Mynotil 250mg Film Coated Tablets
Mynotil 500mg Film Coated Tablets

1. NAME OF THE MEDICINAL PRODUCT

Mynotil 250mg Film Coated Tablets
Mynotil 500mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Mynotil 250mg Film Coated Tablets: Each tablet contains 250mg of Mycophenolate Mofetil.

Mynotil 500mg Film Coated Tablets: Each tablet contains 500mg of Mycophenolate Mofetil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Mynotil 250mg Film Coated Tablets: Lavender-colored, oval-shaped tablets debossed with "250" on one side and "M" on the other side.

Mynotil 500mg Film Coated Tablets: Lavender-colored, capsule-shaped tablets debossed with "500" on one side and "M" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Mynotil tablets are indicated for the prophylaxis of acute organ rejection in patients receiving allogeneic renal transplants.

Mynotil tablets are indicated for the prophylaxis of acute organ rejection in patients receiving allogeneic cardiac transplants.

Mynotil tablets are indicated for the prophylaxis of acute organ rejection in patients receiving allogeneic hepatic transplants.

Mynotil should be used concomitantly with ciclosporin and corticosteroids.

Mynotil is indicated for induction and maintenance treatment of lupus nephritis. Mynotil should be used concomitantly with corticosteroids.

4.2 Posology and Method of Administration

Please refer to full prescribing information for corticosteroids and either ciclosporin or tacrolimus, which are used in combination with Mynotil.

Transplant patients
Standard dosage for prophylaxis of renal rejection
A dose of 1 g administered orally twice a day (daily dose of 2 g) is recommended for use in renal transplant patients. Although a dose of 1.5 g administered twice daily (daily dose of 3 g) was used in clinical trials and was shown to be safe and effective, no efficacy advantage could be established for

renal transplant patients. Patients receiving 2 g per day of mycophenolate mofetil demonstrated an overall better safety profile compared to patients receiving 3 g per day of mycophenolate mofetil.

Standard dosage for prophylaxis of cardiac rejection
A dose of 1.5 g administered orally twice a day (daily dose of 3 g) is recommended for use in cardiac transplant patients.

Standard dosage for prophylaxis of hepatic rejection
A dose of 1.5 g administered orally twice daily (daily dose of 3 g) is recommended for use in hepatic transplant patients.

Oral administration
The initial dose of Mynotil should be given as soon as possible following renal, cardiac and hepatic transplantation.

Lupus nephritis patients
Induction and maintenance treatment of lupus nephritis
The recommended dose is 1 g administered twice a day (daily dose of 2 g).

Mynotil should be used in combination with corticosteroids. Doses should be introduced gradually and adjusted according to clinical response. Therapeutic drug monitoring could help prevent sub-therapeutic exposure (C_{min} ≥3.0 mg/L or inter-dose AUC ≥35 h*mg/L).

Special dosage instructions
Pediatric use
See *Posology and Method of Administration* and *Pharmacokinetics in Special Populations*.

Geriatric use
For transplant patients, no oral dosage adjustment is recommended. For lupus nephritis patients, no recommendation is available.

Renal impairment
For renal transplant patients with severe chronic renal impairment (glomerular filtration rate <25 mL/min/1.73m^2) outside of the immediate post-transplant period or after treatment of acute or refractory rejection, administration of doses greater than 1 g twice daily should be avoided.

For post-transplant patients with delayed renal graft function, no dose adjustment is recommended but patients should be carefully monitored.

For cardiac or hepatic transplant patients with severe renal impairment, no data are available.

For lupus nephritis patients with GFR <30 mL/min, therapeutic drug monitoring is advised.

Hepatic impairment
For renal transplant patients with severe hepatic parenchymal disease, no dose adjustments are recommended.

For cardiac transplant and lupus nephritis patients with severe hepatic parenchymal disease, no data are available.

Patients with neutropenia
For patients that develop neutropenia (absolute neutrophil count <1.3 x 10_3/µl), dosing with Mynotil should be interrupted or the dose should be reduced.

