 2 g of the medicine taken as 2 separate doses.
- This will be given as 1 g in the morning and then 1 g in the evening.

Liver transplant**Adults**

- The first dose is given to you as soon as possible after the transplant operation.
- You will have the medicine for at least 4 days.
- The daily dose is 2 g of the medicine taken as 2 separate doses.
- This will be given as 1 g in the morning and then 1 g in the evening.
- When you are able to swallow, you will be given this medicine by mouth.

Making up the medicine

The medicine comes as a powder. This needs mixing with glucose before using. Your doctor or nurse will make up the medicine and give it to you. They will follow the instructions under section 7 "Making up the medicine".

If you take more CellCept than you should

If you think that you have had too much medicine, talk to your doctor or nurse straight away.

If you forget to take CellCept

If a dose of CellCept is missed, this will be given to you as soon as possible. Your treatment will then continue at the normal times.

If you stop taking CellCept

Do not stop having CellCept unless your doctor tells you to. If you stop your treatment you may increase the chance of rejection of your transplant organ.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, CellCept can cause side effects, although not everybody gets them.

Talk to a doctor or nurse straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

- you have a sign of infection such as a fever or sore throat
- you have any unexpected bruising or bleeding
- you have a rash, swelling of your face, lips, tongue or throat, with difficulty breathing - you may be having a serious allergic reaction to the medicine (such as anaphylaxis, angioedema).

Usual problems

Some of the more usual problems are diarrhoea, fewer white cells or red cells in your blood, infection and vomiting. Your doctor will do regular blood tests to check for any changes in:

- the number of your blood cells or signs of infections.

Fighting infections

CellCept reduces your body's defences. This is to stop you rejecting your transplant. As a result, your body will not be as good as normal at fighting infections. This means you may catch more infections than usual. This includes infections of the brain, skin, mouth, stomach and gut, lungs and urinary system.

Lymph and skin cancer

As can happen in patients having this type of medicine (immune-suppressants), a very small number of patients on CellCept have developed cancer of the lymphoid tissues and skin.

General unwanted effects

You may get general side effects affecting your body as a whole. These include serious allergic reactions (such as anaphylaxis, angioedema), fever, feeling very tired, difficulty sleeping, pains (such as stomach, chest, joint or muscle), headache, flu symptoms and swelling.

Other unwanted effects may include:

Skin problems such as:

- acne, cold sores, skin growth, shingles, hair loss, rash, itching.

Urinary problems such as:

- blood in the urine.

Digestive system and mouth problems such as:

- swelling of the gums and mouth ulcers,
- inflammation of the pancreas, colon or stomach,
- gastrointestinal disorders including bleeding,
- liver disorders,
- diarrhoea, constipation, feeling sick (nausea), indigestion, loss of appetite, flatulence.

Nervous system problems such as:

- feeling drowsy or numb,
- tremor, muscle spasms convulsions,
- feeling anxious or depressed, changes in your mood or thoughts.

Heart and blood vessel problems such as:

- change in blood pressure, blood clots, accelerated heartbeat
- pain, redness and swelling of the blood vessels where you had the infusion.

Lung problems such as:

- pneumonia, bronchitis,

- shortness of breath, cough, which can be due to bronchiectasis (a condition in which the lung airways are abnormally dilated) or pulmonary fibrosis (scarring of the lung). Talk to your doctor if you develop a persistent cough or breathlessness
- fluid on the lungs or inside the chest,
- sinus problems.

Other problems such as:

- weight loss, gout, high blood sugar, bleeding, bruising.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store CellCept

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP.
- Powder for concentrate for solution for infusion: do not store above 30 °C.
- Reconstituted solution and the diluted solution: store between 15 °C and 30 °C.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines no longer required. These measures will help protect the environment.

6. Contents of the pack and other information

What CellCept contains

- The active substance is mycophenolate mofetil.

Each vial contains 500 mg mycophenolate mofetil

- The other ingredients are: polysorbate 80, citric acid, hydrochloric acid, sodium chloride (see section 2 “CellCept contains sodium”).

What CellCept looks like and contents of the pack

- CellCept is provided as white to off-white powder in a 20 ml type I clear glass vial with a grey butyl rubber stopper and aluminium seal with a plastic flip-off cap.
- The reconstituted solution is slightly yellow.
- It is available in packs of 4 vials.

7. Making up the medicine

Method and route of administration

CellCept 500 mg powder for concentrate for solution for infusion does not contain an antibacterial preservative; therefore, reconstitution and dilution of the product must be performed under aseptic conditions.

