ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Myfenax 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

Hard capsule (capsule)

The capsule body is caramel opaque, printed with ‘250’ axially in black ink.
The capsule cap is light blue opaque printed ‘M’ axially in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Myfenax 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/m^2 (of body surface area (BSA)), administered orally, twice daily (initial total daily dose not to exceed 2 g, or 10 ml of an oral suspension (1 g/5 ml)).

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/m^2 BSA twice daily (maximum total daily dose of 3 g, or 15 ml of an oral suspension (1 g/5 ml)). The recommended maintenance dose for paediatric renal transplant patients remains at 600 mg/m^2 twice daily (maximum total daily dose of 2 g or 10 ml of an oral suspension (1 g/5 ml)).

A mycophenolate mofetil powder for oral suspension (1 g/5 ml) should be used in those patients unable to swallow capsules and tablets and/or with a BSA lower than 1.25 m^2 due to the increased risk of choking. Patients with a BSA of 1.25 to 1.5 m^2 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 m^2 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 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; 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

Myfenax 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 Myfenax, 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 ultraviolet (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 Tlymphocytes, therefore an increased severity of COVID19 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 medicinal products, 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 < $1.3 \times 10^3/\mu l$) 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 inosine monophosphate dehydrogenase (IMPDH) 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.

Excipient

This medicinal product contains less than 1 mmol sodium (23 mg) per hard 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 three times a day (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 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 taken twice a day [BID], morning and evening) 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 must 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 show 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 breast-feeding 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 health-care 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). 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
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**
	Frequency	Frequency	Frequency
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
Vomiting	Very common	Very common	Very common

Adverse reaction (MedDRA) System Organ Class	**Renal transplant**	**Hepatic transplant**	**Cardiac transplant**
	Frequency	Frequency	Frequency
Immune system disorders			
Hypersenstivity	Uncommon	Common	Common
Hypogammaglobulinaemia	Uncommon	Very rare	Very rare
Anaphylactic reactions	Not known	Not known	Not known
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, cytomegalovirus (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 abortions 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/m^2, up to 1 g/m^2 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/m^2, up to 1 g/m^2 BID.])

Adverse reaction (MedDRA) System Organ Class	**< 6 years (n=33)**	**6-11 years (n=34)**	**12-18 years (n=33)**
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%)
Vomitting	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 mycophenolic acid (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 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 potently 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 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 $AUC_{0\text{-}12\ h}$ was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG $AUC_{0\text{-}12\ h}$ 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 $AUC_{0\text{-}12h}$ closest to the target exposure of 27.2 h·mg/l was 600 mg/m^2, 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/m^2, up to 1 g/m^2 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 ± SD AUC_{0-12} (adjusted to a dose of 600 mg/m^2) was 47.0±21.8 h·mg/l, adjusted C_{max} was 14.5±4.21 mg/l, with a median time to maximum concentration of 0.75 h. To achieve the target AUC_{0-12} of 58 h·mg/l in the late post-transplant period, a dose in the range of 740-806 mg/m^2 BID would therefore have been required in the study population.

A comparison of dose-normalised (to 600 mg/m^2) 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 ± SD	Adjusted $AUC_{0-12\,h}$·mg/l mean ± SD (CI)[A]
Day 7			
< 6 y	(17)	13.2±7.16	27.4±9.54 (22.8-31.9)
6 - < 12 y	(16)	13.1±6.30	33.2±12.1 (27.3-39.2)
12-18 y	(21)	11.7±10.7	26.3±9.14 (22.3-30.3)[D]
p-value[B]		-	-
< 2 y[C]	*(6)*	*10.3±5.80*	*22.5±6.68 (17.2-27.8)*
> 18 y	(141)		27.2±11.6
Month 3			
< 6 y	(15)	22.7±10.1	49.7±18.2
6 - < 12 y	(14)[E]	27.8±14.3	61.9±19.6
12-18 y	(17)	17.9±9.57	53.6±20.2F
p-value[B]		-	-
< 2 y[C]	*(4)*	*23.8±13.4*	*47.4±14.7*
> 18 y	(104)		50.3±23.1
Month 9			
< 6 y	(12)	30.4±9.16	60.9±10.7
6 - < 12 y	(11)	29.2±12.6	66.8±21.2
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/m^2 (95% confidence intervals (Cls) 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 luteinizing hormone (LH), follicle-stimulating hormone (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 doses. 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 nonclinical 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