4.3 Contraindications

Allergic reactions to mycophenolate mofetil have been observed. Therefore, Mynotil is contraindicated in patients with a known hypersensitivity to mycophenolate mofetil or mycophenolic acid (MPA).

Mynotil is contraindicated during pregnancy due to its mutagenic and teratogenic potential. (See Pregnancy)

Mynotil is contraindicated in women of childbearing potential not using highly effective contraceptive methods. (See Pregnancy)

Mynotil is contraindicated in women who are breastfeeding. (See Lactation)

4.4 Special Warnings and Precautions for Use

Neoplasms
As in all patients receiving immunosuppressive regimens involving combinations of drugs, patients receiving mycophenolate mofetil as part of an immunosuppressive regimen 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 with all patients at an increased 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
Oversuppression of the immune system can also increase susceptibility to infection including opportunistic infections, fatal infections and sepsis. Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation, or infections caused by polyomaviruses. Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. Cases of Progressive Multifocal Leukoencephalopathy (PML) associated with the JC virus, sometimes fatal, have been reported in mycophenolate mofetil treated patients. The reported cases generally had risk factors for PML, including immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a Neurologist should be considered as clinically indicated.

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

Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus associated nephropathy which has been observed in patients receiving immunosuppressants. These infections may lead to serious, including fatal outcomes.

Blood and immune system
Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil in combination with other immunosuppressive agents. The mechanism for mycophenolate mofetil induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppression regimen are also unknown. In some cases PRCA was found

to be reversible with dose reduction or cessation of mycophenolate mofetil therapy. In transplant patients however reduced immunosuppression may place the graft at risk.

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

Blood donation
Patients should not donate blood during therapy and for at least 6 weeks following discontinuation of mycophenolate mofetil.

Vaccination
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, hemorrhage, and perforation. mycophenolate mofetil should be administered with caution in patients with active digestive system disease.

Mycophenolate mofetil is an inosine monophosphate dehydrogenase (IMPDH) inhibitor; therefore it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Interactions
Caution should be exercised when switching combination therapy from regimens containing immunosuppressants, which interfere with MPA enterohepatic recirculation e.g. ciclosporin to others devoid of this effect e.g. tacrolimus, sirolimus, belatacept, or vice versa, as this might result in changes of MPA exposure. 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).

Drugs which interfere with MPA's enterohepatic cycle (e.g. cholestyramine, sevelamer, antibiotics) should be used with caution due to their potential to reduce the plasma levels and efficacy of mycophenolate mofetil. Sevelamer and other calcium free phosphate binders should be taken 2 hours after mycophenolate mofetil intake to minimise the impact on the absorption of MPA.

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

Special populations
Geriatric population
Elderly patients may be at an increased risk of adverse events such as certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary

oedema, compared with younger individuals.

Pregnancy and breastfeeding
Mycophenolate mofetil is contraindicated in pregnancy and during breastfeeding.

Semen donation
Men should not donate semen during therapy and for 90 days following discontinuation of mycophenolate mofetil.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

DNA Polymerase Inhibitors (acyclovir, ganciclovir)
Acyclovir: Higher MPAG (the phenolic glucuronide of MPA) and acyclovir plasma concentrations were observed when mycophenolate mofetil was administered with acyclovir than when the drugs were administered alone. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for mycophenolate and acyclovir or its prodrugs e.g. valacyclovir to compete for tubular secretion, further increasing the concentrations of both drugs.

Ganciclovir: Based on the results of a single dose administration study of recommended doses of oral mycophenolate and i.v. ganciclovir and the known effects of renal impairment on the pharmacokinetics of MMF and ganciclovir, it is anticipated that coadministration 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 MMF dose adjustment is not required. In patients with renal impairment in whom MMF and ganciclovir or its prodrugs valganciclovir are co-administered, patients should be monitored carefully.

Antacids and proton pump inhibitors (PPIs)
Decreased mycophenolic acid (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 lower than when mycophenolate mofetil was co-administered with PPIs.