The contents of CellCept 500 mg powder for concentrate for solution for infusion vials must be reconstituted with 14 ml of glucose intravenous infusion 5% each. A further dilution with glucose intravenous infusion 5% is required to a final concentration of 6 mg/ml. This means that to prepare a 1 g dose of mycophenolate mofetil the content of 2 reconstituted vials (approx. 2 x 15 ml) must be further diluted into 140 ml glucose intravenous infusion 5% solution. If the infusion solution is not prepared immediately prior to administration, the commencement of administration of the infusion solution should be within 3 hours from reconstitution and dilution of the medicinal product.

Take care not to let the made-up medicine get into your eyes.

- If this happens, rinse your eyes with plain water.

Take care not to let the made-up medicine get on your skin.

- If this happens, wash the area thoroughly with soap and water.

CellCept 500 mg powder for concentrate for solution for infusion must be given as an intravenous infusion. The infusion flow rate should be controlled to equate to a 2-hour period of administration.

CellCept intravenous solution should never be administered by rapid or bolus intravenous injection.

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This leaflet was last revised in**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency website:

<http://www.ema.europa.eu>

Package leaflet: Information for the patient

CellCept 1 g/5 ml powder for oral suspension mycophenolate mofetil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What CellCept is and what it is used for
2. What you need to know before you take CellCept
3. How to take CellCept
4. Possible side effects
5. How to store CellCept
6. Contents of the pack and other information
7. Making-up the medicine

1. What CellCept is and what it is used for

CellCept contains mycophenolate mofetil:

- This belongs to a group of medicines called “immuno-suppressants”.

CellCept is used to prevent the body rejecting a transplanted organ in adults and children:

- A kidney, heart or liver.

CellCept should be used together with other medicines:

- Ciclosporin and corticosteroids.

2. What you need to know before you take CellCept

WARNING

Mycophenolate causes birth defects and miscarriage. If you are a woman who could become pregnant, you must provide a negative pregnancy test before starting treatment and must follow the contraception advice given to you by your doctor.

Your doctor will speak to you and give you written information, particularly on the effects of mycophenolate on unborn babies. Read the information carefully and follow the instructions.

If you do not fully understand these instructions, please ask your doctor to explain them again before you take mycophenolate. See also further information in this section under “Warnings and precautions” and “Pregnancy and breast-feeding”.

Do not take CellCept:

- If you are allergic to mycophenolate mofetil, mycophenolic acid or any of the other ingredients in this medicine (listed in section 6).
- If you are a woman who could be pregnant and you have not provided a negative pregnancy test before your first prescription, as mycophenolate causes birth defects and miscarriage.
- If you are pregnant or planning to become pregnant or think you may be pregnant
- If you are not using effective contraception (see Contraception, pregnancy, and breast-feeding).

- If you are breast-feeding.

Do not take this medicine if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking CellCept.

Warnings and precautions

Talk to your doctor straight away before starting treatment with CellCept:

- If you are older than 65 years as you may have an increased risk of developing adverse events such as certain viral infections, gastrointestinal bleeding and pulmonary oedema when compared to younger patients
- If you have a sign of infection such as a fever or sore throat
- If you have any unexpected bruising or bleeding
- If you have ever had a problem with your digestive system such as a stomach ulcer
- If you have a rare problem with your metabolism called “phenylketonuria” which runs in families
- If you are planning to become pregnant or if you get pregnant while you or your partner are taking CellCept.
- If you have a hereditary enzyme deficiency such as Lesch-Nyhan and Kelley-Seegmiller syndrome

If any of the above apply to you (or you are not sure), talk to your doctor straight away before starting treatment with CellCept.

The effect of sunlight

CellCept reduces your body’s defences. As a result, there is an increased risk of skin cancer. Limit the amount of sunlight and UV light you get. Do this by:

- wearing protective clothing that covers your head, neck, arms and legs
- using a sunscreen with a high protection factor.

Children

Children, especially those under 6 years old, may be more likely than adults to have some side effects, including diarrhoea, vomiting, infections, fewer red cells and fewer white cells in the blood, and possibly lymph or skin cancer.

Do not give this medicine to children younger than 1 year because based on the limited safety and efficacy data for this age group no dose recommendations can be made.

If you are not sure about anything for your child’s treatment, talk to your doctor or pharmacist before use.

Other medicines and CellCept:

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, such as herbal medicines. This is because CellCept can affect the way some other medicines work. Also, other medicines can affect the way CellCept works.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines before you start CellCept:

- azathioprine or other medicines that suppress your immune system - given after a transplant operation
- cholestyramine - used to treat high cholesterol
- rifampicin - an antibiotic used to prevent and treat infections such as tuberculosis (TB)
- antacids or proton pump inhibitors - used for acid problems in your stomach such as indigestion
- phosphate binders - used by people with chronic kidney failure to reduce how much phosphate gets absorbed into their blood.
- antibiotics – used to treat bacterial infections
- isavuconazole – used to treat fungal infections
- telmisartan – used to treat high blood pressure

Vaccines

If you need to have a vaccination (a live vaccine) while taking CellCept, talk to your doctor or pharmacist first. Your doctor will have to advise you on which vaccines you can have.