Capsule content
Pregelatinised starch (maize)
Povidone K-30
Croscarmellose sodium
Magnesium stearate

Capsule shell
Cap
Indigo carmine (E132)
Titanium dioxide (E171)
Gelatin
Body
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Gelatin
Black ink containing: shellac, black iron oxide (E172), propylene glycol and potassium hydroxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Transparent PVC/PVdC-aluminium blisters

Pack sizes of 100, 300 or 100 x 1 and multipacks containing 300 (3 packs of 100) capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/438/001 (100 capsules)
EU/1/07/438/002 (300 capsules)

EU/1/07/438/006 (100 x 1 capsules)
EU/1/07/438/009 (300 (3 x 100) capsules)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 February 2008
Date of latest renewal: 19 November 2012

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Myfenax 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 tablet (tablet)

Pale purple, oval shaped film-coated tablet, debossed with "M500" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Myfenax 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/m^2 (of body surface area (BSA)), administered orally, twice daily (initial total daily dose not to exceed 2 g, or 10 ml of an oral suspension (1 g/5 ml)).

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/m^2 BSA twice daily (maximum total daily dose of 3 g, or 15 ml of an oral suspension (1 g/5 ml)). The recommended maintenance dose for paediatric renal transplant patients remains at 600 mg/m^2 twice daily (maximum total daily dose of 2 g or 10 ml of an oral suspension (1 g/5 ml)).

A mycophenolate mofetil powder for oral suspension (1 g/5 ml) should be used in those patients unable to swallow capsules and tablets and/or with a BSA lower than 1.25 m^2 due to the increased risk of choking. Patients with a BSA of 1.25 to 1.5 m^2 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 m^2 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 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; 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

Myfenax 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 Myfenax, 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 ultraviolet (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 Tlymphocytes, therefore an increased severity of COVID19 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 medicinal products, 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 < $1.3 \times 10^3/\mu l$) 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 inosine monophosphate dehydrogenase (IMPDH) 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.

Excipient

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated 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 three times a day (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 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 taken twice a day [BID], morning and evening) 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 must 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 show 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 breast-feeding 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 health-care 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). 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**
	Frequency	Frequency	Frequency
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
Headache	Very common	Very common	Very common

Adverse reaction (MedDRA) System Organ Class	**Renal transplant**	**Hepatic transplant**	**Cardiac transplant**
	Frequency	Frequency	Frequency
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
Vomiting	Very common	Very common	Very common
Immune system disorders			

Adverse reaction (MedDRA) System Organ Class	Renal transplant	Hepatic transplant	Cardiac transplant
	Frequency	Frequency	Frequency
Hypersenstivity	Uncommon	Common	Common
Hypogammaglobulinaemia	Uncommon	Very rare	Very rare
Anaphylactic reactions	Not known	Not known	Not known
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, cytomegalovirus (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 abortions 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/m^2, up to 1 g/m^2 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/m^2, up to 1 g/m^2 BID.])

Adverse reaction (MedDRA) System Organ Class	**< 6 years (n=33)**	**6-11 years (n=34)**	**12-18 years (n=33)**
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%)
Vomitting	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 mycophenolic acid (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 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 potently 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 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 $AUC_{0\text{-}12\ h}$ was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG $AUC_{0\text{-}12\ h}$ 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 $AUC_{0\text{-}12h}$ closest to the target exposure of 27.2 h·mg/l was 600 mg/m^2, 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/m^2, up to 1 g/m^2 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 ± SD $AUC_{0\text{-}12}$ (adjusted to a dose of

600 mg/m^2) was 47.0±21.8 h·mg/l, adjusted C_{max} was 14.5±4.21 mg/l, with a median time to maximum concentration of 0.75 h. To achieve the target AUC_{0-12} of 58 h·mg/l in the late post-transplant period, a dose in the range of 740-806 mg/m^2 BID would therefore have been required in the study population.

