SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Mycophenolate Mofetil USP 500 mg Tablets

2. Qualitative and quantitative composition

Each Film Coated Tablet Contains:

Mycophenolate Mofetil USP 500 mg

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Brown colour capsule shape biconvex film coated tablet with break line on one side.

4. Clinical particulars

4.1 Therapeutic indications

4.2 Posology and method of administration

For oral administration only.

Posology

Use in renal transplant

Adults: Oral Mycophenolate mofetil 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).

Paediatric population aged 2 to 18 years: The recommended dose of mycophenolate mofetil is 600 mg/m2 administered orally twice daily (up to a maximum of 2 g daily). Mycophenolate mofetil tablets should only be prescribed to patients with a body surface area greater than 1.5 m2, at a dose of 1 g twice daily (2 g daily dose). As some adverse reactions occur with greater frequency in this age groupcompared 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: Oral Mycophenolate mofetil 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 m2), outside the immediate post-transplant period, doses greater than 1 g administered twice a day should be avoided. These patients should also be carefully observed. No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively. 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.

4.3 Contraindications

- Hypersensitivity to Mycophenolate Mofetil or to any of the tablet excipients listed in section 6.1
- Mycophenolate Mofetil should not be given to patients with hypersensitivity, mycophenolic acid or to any of the excipients.
- Hypersensitivity reactions to Mycophenolate Mofetil have been observed. Mycophenolate Mofetil should not be given to women of childbearing potential who are not using highly effective contraception.
- Mycophenolate Mofetil treatment should not be initiated in women of childbearing potential without providing a pregnancy test result to rule out unintended use in pregnancy.
- Mycophenolate Mofetil should not be used during pregnancy unless there is no suitable alternative treatment to prevent transplant rejection.
- Mycophenolate Mofetil should not be given to women who are breastfeeding.
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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. 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. 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.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 103/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 t 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.

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. 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.
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.
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 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 (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: 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 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

Cholestyramine: Following single dose administration of 1.5 g of mycophenolate mofetil to normal healthy subjects pre-treated with 4 g TID of cholestyramine for 4 days, there was a 40% reduction in the AUC of MPA.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. 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 AUC0-∞ 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 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.

4.6 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 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 unaffected by co-administration of Mycophenolate mofetil.
Rifampicin: In patients not also taking ciclosporin, concomitant administration of Mycophenolate mofetil and rifampicin resulted in a decrease in MPA exposure (AUC0-12h) 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 Cmax and AUC0-12h 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 Cmax 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.Fertility, pregnancy and lactation

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 childbearing potential should have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/ml in order to exclude unintended exposure of 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 performed 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.

Breast-feeding: Mycophenolate mofetil has been shown to be excreted in the milk of lactating rats. It is not known whether this substance 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.

4.7 Effects on ability to drive and use machines
Mycophenolate mofetil has a 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
Tabulated list of adverse reactions
The adverse drug reactions (ADRs), the frequency is presented separately for renal, hepatic and cardiac transplant patients.

Table 1 Summary of adverse drug reactions occurring in patients treated with mycophenolate mofetil reported from clinical trials and post marketing experience

Adverse drug reaction (MedDRA) System Organ Class	**Renal transplant n = 991**	**Hepatic transplant n = 277**	**Cardiac transplant n = 289**
	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
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
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
Hypophosphatemia	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
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
Dyspnea	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
Diarrhea	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			
Hypersenstivity	Uncommon	Common	Common
Hypogammaglobulinaemia	Uncommon	Very rare	Very rare
Hepatobiliary disorders			

Blood alkaline phosphatase increased	Common	Common	Common
Blood lactate dehydrogenase increased	Common	Uncommon	Very common
Hepatic enzyme increased	Common	Very common	Very common
Hepatitis	Common	Very common	Uncommon
Hyperbilirubinaemia	Common	Very common	Very common
Jaundice	Uncommon	Common	Common
Skin and subcutaneous tissue disorders			
Acne	Common	Common	Very common
Alopecia	Common	Common	Common
Rash	Common	Very common	Very common
Skin hypertrophy	Common	Common	Very common
Musculoskeletal and connective tissue disorders			
Arthralgia	Common	Common	Very common
Muscular weakness	Common	Common	Very common
Renal and urinary disorders			
Blood creatinine increased	Common	Very common	Very common
Blood urea increased	Uncommon	Very common	Very common
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

Note: 991 (2 g/3 g mycophenolate mofetil daily), 289 (3 g mycophenolate mofetil daily) and 277 (2 g IV/3 g oral mycophenolate mofetil daily) patients were treated in Phase III studies for the prevention of rejection in renal, cardiac and hepatic transplantation, respectively.

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 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 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 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 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 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
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 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:
Healthcare professionals are requested to report any suspected adverse reactions via the national Pharmacovigilance Electronic Reporting Systems to the respective national regulatory authorities.

4.9 Overdose
Reports of overdoses with mycophenolate mofetil have been received from clinical trials and during post-marketing experience. In many of these cases, no adverse events were reported. In those overdose cases in which adverse events were reported, the events fall within the known safety profile of the medicinal product.
It is expected that an overdose of mycophenolate mofetil could possibly result in oversuppression of the immune system and increase susceptibility to infections and bone marrow suppression. If neutropenia develops, dosing with Mycophenolate mofetil should be interrupted or the dose reduced.
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

5. Pharmacological properties
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: immunosuppressive agents ATC code: L04A
A06 Mechanism of action
Mycophenolate Mofetil is the 2-morpholinoethyl ester of mycophenolic acid (MPA). MPA is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (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

5.2 Pharmacokinetic properties
Absorption
Following oral administration, Mycophenolate Mofetil undergoes rapid and extensive absorption and complete presystolic 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 Cmax 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 Cmax 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 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 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.
In the early post-transplant period (< 40 days post-transplant), renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30% lower and Cmax approximately 40% lower compared to the late post-transplant period (3 – 6 months post-transplant).

Special populations
Renal impairment
In a single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate < 25 ml/min/1.73 m2) were 28-75% higher relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. The mean single dose

MPAG AUC was 3-6-fold higher in subjects with severe renal impairment than in subjects with mild renal impairment or normal healthy subjects, consistent with the known renal elimination of MPAG. Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.
Delayed renal graft function
In patients with delayed renal graft function post-transplant, mean MPA AUC0-12 h was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC0-12 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
Pharmacokinetic parameters were evaluated in 49 paediatric renal transplant patients (aged 2 to 18 years) given 600 mg/m2 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 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 tumorigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2-3 times the systemic exposure (AUC or Cmax) observed in renal transplant patients at the recommended clinical dose of 2 g/day and 1.3-2 times the systemic exposure (AUC or Cmax) 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

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

- Maize Starch
- Microcrystalline Cellulose
- Croscarmellose Sodium
- Povidone
- Isopropyl Alcohol
- Colloidal Silicon Dioxide
- Sodium Starch Glycolate
- Purified Talc
- Magnesium Stearate
- Hydroxy Propyl Methyl Cellulose (E-15)
- Polyethylene Glycol (macrogol) 6000
- Titanium dioxide
- Isopropyl Alcohol
- Red oxide of Iron
- Indigo Carmine
- Dichloromethane

6.2 Incompatibilities Not applicable

6.3 Shelf life: 36 months

6.4 Special precautions for storage

Store in a dry place, below 30°C.Protected from direct sunlight Keep all medicines out of reach of children

6.5 Nature and contents of container

Alu-PVC blister pack of 3x10s, packed in a unit boxes, with literature insert.

6.6 Special precautions for disposal and other handling

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

7. Marketing Authorisation Holder

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Manufactured for:
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