You must not donate blood during treatment with CellCept and for at least 6 weeks after stopping treatment. Men must not donate semen during treatment with CellCept and for at least 90 days after stopping treatment.

CellCept with food and drink

Taking food and drink has no effect on your treatment with CellCept.

Contraception in women taking CellCept

If you are a woman who could become pregnant, you must use an effective method of contraception with CellCept. This includes:

- Before you start taking CellCept
- During your entire treatment with CellCept
- For 6 weeks after you stop taking CellCept.

Talk to your doctor about the most suitable contraception for you. This will depend on your individual situation. Two forms of contraception are preferable as this will reduce the risk of unintended pregnancy. **Contact your doctor as soon as possible, if you think your contraception may not have been effective or if you have forgotten to take your contraceptive pill.**

You cannot become pregnant if any of the following conditions applies to you:

- You are post-menopausal, i.e. at least 50 years old and your last period was more than a year ago (if your periods have stopped because you have had treatment for cancer, then there is still a chance you could become pregnant)
- Your fallopian tubes and both ovaries have been removed by surgery (bilateral salpingo-oophorectomy)
- Your womb (uterus) has been removed by surgery (hysterectomy)
- Your ovaries no longer work (premature ovarian failure, which has been confirmed by a specialist gynaecologist)
- You were born with one of the following rare conditions that make pregnancy impossible: the XY genotype, Turner's syndrome or uterine agenesis
- You are a child or teenager who has not started having periods.

Contraception in men taking CellCept

The available evidence does not indicate an increased risk of malformations or miscarriage if the father takes mycophenolate. However, a risk cannot be completely excluded. As a precaution, you or your female partner are recommended to use reliable contraception during treatment and for 90 days after you stop taking CellCept.

If you are planning to have a child, talk to your doctor about the potential risks and alternative therapies.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will talk to you about the risks in case of pregnancy and the alternatives you can take to prevent rejection of your transplant organ if:

- You plan to become pregnant.
- You miss or think you have missed a period, or you have unusual menstrual bleeding, or suspect you are pregnant.
- You have sex without using effective methods of contraception.

If you do become pregnant during the treatment with mycophenolate, you must inform your doctor immediately. However, keep taking CellCept until you see him or her.

Pregnancy

Mycophenolate causes a very high frequency of miscarriage (50%) and of severe birth defects (23 - 27 %) in the unborn baby. Birth defects which have been reported include anomalies of ears, of eyes, of face (cleft lip/palate), of development of fingers, of heart, oesophagus (tube that connects the throat with the stomach), kidneys and nervous system (for example spina bifida (where the bones of the spine are not properly developed)). Your baby may be affected by one or more of these.

If you are a woman who could become pregnant, you must provide a negative pregnancy test before starting treatment and must follow the contraception advice given to you by your doctor. Your doctor may request more than one test to ensure you are not pregnant before starting treatment.

Breast-feeding

Do not take CellCept if you are breast-feeding. This is because small amounts of the medicine can pass into the mother's milk.

Driving and using machines

CellCept has a moderate influence on your ability to drive or use any tools or machines. If you feel drowsy, numb or confused, talk to your doctor or nurse and do not drive or use any tools or machines until you feel better.

Important information about some of the ingredients of CellCept

- CellCept contains aspartame. If you have a rare problem with your metabolism called "phenylketonuria", talk to your doctor before you start taking this medicine.
- CellCept contains sorbitol (a type of sugar). If you have been told by your doctor that you cannot tolerate or digest some sugars, talk to your doctor before taking this medicine.

CellCept contains methyl parahydroxybenzoate

This medicinal product contains methyl parahydroxybenzoate (E218) which may cause allergic reactions (possibly delayed).

CellCept contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to take CellCept

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take

The amount you take depends on the type of transplant you have had. The usual doses are shown below. Treatment will continue for as long as you need to prevent rejection of your transplant organ.

Kidney transplant

Adults

- The first dose is given within 3 days of the transplant operation.
- The daily dose is 10 ml suspension (2 g of the medicine) taken as 2 separate doses.
- Take 5 ml suspension in the morning and then 5 ml suspension in the evening.

Children (aged 1 to 18 years)

- The dose given will vary depending on the size of the child.
- Your doctor will decide the most appropriate dose based on your child's height and weight (body surface area – measured as square metres or "m²"). The recommended initial dose is 600 mg/m² taken twice a day. The recommended maintenance dose remains at 600 mg/m² twice a day (maximum total daily dose of 2 g or 10 ml of the oral suspension). The dose should be individualised based on the doctor's clinical assessment.