A comparison of dose-normalised (to 600 mg/m^2) 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 ± SD	Adjusted $AUC_{0-12\ h}$·mg/l mean ± SD (CI)[A]
Day 7			
< 6 y	(17)	13.2±7.16	27.4±9.54 (22.8-31.9)
6 - < 12 y	(16)	13.1±6.30	33.2±12.1 (27.3-39.2)
12-18 y	(21)	11.7±10.7	26.3±9.14 (22.3-30.3)[D]
p-valueB		-	-
< 2 y[C]	*(6)*	*10.3±5.80*	*22.5±6.68 (17.2-27.8)*
> 18 y	(141)		27.2±11.6
Month 3			
< 6 y	(15)	22.7±10.1	49.7±18.2
6 - < 12 y	(14)[E]	27.8±14.3	61.9±19.6
12-18 y	(17)	17.9±9.57	53.6±20.2F
p-value[B]		-	-
< 2 y[C]	*(4)*	*23.8±13.4*	*47.4±14.7*
> 18 y	(104)		50.3±23.1
Month 9			
< 6 y	(12)	30.4±9.16	60.9±10.7
6 - < 12 y	(11)	29.2±12.6	66.8±21.2
12-18 y	(14)	18.1±7.29	56.7±14.0
p-valueB		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/m^2 (95% confidence intervals (Cls) 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 luteinizing hormone (LH), follicle-stimulating hormone (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 doses. 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 nonclinical 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

Tablet core
Microcrystalline cellulose

Povidone K-30
Magnesium stearate
Croscarmellose sodium

Tablet coat
Hypromellose (HPMC 2910)
Titanium dioxide (E171)
Macrogol (PEG 400)
Talc
Indigo carmine aluminium lake (E132)
Iron oxide black (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Transparent PVC/PVdC-aluminium blisters

Pack sizes of 50, 100, 150, 50 x 1 or 100 x 1 and multipacks containing 150 (3 packs of 50) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/438/003 (50 tablets)
EU/1/07/438/004 (150 tablets)
EU/1/07/438/005 (50 x 1 tablets)
EU/1/07/438/007 (100 tablets)
EU/1/07/438/008 (100 x 1 tablets)
EU/1/07/438/010 (150 (3 x 50) tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 February 2008
Date of latest renewal: 19 November 2012

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) 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. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Teva Pharmaceutical Works Private Limited Company
Pallagi út 13.
Debrecen H-4042
Hungary

Teva Operations Poland Sp. Z.o.o.
Mogilska 80 Str.
31-546 Krakow
Poland

Pharmachemie B.V.
Swensweg 5
2031 GA Haarlem
The Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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)**

Not applicable

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

The MAH shall ensure that in each MS where Myfenax is marketed, all healthcare professionals and patients who are expected to prescribe, dispense or use Myfenax 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 minimize 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 to 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. Furthermore, men should not donate semen during therapy or for 90 days following discontinuation of mycophenolate.

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.

In addition, a pregnancy follow-up questionnaire including details of exposure during pregnancy, including timing and dose; duration of therapy, before and during pregnancy; concomitant drugs; known teratogenic risks and full details of congenital malformations should be agreed to with the national competent authorities.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Myfenax 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 capsules
300 capsules
100 x 1 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet 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

Myfenax capsules should be handled with care.
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

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

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/438/001 (100 capsules)
EU/1/07/438/002 (300 capsules)
EU/1/07/438/006 (100 x 1 capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Myfenax 250 mg capsules

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

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Myfenax 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) capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet 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

Myfenax capsules should be handled with care.
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

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

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/438/009 300 capsules (3 packs of 100)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Myfenax 250 mg capsules

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

Myfenax 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 capsules
Component of a multipack, not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet 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

Myfenax capsules should be handled with care.
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

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

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/438/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Myfenax 250 mg capsules

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Myfenax 250 mg hard capsules
mycophenolate mofetil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Myfenax 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
100 tablets
150 tablets
50 x 1 tablets
100 x 1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet 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

Myfenax film-coated tablets should be handled with care.
Do not crush the tablets.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/438/003 (50 tablets)
EU/1/07/438/004 (150 tablets)
EU/1/07/438/005 (50 x 1 tablets)
EU/1/07/438/007 (100 tablets)
EU/1/07/438/008 (100 x 1 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Myfenax 500 mg film-coated tablets