Sequestrants
Cholestyramine: Following single-dose administration of 1.5 g of mycophenolate mofetil to normal healthy subjects pretreated with 4 g three times daily of cholestyramine for 4 days, there was a 40% reduction in the AUC of MPA. Caution should be used during concomitant administration of drugs that interfere with enterohepatic circulation.

Sevelamer: Concomitant administration of sevelamer and mycophenolate mofetil in adults and pediatric patients decreased the MPA C_{max} and AUC_{0-12} by 30% and 25%, respectively.

Immunosuppressants
Ciclosporin A: Ciclosporin A (CsA) pharmacokinetics were unaffected by mycophenolate mofetil. However, CsA interferes with MPA enterohepatic recycling, resulting in reduced MPA exposures 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 do not interfere with MPA's enterohepatic cycle.

Tacrolimus: Exposure to tacrolimus concomitantly administered with mycophenolate mofetil had no

effect on the AUC or C_{max} of MPA in liver transplant recipients.
In renal transplant patients it was shown that the tacrolimus concentration did not appear to be altered by mycophenolate mofetil.

However, in hepatic transplant patients, there was an increase in tacrolimus AUC when multiple doses of mycophenolate mofetil (1.5 g twice daily) were administered to patients taking tacrolimus.

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

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

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

Norfloxacin and metronidazole: Norfloxacin in combination with metronidazole reduced the MPA AUC_{0-48} following a single dose of mycophenolate mofetil. No such effect on the systemic exposure of MPA with either of these antibiotics occurred when they were administered separately.

Trimethoprim/sulphamethoxazole: No effect on the systemic exposure of MPA (AUC, C_{max}) was seen with the combination trimethoprim/sulfamethoxazole.

Oral contraceptives
A study of coadministration of mycophenolate mofetil (1 g twice daily) and combined oral contraceptives containing ethinylestradiol (0.02 - 0.04 mg) and levonorgestrel (0.05 - 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 - 0.10 mg) conducted in 18 women with psoriasis over 3 menstrual cycles showed no clinically relevant influence of mycophenolate mofetil on serum levels of progesterone, LH and FSH, thus indicating no influence of mycophenolate mofetil on the ovulation-suppressing action of the oral contraceptives. The pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by coadministration of mycophenolate mofetil.

Other interactions
Concomitant administration of drugs inhibiting glucuronidation of MPA may increase MPA exposure. Caution is therefore recommended when administering these drugs concomitantly with mycophenolate mofetil.

Concomitant administration of telmisartan and mycophenolate mofetil resulted in decrease of mycophenolic acid (MPA) concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression which in turn results in an enhanced UGT1A9 expression and activity, enhancing glucuronidation. 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 DDI were seen.

Coadministration of probenecid with mycophenolate mofetil in monkeys raises the plasma AUC of

MPAG 3-fold. Thus, other drugs known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion.

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

4.6 Fertility, pregnancy and lactation

Females And Males Of Reproductive Potential

Fertility

Mycophenolate mofetil is contraindicated in women of childbearing potential not using highly effective contraceptive methods. Malformations (including anophthalmia, agnathia, and hydrocephaly) occurred in the first generation offspring of female rats treated with oral doses of mycophenolate mofetil in the absence of maternal toxicity. No effect was seen on the fertility of male rats treated with mycophenolate mofetil.

Pregnancy testing

Prior to starting therapy with mycophenolate mofetil, female patients of childbearing potential must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL. A second test should be performed 8-10 days later. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.

Contraception

Females

Mycophenolate mofetil is contraindicated in women of childbearing potential not using highly effective contraceptive methods.

Before the start of treatment, female patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention, and planning. Women of child bearing potential should use two reliable forms of contraception simultaneously, at least one of which must be highly effective, before beginning mycophenolate mofetil therapy, during therapy, and for six weeks following discontinuation of therapy unless abstinence is the chosen method of contraception.