Heart transplant

Adults

- The first dose is given within 5 days of the transplant operation.
- The daily dose is 15 ml suspension (3 g of the medicine) taken as 2 separate doses.
- Take 7.5 ml suspension in the morning and then 7.5 ml suspension in the evening.

Children (aged 1 to 18 years)

- The dose given will vary depending on the size of the child.
- Your child's doctor will decide the most appropriate dose based on your child's height and weight (body surface area – measured as square metres or “m²”). The recommended initial dose is 600 mg/m² taken twice a day. The dose should be individualised based on the doctor's clinical assessment. If well tolerated, the dose can be increased to 900 mg/m² twice daily if required (maximum total daily dose of 3 g, or 15 ml of the oral suspension).

Liver transplant

Adults

- The first dose of oral CellCept will be given to you at least 4 days after the transplant operation and when you are able to swallow oral medications.
- The daily dose is 15 ml suspension (3 g of the medicine) taken as 2 separate doses.
- Take 7.5 ml suspension in the morning and then 7.5 ml suspension in the evening.

Children (aged 1 to 18 years)

- The dose given will vary depending on the size of the child.
- Your child's doctor will decide the most appropriate dose based on your child's height and weight (body surface area – measured as square metres or “m²”). The recommended initial dose is 600 mg/m² taken twice a day. The dose should be individualised based on the doctor's clinical assessment. If well tolerated, the dose can be increased to 900 mg/m² twice daily if required (maximum total daily dose of 3 g, or 15 ml of the oral suspension).

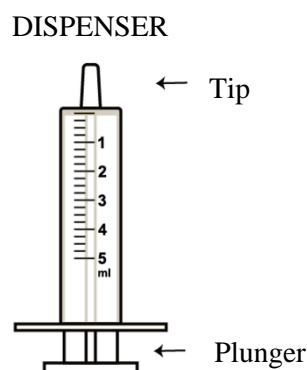
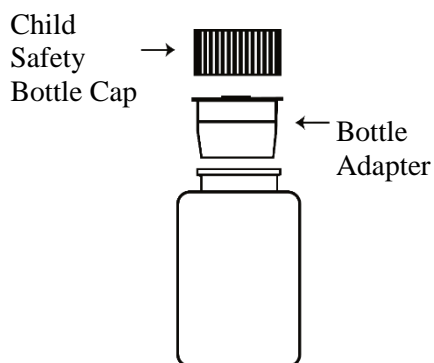
Making up the medicine

The medicine comes as a powder. This needs mixing with purified water before using. Your pharmacist will normally make up the medicine for you. If you need to do it yourself, see section 7 “Making up the medicine”

Taking the medicine

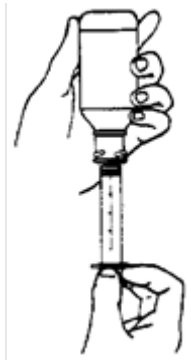
You need to use the dispenser and bottle adapter supplied with the medicine to measure the dose. Try not to inhale the dry powder. Also, try not to get it on your skin, inside your mouth or nose. Take care not to let the made-up medicine get into your eyes.

- If this happens, rinse your eyes with plain water. Take care not to let the made-up medicine get onto your skin.
- If this happens, wash the area thoroughly with soap and water.



1. Shake the closed bottle well for about 5 seconds before each use.
2. Take off the child safety bottle cap.
3. Take the dispenser and push the plunger completely down toward the tip of the dispenser.

4. Then put the tip of the dispenser firmly into the opening of the bottle adapter.
5. Turn the whole thing upside down (bottle and dispenser – see picture below).



6. Pull the plunger out slowly.
Keep pulling it out until the desired amount of medicine is in the dispenser.
7. Turn the whole thing back round the right way.
Holding onto the body of the dispenser, carefully pull the dispenser out of the bottle adapter.
The bottle adapter should stay in the bottle.
Put the end of the dispenser directly into your mouth and swallow the medicine.
8. Immediately after use – take the dispenser to pieces and rinse it under running tap water. Allow it to dry in the air before using it again.

Do not boil the oral dispenser. **Do not** use solvent-containing wipes for cleaning. **Do not** use cloths or wipes for drying.

Contact your doctor, pharmacist or nurse if both dispensers are lost or damaged, and they will advise you on how to continue to take your medication.

If you take more CellCept than you should

If you take more CellCept than you should, talk to a doctor or go to a hospital straight away. Also do this if someone else accidentally takes your medicine. Take the medicine pack with you.

If you forget to take CellCept

If you forget to take your medicine at any time, take it as soon as you remember. Then continue to take it at the usual times. Do not take a double dose to make up for a missed dose.

If you stop taking CellCept

Do not stop taking CellCept unless your doctor tells you to. If you stop your treatment you may increase the chance of rejection of your transplant organ.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, CellCept can cause side effects, although not everybody gets them.