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

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Myfenax 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) tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet 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

Myfenax film-coated tablets should be handled with care.
Do not crush the tablets.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/438/010 150 tablets (3 packs of 50)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Myfenax 500 mg film-coated tablets

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

Myfenax 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
Component of a multipack, not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet 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

Myfenax film-coated tablets should be handled with care.
Do not crush the tablets.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/438/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Myfenax 500 mg film-coated tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Myfenax 500 mg film-coated tablets
mycophenolate mofetil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Myfenax 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What Myfenax is and what it is used for

Myfenax is a medicine that is used to suppress immune activity.

The active substance in this medicine is called mycophenolate mofetil.

Myfenax is used to prevent the body rejecting a transplanted kidney, heart or liver in adults and children. It is used in combination with other medicines with a similar function (i.e. ciclosporin and corticosteroids).

2. What you need to know before you take Myfenax

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 “Contraception, pregnancy and breast-feeding”.

Do not take Myfenax,
- 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 Myfenax.

Warnings and precautions
Talk to your doctor straight away before starting treatment with Myfenax:
- 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 experience any evidence of infection (e.g. fever, sore throat), unexpected bruising and/or bleeding.
- if you have or ever have had any problems with your digestive system, e.g. stomach ulcers.
- if you are planning to become pregnant, or if you get pregnant while you or your partner are taking Myfenax.
- if you have a hereditary enzyme deficiency such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Myfenax reduces your body's defence mechanism. Because of this, there is an increased risk of skin cancer. Therefore you should limit your exposure to sunlight and ultraviolet (UV) light by wearing appropriate protective clothing and using a sunscreen with a high protection factor.

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

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.
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 Myfenax
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

If you answer yes to any of the following questions talk to your doctor before you start to take Myfenax:
- Are you taking any medicines containing:
  - azathioprine or other immunosuppressive agents (which are sometimes given to patients after a transplant operation),
  - cholestyramine (used to treat patients with high blood cholesterol),
  - rifampicin (antibiotic),
  - antacids or proton pump inhibitors (used for acid problem in your stomach such as indigestion),
  - phosphate binders (used in patients with chronic kidney failure to reduce the absorption of phosphate),
  - antibiotics (used to treat bacterial infections),
  - isavuconazole (used to treat fungal infections),
  - telmisartan (used to treat high blood pressure)
  - or any other medicines (including those you can buy without a prescription) that your doctor does not know about?
- Do you need to have a vaccination (live vaccines)? Your doctor will have to advise you what is indicated for you.

Contraception, pregnancy and breast-feeding

Contraception in women taking Myfenax
If you are a woman who could become pregnant you must use an effective method of contraception with Myfenax. This includes:

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

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 Myfenax
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 Myfenax.

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 Myfenax 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 Myfenax if you are breast-feeding. This is because small amounts of the medicine can pass into the mother’s milk.

Driving and using machines
Myfenax 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.

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

3. How to take Myfenax

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

Your treatment is started and monitored by a doctor who is specialised in transplants.

The usual way to take Myfenax is as follows:

Kidney Transplant

Adults
The first dose will be given within 72 hours after the transplant operation. The recommended daily dose is 8 capsules (2 g of the active ingredient) taken as 2 separate doses. This means taking 4 capsules in the morning 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 "m^2"). The recommended initial dose is 600 mg/m^2 taken twice a day. The recommended maintenance dose remains at 600 mg/m^2 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 will be given within 5 days following the transplant operation. The recommended daily dose is 12 capsules (3 g of the active ingredient) taken as 2 separate doses. This means taking 6 capsules in the morning 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 "m^2"). The recommended initial dose is 600 mg/m^2 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/m^2 twice daily if required (maximum total daily dose of 3 g).

Liver Transplant

Adults

The first dose of oral Myfenax will be given to you at least 4 days after the transplant operation and when you are able to swallow oral medicines. The recommended daily dose is 12 capsules (3 g of the active ingredient) taken as 2 separate doses. This means taking 6 capsules in the morning 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 "m^2"). The recommended initial dose is 600 mg/m^2 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/m^2 twice daily if required (maximum total daily dose of 3 g).

