# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Mycophenolate mofetil 1 g/5 ml powder for oral suspension

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle contains 35 g Mycophenolate mofetil in 110 g powder for oral suspension. 5 ml of the reconstituted suspension contains 1 g of mycophenolate mofetil.
Excipient(s) with known effect
Sodium less than 1 mmol (23 mg) per dose
For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Powder for oral suspension.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Mycophenolate mofetil powder for oral suspension is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in 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
*Use in renal transplant*
Adults
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), i.e. 5 ml oral suspension twice daily.

*Paediatric population aged 2 to 18 years*
The recommended dose of mycophenolate mofetil powder for oral suspension is 600 mg/$m^2$ administered twice daily (up to a maximum of 2 g/10 ml oral suspension daily). 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.
Paediatric population < 2 years
There are limited safety and efficacy data in children below the age of 2 years. These are insufficient to make dosage recommendations and therefore use in this age group is not recommended.
*Use in cardiac transplant*

*Adults*
Treatmemt 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).
Paediatric population
No data are available for paediatric cardiac transplant patients.
*Use in hepatic transplant*
*Adults*
IV 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*
No data are available for paediatric hepatic transplant patients.
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*
Mycophenolic acid (MPA) is the active metabolite of mycophenolate mofetil. Renal transplant rejection does not lead to changes in MPA pharmacokinetics; dosage reduction or interruption of mycophenolate mofetil is not required. There is no basis for mycophenolate mofetil dose adjustment following cardiac

transplant rejection. No pharmacokinetic data are available during hepatic transplant rejection.
Paediatric population
No data are available for treatment of first or refractory rejection in paediatric transplant patients

Method of administration
For oral use.

Note: If required, mycophenolate mofetil powder for oral suspension can be administered via a nasogastric tube with a minimum size of 8 French (minimum 1.7 mm interior diameter).

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

Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits, avoid inhalation or direct contact with skin or mucous membranes of the dry powder as well as direct contact of the reconstituted suspension with the skin. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.
For instruction on reconstitution of the medicinal product before administration, see section 6.6.

## 4.3 Contraindications

- Mycophenolate mofetil 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 mycophenolate mofetil have been observed (see section 4.8).
- Mycophenolate mofetil should not be given to women of childbearing potential who are not using highly effective contraception (see section 4.6).
- Mycophenolate mofetil treatment should not be initiated in women of child bearing potential without providing a pregnancy test result to rule out unintended use in pregnancy (see section 4.6).
- Mycophenolate mofetil should not be used in pregnancy unless there is no suitable alternative treatment to prevent transplant rejection (see section 4.6).
- Mycophenolate mofetil 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 mycophenolate mofetil are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.8). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As general advice to minimise the risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Infections

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

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 mycophenolate mofetil itself, concomitant medications, viral infections, or some combination of these

causes. Patients taking mycophenolate mofetil should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If neutropenia develops (absolute neutrophil count < 1.3 x $10^3$/µl), 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 depression.
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.
Gastro-intestinal
Mycophenolate mofetil has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, haemorrhage and perforation. Mycophenolate mofetil should be administered with caution in patients with active serious digestive system disease.
Mycophenolate mofetil is an IMPDH (inosine monophosphate dehydrogenase) inhibitor. Therefore, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.
Interactions
Caution should be exercised when switching combination therapy from regimens containing immunosuppressants, which interfere with MPA enterohepatic recirculation e.g. ciclosporin to others devoid of this effect e.g. tacrolimus, sirolimus, belatacept, or vice versa, as this might result in changes of MPA exposure. Drugs which interfere with MPA's enterohepatic cycle (e.g. cholestyramine, antibiotics) should be used with caution due to their potential to reduce plasma levels and efficacy of mycophenolate mofetil (see also section 4.5). 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).
It is recommended that mycophenolate mofetil should not be administered concomitantly with azathioprine because such concomitant administration has not been studied.
Mycophenolate mofetil 1g/5ml powder for oral suspension contains aspartame. Therefore, care should be taken if Mycophenolate mofetil 1g/5ml powder for oral suspension is administered to patients with phenylketonuria (see section 6.1).

The risk/benefit ratio of mycophenolate mofetil in combination with sirolimus has not been established (see also section 4.5).
Mycophenolate mofetil 1g/5ml powder for oral suspension contains methyl parahydroxybenzoate. It may cause allergic c reactions (possibly delayed).
This medicinal product contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Special populations
Elderly patients may be at an increased risk of adverse events such as certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared with younger individuals (see section 4.8).
Teratogenic effects
Mycophenolate is a powerful human teratogen. Spontaneous abortion (rate of 45% to 49%) and congenital malformations (estimated rate of 23% to 27%) have been reported following MMF exposure during pregnancy. Therefore Mycophenolate mofetil 1g/5ml powder for oral suspension 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 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. Men should not donate semen during therapy or for 90 days following discontinuation of mycophenolate.