Talk to a doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

- you have a sign of infection such as a fever or sore throat
- you have any unexpected bruising or bleeding
- you have a rash, swelling of your face, lips, tongue or throat, with difficulty breathing – you may be having a serious allergic reaction to the medicine (such as anaphylaxis, angioedema).

Usual problems

Some of the more usual problems are diarrhoea, fewer white cells or red cells in your blood, infection and vomiting. Your doctor will do regular blood tests to check for any changes in:

- the number of your blood cells or signs of infections.

Fighting infections

CellCept reduces your body's defences. This is to stop you rejecting your transplant. As a result, your body will not be as good as normal at fighting infections. This means you may catch more infections than usual. This includes infections of the brain, skin, mouth, stomach and gut, lungs and urinary system.

Lymph and skin cancer

As can happen in patients taking this type of medicine (immune-suppressants), a very small number of patients on CellCept have developed cancer of the lymphoid tissues and skin.

General unwanted effects

You may get general side effects affecting your body as a whole. These include serious allergic reactions (such as anaphylaxis, angioedema), fever, feeling very tired, difficulty sleeping, pains (such as stomach, chest, joint or muscle), headache, flu symptoms and swelling.

Other unwanted effects may include:

Skin problems such as:

- acne, cold sores, shingles, skin growth, hair loss, rash, itching.

Urinary problems such as:

- blood in the urine.

Digestive system and mouth problems such as:

- swelling of the gums and mouth ulcers,
- inflammation of the pancreas, colon or stomach,
- gastrointestinal disorders including bleeding,
- liver disorders,
- diarrhoea, constipation, feeling sick (nausea), indigestion, loss of appetite, flatulence.

Nervous system problems such as:

- feeling dizzy, drowsy or numb,
- tremor, muscle spasms, convulsions,
- feeling anxious or depressed, changes in your mood or thoughts.

Heart and blood vessel problems such as:

- change in blood pressure, accelerated heartbeat, widening of blood vessels.

Lung problems such as:

- pneumonia, bronchitis,
- shortness of breath, cough, which can be due to bronchiectasis (a condition in which the lung airways are abnormally dilated) or pulmonary fibrosis (scarring of the lung). Talk to your doctor if you develop a persistent cough or breathlessness
- fluid on the lungs or inside the chest,
- sinus problems.

Other problems such as:

- weight loss, gout, high blood sugar, bleeding, bruising.

Additional side effects in children and adolescents

Children, especially those under 6 years old, may be more likely than adults to have some side effects, including diarrhoea, vomiting, infections, fewer red cells and fewer white cells in the blood, and possibly lymph or skin cancer.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store CellCept

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and bottle label after EXP.
- The shelf-life of the reconstituted suspension is two months. Do not use the suspension past this expiry date.
- Powder for oral suspension: do not store above 30 °C.
- Reconstituted suspension: do not store above 30 °C.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines no longer required. These measures will help protect the environment.

6. Contents of the pack and other information

What CellCept contains

- The active substance is mycophenolate mofetil.
Each bottle contains 35 g mycophenolate mofetil.
- The other ingredients are sorbitol, colloidal anhydrous silica, sodium citrate, soybean lecithin, mixed fruit flavour, xanthan gum, aspartame* (E951), methyl parahydroxybenzoate (E218), citric acid anhydrous. Please also read in section 2 “Important information about some of the ingredients of CellCept” and “CellCept contains sodium”.
* contains phenylalanine equivalent to 2.78 mg/5 ml of suspension.

What CellCept looks like and contents of the pack

- Each bottle of 110 g powder for oral suspension contains 35 g of mycophenolate mofetil. Reconstitute with 94 ml of purified water. When reconstituted, the volume of the suspension is 175 ml, providing a usable volume of 160 – 165 ml. 5 ml of the reconstituted suspension contain 1 g of mycophenolate mofetil.
- A bottle adapter and 2 oral dispensers are also provided.

7. Making up the medicine

Your pharmacist will normally make up the medicine for you. If you need to do it yourself, follow the steps below:

Try not to inhale the dry powder. Also try not to get it on your skin, inside your mouth or nose.

Take care not to let the made-up medicine get into your eyes.

- If this happens, rinse your eyes with plain water.

Take care not to let the made-up medicine get on your skin.

- If this happens, wash the area thoroughly with soap and water.

1. Tap the bottom of the closed bottle several times to loosen the powder.
2. Measure 94 ml of purified water in a measuring cylinder.
3. Add about half of the total amount of purified water to the bottle.
- Then shake the closed bottle well for about 1 minute.

4. Add the rest of the water.
 - Then shake the closed bottle well for about another minute.
5. Take off the child safety bottle cap and push the bottle adapter into the neck of the bottle.
6. Then, tightly close the bottle with the child safety bottle cap.
 - This will make sure that the bottle adapter and child safety bottle cap are in the right position.
7. Write the expiry date of the made-up medicine on the bottle label.
 - The made-up medicine can be used for 2 months.