Method and route of administration
Swallow your capsules whole with a glass of water. You can take them with or without food. Do not break or crush them and do not take any capsules that have broken open or split. Avoid contact with any powder that spills out from damaged capsules. If a capsule breaks open accidentally, wash any powder from your skin with soap and water. If any powder gets into your eyes or mouth, rinse thoroughly with plenty of plain, fresh water.

Treatment will continue for you as long as you need immunosuppression to prevent rejection of your transplanted organ.

If you take more Myfenax than you should
It is important not to take too many capsules. Contact your nearest hospital Accident and Emergency department or a doctor for advice if you have swallowed more capsules than you have been told to take or if you think a child has swallowed any.

If you forget to take Myfenax
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 forgotten dose.

If you stop taking Myfenax
Do not stop taking Myfenax because you feel better. It is important to take the medicine for as long as the doctor has told you to. Stopping your treatment with Myfenax may increase the chance of rejection of your transplanted organ. Do not stop taking your medicine unless your doctor tells you to.

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

4. Possible side effects

Like all medicines, this medicine 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.
- rash, itching, hives, breathlessness or difficult breathing, wheezing or coughing, lightheadedness, dizziness, changes in levels of consciousness, hypotension, with or without mild generalized itching, skin reddening and facial/throat swelling (symptoms of severe allergic reaction).
- you have black or bloody stool or if you vomit blood or dark particles that look like coffee grounds. These may be signs of bleeding in the stomach or intestines.

The frequency of certain side effects is dependent on the transplanted organ, i.e. some side effects can occur more or less often depending on whether this medicinal product is being taken to prevent your body from rejecting a transplanted heart or a transplanted kidney. For the sake of clarity each side effect is always listed under its highest frequency.

Other side effects

Very common (may affect more than 1 in 10 people)
- bacterial, viral and/or fungal infections
- serious infection which may affect the whole body
- decrease in the number of white blood cells, platelets or red blood cells, which can result in increased risk of infections, bruising, bleeding, breathlessness and weakness
- bleeding underneath the skin
- increase in the number of white blood cells
- too much acid in the body
- high level of cholesterol and/or lipids in the blood
- high level of sugar in the blood
- high level of potassium in the blood, low level of potassium, magnesium, calcium and/or phosphate in the blood
- high level of uric acid in the blood, gout
- feeling restless, abnormalities of thought, perception and levels of awareness, depression, feeling anxious, difficulty in sleeping
- increased tension of the muscles, shaking, sleepiness, feeling dizzy, headache, tingling, pricking or numbness
- faster heart beat
- low/high blood pressure, widening of blood vessels
- accumulation of fluid in the lung, shortness of breath, cough
- bloated belly
- vomiting, stomach pain, diarrhoea, feeling sick
- constipation, indigestion, wind (flatulence)
- decreased appetite
- changes in different laboratory parameters
- inflammation of the liver, yellowing of the skin and whites of the eyes
- growth of the skin, rash, acne
- muscle weakness
- joint pain
- kidney problems
- blood in the urine
- fever, feeling of coldness, pain, feeling weak and feeble
- fluid retention in the body
- part of an internal organ or tissue bulging through a weak spot in the abdominal muscles
- muscle pain, neck and back pain

Common (may affect up to 1 in 10 people)
- skin cancer, non-cancerous growth of the skin
- abnormal and excessive growth of tissue
- decrease in the number of all blood cells
- benign enlargement of the lymph nodes, inflammatory changes of the skin (pseudolymphoma)
- decreased weight
- abnormal thinking
- fit
- distortion of the sense of taste
- blood clot that forms within a vein

- inflammation of the tissue that lines the inner wall of the abdomen and covers most of the abdominal organs
- bowel blockage
- inflammation of the colon which causes abdominal pain or diarrhoea (sometimes caused by cytomegalovirus), ulcer of the mouth and/or stomach and/or duodenum, inflammation of the stomach, oesophagus and/or mouth and lips
- belching
- hair loss
- feeling unwell
- overgrowth of the gum tissue
- inflammation of the pancreas, which causes severe pain in the abdomen and back