## 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 mycophenoalte 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, ciclosposrin A, antibiotics)

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

*Cholestyramine*

Following single dose administration of 1.5 g of mycophenolate mofetil to normal healthy subjects pre-treated with 4 g TID of cholestyramine for 4 days, there was a 40% reduction in the AUC of MPA (see section 4.4 and section 5.2). Caution should be used during concomitant administration because of the potential to reduce efficacy of mycophenoalte 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 glucuronyltranferase isoform 1A9 (UGT1A9) expression and activity. When comparing rates of transplant rejection, rates of graft loss or adverse event profiles between mycophenolate mofetil patients 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 and IV ganciclovir and the known effects of renal impairment on the pharmacokinetics of mycophenolate mofetil (see section 4.2) and ganciclovir, it is anticipated that co-administration of these agents (which compete for mechanisms of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics is anticipated and mycophenolate mofetil dose

adjustment is not required. In patients with renal impairment in whom mycophenolate mofetil and ganciclovir or its prodrugs, e.g. valganciclovir, are co-administered, the dose recommendations for ganciclovir should be observed and patients should be monitored carefully.

Oral contraceptives

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

Rifampicin

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

Sevelamer

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

Tacrolimus

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

Live vaccines

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

Paediatric population

Interaction studies have only been performed in adults.

Potential interaction

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

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Pregnancy whilst taking mycophenolate must be avoided. Therefore, women of 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.

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.

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 mycophenolate mofetil treatment, women of child bearing potential should have two negative serum or urine pregnancy tests with a sensitivity of atleast 25mIU/ml in order to exclude unintended exposure of the 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 mofetil during pregnancy in combination with other immunosuppressants. The following malformations were most frequently reported:

- Abnormalities of the ear (e.g. abnormally formed or absent external ear), external auditory canal atresia (middle ear);
- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;

- Abnormalities of the eye (e.g. coloboma);
- Congenital heart disease such as atrial and ventricular septal defects;
- Malformations of the fingers (e.g. polydactyly, syndactyly);
- Tracheo-Oesophageal malformations (e.g. oesophageal atresia);
- Nervous system malformations such as spina bifida;
- Renal abnormalities.

  In addition there have been isolated reports of the following malformations:
- Microphthalmia;
- congenital choroid plexus cyst;
- septum pellucidum agenesis;
- olfactory nerve agenesis.

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

Breast-feeding

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

Men

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

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

Diarrhoea (up to 52.6%), leucopenia (up to 45.0%), bacterial infections (up to 39.9%) and vomiting (up to 39.1%) were among the most common and/or serious adverse drug reactions associated with the administration of mycophenolate mofetil in combination with ciclosporin and corticosteroids. There is evidence of a higher frequency of certain types of infections (see section 4.4).

Tabulated list of adverse reactions

The adverse reactions from clinical trials and post-marketing experience are listed in Table 1, by MedDRA system organ class (SOC) along with their frequencies. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), 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

| Adverse drug reaction<br><br>(MedDRA) | Renal transplant | Hepatic transplant | Cardiac transplant |
|---|---|---|---|

| System Organ Class | | | |
|---|---|---|---|
| | 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** | | | |
| Anemia | 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 |
| Leucopenia | 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 |
| Hypercholesterolemia | Very common | Common | Very common |
| Hyperglycemia | Common | Very common | Very common |
| Hyperkalemia | Common | Very common | Very common |
| Hyperlipidemia | Common | Common | Very common |
| Hypocalcemia | Common | Very common | Common |
| Hypokalemia | Common | Very common | Very common |
| Hypomagnesemia | Common | Very common | Very common |
| Hypophosphotemia | Very common | Very commoon | Common |
| Hyperuricemia | 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 |
| 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 |
| Dysguesia | Uncommon | Uncommon | Common |

| | | | |
|---|---|---|---|
| **Cardiac disorders** | | | |
| Tachycardia | Common | Very common | Very common |
| **Vascular disorders** | | | |
| Hypertenison | 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 hemorrhage | 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** | | | |
| Hypersensitivity | 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 |
| Hyperbilirubinemia | 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 |
| Hematuria | 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 |
| Edema | 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 opprtunistic 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 mycobacteial infection. The most common opportunistic infections in patients receiving mycophenolate mofetil (2 g or 3 g daily) with other immunosuppressants in controlled clinical trials in renal, cardiac and hepatic transplant patients followed for at least 1 year were candida mucocutaneous, CMV viraemia/syndrome and Herpes simplex. The proportion of patients with CMV viraemia/syndrome was 13.5%. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including mycophenolate mofetil.

*Blood and lymphatic disorders*

Cytopenias, including leucopenia, anemia, thrombocytopenia and pancytopenia, are known risks associated with mycophenolate mofetil and may lead or contribute to the occurrence of infections and hemorrhages (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 hemorrhage which are known risks associated with mycophenolate mofetil. Mouth, esophageal, gastric, duodenal, and intestinal ulcers often complicated by hemorrhage, as well as hematemesis, melena, and hemorrhagic forms of gastritis and colitis were commonly reported during the pivotal clinical trials. The most common gastrointestinal disorders, however, were diarrhea, nausea and vomiting. Endoscopic investigation of patients with mycophenolate mofetil-related diarrhea 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 mofetil 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*

Edema, including peripheral, face and scrotal edema, 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 in a clinical study, which recruited 92 paediatric patients aged 2 to 18 years who were given 600 mg/m$^2$ mycophenolate mofetil orally twice daily, were generally similar to those observed in adult patients given 1 g mycophenolate mofetil twice daily. However, the following treatment-related adverse events were more frequent in the paediatric population, particularly in children under 6 years of age, when compared to adults: diarrhoea, sepsis, leucopenia, anaemia and infection.