Marketing Authorisation Holder

Roche Registration GmbH
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Germany

Manufacturer

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This leaflet was last revised in**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>

Package leaflet: Information for the patient

CellCept 500 mg film-coated tablets mycophenolate mofetil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What in this leaflet:

1. What CellCept is and what it is used for
2. What you need to know before you take CellCept
3. How to take CellCept
4. Possible side effects
5. How to store CellCept
6. Contents of the pack and other information

1. What CellCept is and what it is used for

CellCept contains mycophenolate mofetil:

- This belongs to a group of medicines called “immunosuppressants”.

CellCept is used to prevent the body rejecting a transplanted organ in adults and children:

- A kidney, heart or liver.

CellCept should be used together with other medicines:

- Ciclosporin and corticosteroids.

2. What you need to know before you take CellCept

WARNING

Mycophenolate causes birth defects and miscarriage. If you are a woman who could become pregnant, you must provide a negative pregnancy test before starting treatment and must follow the contraception advice given to you by your doctor.

Your doctor will speak to you and give you written information, particularly on the effects of mycophenolate on unborn babies. Read the information carefully and follow the instructions.

If you do not fully understand these instructions, please ask your doctor to explain them again before you take mycophenolate. See also further information in this section under “Warnings and precautions” and “Pregnancy and breast-feeding”.

Do not take CellCept:

- If you are allergic to mycophenolate mofetil, mycophenolic acid or any of the other ingredients in this medicine (listed in section 6)
- If you are a woman who could be pregnant and you have not provided a negative pregnancy test before your first prescription, as mycophenolate causes birth defects and miscarriage.
- If you are pregnant or planning to become pregnant or think you may be pregnant
- If you are not using effective contraception (see Contraception, pregnancy and breast-feeding).
- If you are breast-feeding.

Do not take this medicine if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking CellCept.

Warnings and precautions

Talk to your doctor straight away before starting treatment with CellCept:

- If you are older than 65 years as you may have an increased risk of developing adverse events such as certain viral infections, gastrointestinal bleeding and pulmonary oedema when compared to younger patients
- If you have a sign of infection such as a fever or sore throat
- If you have any unexpected bruising or bleeding
- If you have ever had a problem with your digestive system such as a stomach ulcer
- If you are planning to become pregnant or if you get pregnant while you or partner are taking CellCept.
- If you have a hereditary enzyme deficiency such as Lesch-Nyhan and Kelley-Seegmiller syndrome

If any of the above apply to you (or you are not sure), talk to your doctor straight away before starting treatment with CellCept.

The effect of sunlight

CellCept reduces your body's defences. As a result, there is an increased risk of skin cancer. Limit the amount of sunlight and UV light you get. Do this by:

- wearing protective clothing that also covers your head, neck, arms and legs
- using a sunscreen with a high protection factor.

Children

Children, especially those under 6 years old, may be more likely than adults to have some side effects, including diarrhoea, vomiting, infections, fewer red cells and fewer white cells in the blood, and possibly lymph or skin cancer.

Tablets are only appropriate for children who are capable of swallowing solid medication without the risk of choking. The medicine should therefore only be given in line with the doctor's prescription.

If you are not sure about anything for your child's treatment, talk to your doctor or pharmacist before use.

Other medicines and CellCept

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, such as herbal medicines. This is because CellCept can affect the way some other medicines work. Also other medicines can affect the way CellCept works.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines before you start CellCept:

- azathioprine or other medicines that suppress your immune system – given after a transplant operation
- cholestyramine – used to treat high cholesterol
- rifampicin – an antibiotic used to prevent and treat infections such as tuberculosis (TB)
- antacids or proton pump inhibitors – used for acid problems in your stomach such as indigestion
- phosphate binders – used by people with chronic kidney failure to reduce how much phosphate gets absorbed into their blood.
- antibiotics – used to treat bacterial infections
- isavuconazole – used to treat fungal infections
- telmisartan – used to treat high blood pressure

Vaccines

If you need to have a vaccination (a live vaccine) while taking CellCept, talk to your doctor or pharmacist first. Your doctor will have to advise you on what vaccines you can have.

You must not donate blood during treatment with CellCept and for at least 6 weeks after stopping treatment. Men must not donate semen during treatment with CellCept and for at least 90 days after stopping treatment.

CellCept with food and drink

Taking food and drink has no effect on your treatment with CellCept.

Contraception in women taking CellCept

If you are a woman who could become pregnant, you must use an effective method of contraception with CellCept. This includes:

- Before you start taking CellCept
- During your entire treatment with CellCept
- For 6 weeks after you stop taking CellCept.