Uncommon (may affect up to 1 in 100 people)
- protozoal infections
- proliferation of the lymphatic tissue, including malignant tumours
- insufficient production of red blood cells
- serious diseases of the bone marrow
- accumulation of lymphatic fluid within the body
- 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.
- decrease in the amount of antibodies in the blood
- severe reduction in the number of certain white blood cells (possible symptoms are fever, sore throat, frequent infections) (agranulocytosis)

Not known (frequency cannot be estimated from the available data)
- alterations of the inner wall of the small intestine (intestinal villous atrophy)
- serious inflammation of the membrane that covers the brain and spinal cord
- serious inflammation of the heart and its valves
- bacterial infections usually resulting in a serious lung disorder (tuberculosis, atypical mycobacterial infection)
- serious disease of the kidney (BK virus associated nephropathy)
- serious disease of the central nervous system (JC virus associated progressive multifocal leucoencephalopathy)
- decrease in the number of certain white blood cells (neutropenia)
- change of the shape of certain white blood cells

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.

Do not stop taking your medicine unless you have discussed this with your doctor first.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist 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 Myfenax

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 blister and carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

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 to protect the environment.

6. Contents of the pack and other information

What Myfenax contains

- The active substance is mycophenolate mofetil.
  Each capsule contains 250 mg mycophenolate mofetil.
- The other ingredients are:
  Capsule content
  Pregelatinised maize starch
  Povidone K-30
  Croscarmellose sodium
  Magnesium stearate
  Capsule shells
  Cap
  Indigo carmine (E132)
  Titanium dioxide (E171)
  Gelatin
  Body
  Red iron oxide (E172)
  Yellow iron oxide (E172)
  Titanium dioxide (E171)
  Gelatin
  Black ink containing: shellac, black iron oxide (E172), propylene glycol and potassium hydroxide

What Myfenax looks like and contents of the pack

Hard capsules
Body: caramel opaque, printed ‘250’ axially in black ink.
Cap: light blue opaque printed ‘M’ axially in black ink.

Myfenax 250 mg hard capsules are available in PVC/PVdC-aluminium blisters in pack sizes of 100, 300 or 100 x 1 capsules and in multipacks containing 300 (3 packs of 100) capsules.

Not all pack sizes may be marketed.

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This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the website of the European Medicines Agency https://www.ema.europa.eu.

Package leaflet: Information for the patient

Myfenax 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What Myfenax is and what it is used for

Myfenax is a medicine that is used to suppress immune activity.

The active substance in this medicine is called mycophenolate mofetil.

Myfenax is used to prevent the body rejecting a transplanted kidney, heart or liver in adults and children. It is used in combination with other medicines with a similar function (i.e. ciclosporin and corticosteroids).

2. What you need to know before you take Myfenax

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 “Contraception, pregnancy and breast-feeding”.

Do not take Myfenax,
- 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 Myfenax.

Warnings and precautions
Talk to your doctor straight away before starting treatment with Myfenax:
- 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 experience any evidence of infection (e.g. fever, sore throat), unexpected bruising and/or bleeding.
- if you have or ever have had any problems with your digestive system, e.g. stomach ulcers.
- if you are planning to become pregnant, or if you get pregnant while you or your partner are taking Myfenax.
- if you have a hereditary enzyme deficiency such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Myfenax reduces your body's defence mechanism. Because of this, there is an increased risk of skin cancer. Therefore you should limit your exposure to sunlight and ultraviolet (UV) light by wearing appropriate protective clothing and using a sunscreen with a high protection factor.

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

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.
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 Myfenax
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

If you answer yes to any of the following questions talk to your doctor before you start to take Myfenax:
- Are you taking any medicines containing:
  - azathioprine or other immunosuppressive agents (which are sometimes given to patients after a transplant operation),
  - cholestyramine (used to treat patients with high blood cholesterol),
  - rifampicin (antibiotic),
  - antacids or proton pump inhibitors (used for acid problem in your stomach such as indigestion),
  - phosphate binders (used in patients with chronic kidney failure to reduce the absorption of phosphate),
  - antibiotics (used to treat bacterial infections),
  - isavuconazole (used to treat fungal infections),
  - telmisartan (used to treat high blood pressure)
  - or any other medicines (including those you can buy without a prescription) that your doctor does not know about?
- Do you need to have a vaccination (live vaccines)? Your doctor will have to advise you what is indicated for you.