*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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

Reports of overdoses with mycophenolate mofetil have been received from clinical trials and during post-marketing experience. In many of these cases, no adverse events were reported. In those overdose cases in which adverse events were reported, the events fall within the known safety profile of the medicinal product.

It is expected that an overdose of mycophenolate mofetil could possibly result in over suppression 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 re-circulation of the drug (see section 5.2).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressive agents ATC code L04AA06

Mechanism of action

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

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

## 5.2 Pharmacokinetic properties

Absorption

Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, MPA. As evidenced by suppression of acute rejection following renal transplantation, the immunosuppressant activity of mycophenolate mofetil is correlated with MPA concentration. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94% relative to IV 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 MMF´s side effects (diarrhoea, leucopenia).

Elimination

A negligible amount of substance is excreted as MPA (< 1% of 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 (> 100µg/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 is seen when mycophenolate mofetil is co-administered with cyclosporine (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 $AUC_{0–12h}$ was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG $AUC_{0-12h}$ was 2 – 3-fold higher than in post-transplant patients without delayed graft function. There may be a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of mycophenolate mofetil does not appear to be necessary.
*Hepatic impairment*
In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease. Effects of hepatic disease on these processes probably depend on the particular disease. Hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.
*Paediatric population*
Pharmacokinetic parameters were evaluated in 49 paediatric renal transplant patients (aged 2 to 18 years) given 600 mg/$m^2$ 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. MPA AUC values across age groups were similar in the early and late post-transplant period.
*Elderly*
The pharmacokinetics of mycophenolate mofetil and its metabolites have not been found to be altered in the elderly patients (≥ 65 years) when compared to younger patients.
*Patients taking oral contraceptives*
A study of the co-administration of mycophenolate mofetil (1 g BID) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.15 mg), desogestrel (0.20 mg) or gestodene (0.05 mg to 0.10 mg) conducted in 18 non-transplant women (not taking other immunosupressants) over 3 consecutive menstrual cycles showed no clinically relevant influence of mycophenolate mofetil on the ovulation suppressing action of the oral contraceptives. Serum levels of LH, FSH and progesterone were not significantly affected. The pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by co-administration of mycophenolate mofetil (see also section 4.5)

## 5.3 Preclinical safety data

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

Two genotoxicity assays (*in vitro* mouse lymphoma assay and *in vivo* mouse bone marrow micronucleus test) showed a potential of mycophenolate mofetil to cause chromosomal aberrations. These effects can be related to the pharmacodynamic mode

of action, i.e. inhibition of nucleotide synthesis in sensitive cells. Other *in vitro* tests for detection of gene mutation did not demonstrate genotoxic activity.

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

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

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

sorbitol
silica colloidal anhydrous
sodium citrate
soybean lecithin
powderome mixed fruit premium
xanthan gum
aspartame* (E951)
methyl parahydroxybenzoate (E218)
citric acid
* contains phenylalanine equivalent to 2.78 mg/5 mL of suspension.

## 6.2 Incompatibilities

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

## 6.3 Shelf life

The shelf-life of the powder for oral suspension is 3 years.

The shelf-life of the reconstituted suspension is 2 months.

## 6.4 Special precautions for storage

Powder for oral suspension and reconstituted suspension: This medicinal product does not require any special storage condition.

## 6.5 Nature and contents of container

• Container Material – white, opaque, round HDPE bottle

• Container Closure - white, opaque PP (polypropylene) child-resistant closure with liner

• Bottle adaptor (adaptor plug)

• 2 x 5ml oral syringes (dispensers)

Each bottle contains 35 g mycophenolate mofetil in 110 g powder for oral suspension. When reconstituted, the volume of the suspension is 175 mL, providing a usable volume of not less than 160 ml. 5 ml of the reconstituted suspension contains 1g of mycophenolate mofetil.

## 6.6 Special precautions for disposal

It is recommended that Mycophenolate mofetil 1g/5ml powder for oral suspension be reconstituted by the pharmacist prior to dispensing to the patient. Wearing disposable gloves is recommended during reconstitution and when wiping the outer surface of the bottle/cap and the table after reconstitution.

Preparation of suspension

1. Tap the closed bottle several times to loosen the powder.
2. Measure 94 ml of purified water in a graduated cylinder.
3. Add approximately half of the total amount of purified water to the bottle and shake the closed bottle well for about 1 minute.

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

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

## 7 MARKETING AUTHORISATION HOLDER

Tillomed Laboratories Limited,
220 Butterfield, Great Marlings,
Luton, LU2 8DL,
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL GB 11311/0703

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/08/2025

## 10 DATE OF REVISION OF THE TEXT

17/04/2026