Talk to your doctor about the most suitable contraception for you. This will depend on your individual situation. Two forms of contraception are preferable as this will reduce the risk of unintended pregnancy. **Contact your doctor as soon as possible, if you think your contraception may not have been effective or if you have forgotten to take your contraceptive pill.**

You cannot become pregnant if any of the following conditions applies to you:

- You are post-menopausal, i.e. at least 50 years old and your last period was more than a year ago (if your periods have stopped because you have had treatment for cancer, then there is still a chance you could become pregnant)
- Your fallopian tubes and both ovaries have been removed by surgery (bilateral salpingo-oophorectomy)
- Your womb (uterus) has been removed by surgery (hysterectomy)
- Your ovaries no longer work (premature ovarian failure, which has been confirmed by a specialist gynaecologist)
- You were born with one of the following rare conditions that make pregnancy impossible: the XY genotype, Turner's syndrome or uterine agenesis
- You are a child or teenager who has not started having periods.

Contraception in men taking CellCept

The available evidence does not indicate an increased risk of malformations or miscarriage if the father takes mycophenolate. However, a risk cannot be completely excluded. As a precaution you or your female partner are recommended to use reliable contraception during treatment and for 90 days after you stop taking CellCept.

If you are planning to have a child, talk to your doctor about the potential risks and alternative therapies.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will talk to you about the risks in case of pregnancy and the alternatives you can take to prevent rejection of your transplant organ if:

- You plan to become pregnant.
- You miss or think you have missed a period, or you have unusual menstrual bleeding, or suspect you are pregnant.
- You have sex without using effective methods of contraception.

If you do become pregnant during the treatment with mycophenolate, you must inform your doctor immediately. However, keep taking CellCept until you see him or her.

Pregnancy

Mycophenolate causes a very high frequency of miscarriage (50%) and of severe birth defects (23 - 27 %) in the unborn baby. Birth defects which have been reported include anomalies of ears, of eyes, of face (cleft lip/palate), of development of fingers, of heart, oesophagus (tube that connects the throat

with the stomach), kidneys and nervous system (for example spina bifida (where the bones of the spine are not properly developed)). Your baby may be affected by one or more of these.

If you are a woman who could become pregnant, you must provide a negative pregnancy test before starting treatment and must follow the contraception advice given to you by your doctor. Your doctor may request more than one test to ensure you are not pregnant before starting treatment.

Breast-feeding

Do not take CellCept if you are breast-feeding. This is because small amounts of the medicine can pass into the mother's milk.

Driving and using machines

CellCept has a moderate influence on your ability to drive or use any tools or machines. If you feel drowsy, numb or confused, talk to your doctor or nurse and do not drive or use any tools or machines until you feel better.

CellCept contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take CellCept

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take

The amount you take depends on the type of transplant you have had. The usual doses are shown below. Treatment will continue for as long as you need to prevent rejection of your transplant organ.

Kidney transplant

Adults

- The first dose is given within 3 days of the transplant operation.
- The daily dose is 4 tablets (2 g of the medicine) taken as 2 separate doses.
- Take 2 tablets in the morning and then 2 tablets in the evening.

Children

- Tablets are only appropriate for children who are capable of swallowing solid medication without the risk of choking. The medicine should therefore only be given in line with the doctor's prescription. If you are not sure, talk to your doctor or pharmacist before use.
- The dose given will vary depending on the size of the child.
- Your child's doctor will decide the most appropriate dose based on your child's height and weight (body surface area – measured as square metres or "m²"). The recommended initial dose is 600 mg/m² taken twice a day. The recommended maintenance dose remains at 600 mg/m² twice a day (maximum total daily dose of 2 g). The dose should be individualised based on the doctor's clinical assessment.

Heart transplant

Adults

- The first dose is given within 5 days of the transplant operation.
- The daily dose is 6 tablets (3 g of the medicine) taken as 2 separate doses.
- Take 3 tablets in the morning and then 3 tablets in the evening.

Children

- Tablets are only appropriate for children who are capable of swallowing solid medication without the risk of choking. The medicine should therefore only be given in line with the doctor's prescription. If you are not sure, talk to your doctor or pharmacist before use.
- The dose given will vary depending on the size of the child.

- Your child's doctor will decide the most appropriate dose based on your child's height and weight (body surface area – measured as square metres or “m²”). The recommended starting dose is 600 mg/m² taken twice a day. The dose should be individualised based on the doctor's clinical assessment. If well tolerated, the dose can be increased to 900 mg/m² twice daily if required (maximum total daily dose of 3 g).

Liver transplant

Adults

- The first dose of oral CellCept will be given to you at least 4 days after the transplant operation and when you are able to swallow oral medicines.
- The daily dose is 6 tablets (3 g of the medicine) taken as 2 separate doses.
- Take 3 tablets in the morning and then 3 tablets in the evening.