Contraception, pregnancy and breast-feeding

Contraception in women taking Myfenax
If you are a woman who could become pregnant you must use an effective method of contraception with Myfenax. This includes:

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

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 Myfenax
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 Myfenax.

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 Myfenax 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 Myfenax if you are breast-feeding. This is because small amounts of the medicine can pass into the mother’s milk.

Driving and using machines
Myfenax 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.

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

3. How to take Myfenax

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

Your treatment is started and monitored by a doctor who is specialised in transplants.

The usual way to take Myfenax is as follows:

Kidney Transplant

Adults
The first dose will be given within 72 hours after the transplant operation. The recommended daily dose is 4 tablets (2 g of the active ingredient) taken as 2 separate doses. This means taking 2 tablets in the morning 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 "m^2"). The recommended initial dose is 600 mg/m^2 taken twice a day. The recommended maintenance dose remains at 600 mg/m^2 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 will be given within 5 days following the transplant operation. The recommended daily dose is 6 tablets (3 g of the active ingredient) taken as 2 separate doses. This means taking 3 tablets in the morning 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 "m^2"). The recommended starting dose is 600 mg/m^2 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/m^2 twice daily if required (maximum total daily dose of 3 g).

Liver Transplant

Adults

The first dose of oral Myfenax will be given to you at least 4 days after the transplant operation and when you are able to swallow oral medicines. The recommended daily dose is 6 tablets (3 g of the active ingredient) taken as 2 separate doses. This means taking 3 tablets in the morning 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 "m^2"). The recommended initial dose is 600 mg/m^2 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/m^2 twice daily if required (maximum total daily dose of 3 g).

Method and route of administration
Swallow your tablets whole with a glass of water. You can take them with or without food. Do not break or crush them.

Treatment will continue for you as long as you need immunosuppression to prevent rejection of your transplanted organ.

If you take more Myfenax than you should
It is important not to take too many tablets. Contact your nearest hospital Accident and Emergency department or a doctor for advice if you have swallowed more tablets than you have been told to take or if you think a child has swallowed any.

If you forget to take Myfenax
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 forgotten dose.

If you stop taking Myfenax
Do not stop taking Myfenax because you feel better. It is important to take the medicine for as long as the doctor has told you to. Stopping your treatment with Myfenax may increase the chance of rejection of your transplanted organ. Do not stop taking your medicine unless your doctor tells you to.

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

4. Possible side effects

Like all medicines, this medicine 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.
- rash, itching, hives, breathlessness or difficult breathing, wheezing or coughing, lightheadedness, dizziness, changes in levels of consciousness, hypotension, with or without mild generalized itching, skin reddening and facial/throat swelling (symptoms of severe allergic reaction).
- you have black or bloody stool or if you vomit blood or dark particles that look like coffee grounds. These may be signs of bleeding in the stomach or intestines.

The frequency of certain side effects is dependent on the transplanted organ, i.e. some side effects can occur more or less often depending on whether this medicinal product is being taken to prevent your

body from rejecting a transplanted heart or a transplanted kidney. For the sake of clarity each side effect is always listed under its highest frequency.

Other side effects

Very common (may affect more than 1 in 10 people)
- bacterial, viral and/or fungal infections
- serious infection which may affect the whole body
- decrease in the number of white blood cells, platelets or red blood cells, which can result in increased risk of infections, bruising, bleeding, breathlessness and weakness
- bleeding underneath the skin
- increase in the number of white blood cells
- too much acid in the body
- high level of cholesterol and/or lipids in the blood
- high level of sugar in the blood
- high level of potassium in the blood, low level of potassium, magnesium, calcium and/or phosphate in the blood
- high level of uric acid in the blood, gout
- feeling restless, abnormalities of thought, perception and levels of awareness, depression, feeling anxious, difficulty in sleeping
- increased tension of the muscles, shaking, sleepiness, feeling dizzy, headache, tingling, pricking or numbness
- faster heart beat
- low/high blood pressure, widening of blood vessels
- accumulation of fluid in the lung, shortness of breath, cough
- bloated belly
- vomiting, stomach pain, diarrhoea, feeling sick
- constipation, indigestion, wind (flatulence)
- decreased appetite
- changes in different laboratory parameters
- inflammation of the liver, yellowing of the skin and whites of the eyes
- growth of the skin, rash, acne
- muscle weakness
- joint pain
- kidney problems
- blood in the urine
- fever, feeling of coldness, pain, feeling weak and feeble
- fluid retention in the body
- part of an internal organ or tissue bulging through a weak spot in the abdominal muscles
- muscle pain, neck and back pain