Males

Limited clinical evidence is currently available on paternal exposure to mycophenolate mofetil. This evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to mycophenolate.

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

In absence of sufficient data to exclude a risk of harm to the fetus conceived during or directly after the treatment of the father, the following precautionary measure is recommended: sexually active male patients and/or their female partners are recommended to use effective contraception during treatment and for at least 90 days after cessation of treatment.

Pregnancy

Mycophenolate mofetil is contraindicated during pregnancy and in women of childbearing potential not

using highly effective contraceptive methods. (see Contraindications).

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

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

Due to the mutagenic and teratogenic potential of mycophenolate, **women of child bearing potential** should use **two reliable forms of contraception** simultaneously, including at least one highly effective method, before beginning mycophenolate therapy, during therapy, and for six weeks following discontinuation of therapy, unless abstinence is the chosen method of contraception.

Sexually active men are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomised men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. In addition, **female partners of male patients** are recommended to use highly effective during treatment and for total of 90 days after the last dose of mycophenolate mofetil.

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

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

In the medical literature, malformations in children from mycophenolate-exposed pregnancies have been reported in 23% to 27% of live births. For comparison, the risk of malformations is estimated at approximately 2% of live births in the overall population and at approximately 4% to 5 % in solid organ transplant patients treated with immunosuppressants other than mycophenolate.

Cases of spontaneous abortions have also been reported in patients exposed to mycophenolate, mainly in the first trimester. In the medical literature, the risk has been reported at 45% to 49% following mycophenolate exposure, compared to a reported rate between 12 and 33% in solid organ transplant patients treated with other immunosuppressants.

Studies in animals have shown reproductive toxicity.

Labor and delivery
The safe use of mycophenolate mofetil during labor and delivery has not been established.

Lactation
Mycophenolate mofetil is contraindicated during breastfeeding due to the potential for serious adverse reactions in nursing infants (see Contraindications).

Studies in rats have shown mycophenolate to be excreted in milk. It is not known whether this medicine is excreted in human milk.

4.7 Effects on Ability to Drive and Use Machines

Mycophenolate mofetil may have a moderate influence on the ability to drive and use machines.

Patients should be advised to use caution when driving or using machines if they experience adverse drug reactions such as somnolence, confusion, dizziness, tremor or hypotension during treatment with mycophenolate mofetil.

4.8 Undesirable Effects

Summary of the safety profile
Diarrhoea, leucopenia, bacterial infections and vomiting were among the most common and/or serious adverse reactions associated with the administration of mycophenolate mofetil in combination with ciclosporin and corticosteroids. There is evidence of a higher frequency of certain types of infections.

Tabulated list of adverse reactions
The adverse reactions from clinical trials and post-marketing experience are listed in Table 1, by MedDRA system organ class (SOC) along with their frequencies. The corresponding frequency category for each adverse reaction is based on the following convention: very common, common, uncommon, rare and very rare. 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 reaction (MedDRA) System Organ Class	**Renal transplant**	**Hepatic transplant**	**Cardiac transplant**
	Frequency	Frequency	Frequency
Infections and infestations			
Bacterial infections	Very Common	Very Common	Very Common
Fungal infections	Common	Very Common	Very Common
Viral infections	Very Common	Very Common	Very Common
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Benign neoplasm of skin	Common	Common	Common
Neoplasm	Common	Common	Common
Skin cancer	Common	Uncommon	Common
Blood and lymphatic system disorders			
Anemia	Very Common	Very Common	Very Common
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
Hypophosphatemia	Very Common	Very Common	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
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
Cardiac disorders			
Tachycardia	Common	Very Common	Very Common
Vascular disorders			
Hypertension	Very Common	Very Common	Very Common
Hypotension	Common	Very Common	Very Common
Venous thrombosis*	Common	Common	Common
Respiratory, thoracic and mediastinal disorders			
Cough	Very Common	Very Common	Very Common
Dyspnea	Very Common	Very Common	Very Common
Pleural effusion	Common	Very Common	Very Common
Gastrointestinal disorders			
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
Flatulence	Common	Very Common	Very Common
Gastritis	Common	Common	Common
Gastrointestinal hemorrhage	Common	Common	Common
Gastrointestinal ulcer	Common	Common	Common
Ileus	Common	Common	Common
Nausea	Very Common	Very Common	Very Common
Stomatitis	Common	Common	Common
Vomiting	Very Common	Very Common	Very Common
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
Skin and subcutaneous tissue disorders			
Alopecia	Common	Common	Common
Rash	Common	Very 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
General disorders and administration site conditions			
Asthenia	Very Common	Very Common	Very Common
Chills	Common	Very Common	Very Common
Oedema	Very Common	Very Common	Very Common
Hernia	Common	Very Common	Very Common
Pain	Common	Very Common	Very Common
Pyrexia	Very Common	Very Common	Very Common