Children

- Tablets are only appropriate for children who are capable of swallowing solid medication without the risk of choking. The medicine should therefore only be given in line with the doctor's prescription. If you are not sure, talk to your doctor or pharmacist before use.
- The dose given will vary depending on the size of the child.
- Your child's doctor will decide the most appropriate dose based on your child's height and weight (body surface area – measured as square metres or “m²”). The recommended initial dose is 600 mg/m² taken twice a day. The dose should be individualised based on the doctor's clinical assessment. If well tolerated, the dose can be increased to 900 mg/m² twice daily if required (maximum total daily dose of 3 g).

Taking the medicine

- Swallow your tablets whole with a glass of water.
- Do not break or crush them.

If you take more CellCept than you should

If you take more CellCept than you should, talk to a doctor or go to a hospital straight away. Also do this if someone else accidentally takes your medicine. Take the medicine pack with you.

If you forget to take CellCept

If you forget to take your medicine at any time, take it as soon as you remember. Then continue to take it at the usual times. Do not take a double dose to make up for a missed dose.

If you stop taking CellCept

Do not stop taking CellCept unless your doctor tells you to. If you stop your treatment you may increase the chance of rejection of your transplanted organ.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, CellCept can cause side effects, although not everybody gets them.

Talk to a doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

- you have a sign of infection such as a fever or sore throat
- you have any unexpected bruising or bleeding
- you have a rash, swelling of your face, lips, tongue or throat, with difficulty breathing - you may be having a serious allergic reaction to the medicine (such as anaphylaxis, angioedema).

Usual problems

Some of the more usual problems are diarrhoea, fewer white cells or red cells in your blood, infection and vomiting. Your doctor will do regular blood tests to check for any changes in:

- the number of your blood cells or signs of infections.

Fighting infections

CellCept reduces your body's defences. This is to stop you rejecting your transplant. As a result, your body will not be as good as normal at fighting infections. This means you may catch more infections than usual. This includes infections of the brain, skin, mouth, stomach and gut, lungs and urinary system.

Lymph and skin cancer

As can happen in patients taking this type of medicine (immune-suppressants), a very small number of patients on CellCept have developed cancer of the lymphoid tissues and skin.

General unwanted effects

You may get general side effects affecting your body as a whole. These include serious allergic reactions (such as anaphylaxis, angioedema), fever, feeling very tired, difficulty sleeping, pains (such as stomach, chest, joint or muscle), headache, flu symptoms and swelling.

Other unwanted effects may include:

Skin problems such as:

- acne, cold sores, shingles, skin growth hair loss, rash, itching.

Urinary problems such as:

- blood in the urine.

Digestive system and mouth problems such as:

- swelling of the gums and mouth ulcers,
- inflammation of the pancreas, colon or stomach,
- gastrointestinal disorders including bleeding,
- liver disorders
- diarrhoea, constipation, feeling sick (nausea), indigestion, loss of appetite, flatulence.

Nervous system problems such as:

- feeling dizzy, drowsy or numb,
- tremor, muscle spasms, convulsions,
- feeling anxious or depressed, changes in your mood or thoughts.

Heart and blood vessel problems such as:

- change in blood pressure, accelerated heartbeat, widening of blood vessels.

Lung problems such as:

- pneumonia, bronchitis,
- shortness of breath, cough, which can be due to bronchiectasis (a condition in which the lung airways are abnormally dilated) or pulmonary fibrosis (scarring of the lung). Talk to your doctor if you develop a persistent cough or breathlessness,
- fluid on the lungs or inside the chest,
- sinus problems.

Other problems such as:

- weight loss, gout, high blood sugar, bleeding, bruising.

Additional side effects in children and adolescents

Children, especially those under 6 years old, may be more likely than adults to have some side effects, including diarrhoea, vomiting, infections, fewer red cells and fewer white cells in the blood, and possibly lymph or skin cancer.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store CellCept

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton after EXP.
- Do not store above 30 °C.
- Store in the original package in order to protect from moisture.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What CellCept film coated tablet contains

- The active substance is mycophenolate mofetil.

Each tablet contains 500 mg mycophenolate mofetil.

- The other ingredients are:
- CellCept tablets: microcrystalline cellulose, polyvidone (K-90), croscarmellose sodium, magnesium stearate (see section 2 “CellCept contains sodium”).
- Tablet coating: hydroxypropyl methycellulose, hydroxypropyl cellulose, titanium dioxide (E171), polyethylene glycol 400, indigo carmine aluminium lake (E132), red iron oxide (E172).

What CellCept looks like and contents of the pack

- CellCept tablets are lavender-coloured and caplet-shaped. They have “CellCept 500” engraved on one side and “Roche” on the other.
- They are available as packs of 50 (in blister packs of 10) or Multipacks containing 150 (3 packs of 50) tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Manufacturer

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>