Common (may affect up to 1 in 10 people)
- skin cancer, non-cancerous growth of the skin
- abnormal and excessive growth of tissue
- decrease in the number of all blood cells
- benign enlargement of the lymph nodes, inflammatory changes of the skin (pseudolymphoma)
- decreased weight
- abnormal thinking
- fit
- distortion of the sense of taste
- blood clot that forms within a vein
- inflammation of the tissue that lines the inner wall of the abdomen and covers most of the abdominal organs
- bowel blockage

- inflammation of the colon which causes abdominal pain or diarrhoea (sometimes caused by cytomegalovirus), ulcer of the mouth and/or stomach and/or duodenum, inflammation of the stomach, oesophagus and/or mouth and lips
- belching
- hair loss
- feeling unwell
- overgrowth of the gum tissue
- inflammation of the pancreas, which causes severe pain in the abdomen and back

Uncommon (may affect up to 1 in 100 people)
- protozoal infections
- proliferation of the lymphatic tissue, including malignant tumours
- insufficient production of red blood cells
- serious diseases of the bone marrow
- accumulation of lymphatic fluid within the body
- 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.
- decrease in the amount of antibodies in the blood
- severe reduction in the number of certain white blood cells (possible symptoms are fever, sore throat, frequent infections) (agranulocytosis)

Not known (frequency cannot be estimated from the available data)
- alterations of the inner wall of the small intestine (intestinal villous atrophy)
- serious inflammation of the membrane that covers the brain and spinal cord
- serious inflammation of the heart and its valves
- bacterial infections usually resulting in a serious lung disorder (tuberculosis, atypical mycobacterial infection)
- serious disease of the kidney (BK virus associated nephropathy)
- serious disease of the central nervous system (JC virus associated progressive multifocal leucoencephalopathy)
- decrease in the number of certain white blood cells (neutropenia)
- change of the shape of certain white blood cells

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.

Do not stop taking your medicine unless you have discussed this with your doctor first.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist 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 Myfenax

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 blister and carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

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 to protect the environment.

6. Contents of the pack and other information

What Myfenax contains

- The active substance is mycophenolate mofetil.
  Each tablet contains 500 mg of mycophenolate mofetil.
- The other ingredients are:
  Tablet core
  Microcrystalline cellulose
  Povidone K-30
  Magnesium stearate
  Croscarmellose sodium
  Tablet coat
  Hypromellose (HPMC 2910)
  Titanium dioxide (E171)
  Macrogol (PEG 400)
  Talc
  Indigo carmine aluminium lake (E132)
  Iron oxide black (E172)
  Iron oxide red (E172)

What Myfenax looks like and contents of the pack

Film-coated tablets
Pale purple, oval shaped film-coated tablet, debossed with "M500" on one side and plain on the other side.

Myfenax 500 mg film-coated tablets are available in PVC/PVdC-aluminium blisters in pack sizes of 50, 100, 150, 50 x 1 or 100 x 1 tablets and in multipacks containing 150 (3 packs of 50) tablets.

Not all pack sizes may be marketed.

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This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for mycophenolate mofetil, mycophenolic acid, the scientific conclusions of PRAC are as follows:

In view of available data on anaphylactic reactions from the literature and spontaneous reports including in cases a close temporal relationship, a positive de-challenge and/or re-challenge, the PRAC considers a causal relationship between mycophenolate mofetil, mycophenolic acid and anaphylactic reactions is at least a reasonable possibility. The PRAC concluded that the product information of products containing mycophenolate mofetil, mycophenolic acid should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for mycophenolate mofetil, mycophenolic acid the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing mycophenolate mofetil, mycophenolic acid is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.