*Reported following intravenous administration.

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.

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. The most serious infections were sepsis, peritonitis, meningitis, endocarditis, tuberculosis and atypical mycobacterial infection. 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. Agranulocytosis and neutropenia have been reported; therefore, regular monitoring of patients taking mycophenolate mofetil is advised. 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.

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. The most common gastrointestinal disorders, however, were diarrhoea, nausea and vomiting. Endoscopic investigation of patients with CellCept-related diarrhoea have revealed isolated cases of intestinal villous atrophy.

Hypersensitivity

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

Respiratory, thoracic and mediastinal disorders

There have been isolated reports of interstitial lung disease and pulmonary fibrosis in patients treated with mycophenlate 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 mycophenlate mofetil in combination with other immunosuppressants.

General disorders and administration site conditions
Oedema, including peripheral, face and scrotal oedema, was very commonly reported. 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 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.

Post-marketing experience
Congenital Disorders
Congenital malformations have been reported post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy (see Pregnancy).

Pregnancy, Puerperium and Perinatal Conditions
Cases of spontaneous abortions mainly in the first trimester in patients exposed to mycophenolate have been reported (see Pregnancy).

4.9 Overdose

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

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.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism Of Action

Mycophenolate mofetil (MMF) 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. The mechanism by which MPA inhibits the enzymatic activity of IMPDH appears to be related to the ability of MPA to structurally mimic both nicotinamide adenine dinucleotide cofactor and a catalytic water molecule. This prevents the oxidation of IMP to xanthose-5'-monophosphate which is the committed step in de novo guanosine nucleotide biosynthesis. Two IMPDH isoforms have been identified, isoform type I, which is present in most known cells (including resting human lymphocytes) and isoform type II, which is strongly and predominantly expressed in activated human B- and T-lymphocytes. The type II isoform is nearly five times more sensitive to inhibition by MPRA than is the type I isoform. MPA has more potent cytostatic effects on lymphocytes than on other cells because T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines whereas other cell types can utilize salvage pathways.

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

The pharmacokinetics of MMF have been studied in renal, cardiac and hepatic transplant patients and in patients with lupus nephritis.

In general, the pharmacokinetic profile of MPA is similar in renal and in cardiac transplant patients. In the early transplant period, hepatic transplant patients receiving a 1.5 g oral MMF dose or 1 g i.v. MMF dose have similar MPA levels compared to renal transplant patients receiving 1 g oral MMF or i.v. MMF. The pharmacokinetic profile of MPA in lupus nephritis is similar to that reported in transplantation (including the high variability in exposure to active drug observed) but is complicated by more unpredictable changes in renal function in lupus nephritis patients.

Absorption

Following oral and intravenous administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, MPA. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94% relative to i.v. mycophenolate mofetil. mycophenolate mofetil can be measured systemically during intravenous infusion; however, after oral administration it is below the limit of quantitation (0.4 μg/ml).

Immediately post-transplant (<40 days) renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30% lower and C_{max} approximately 40% lower compared to the late transplant period (3-6 months posttransplant). This is referred to as non-stationarity of MPA pharmacokinetics. MPA AUC values obtained following administration of 1 g twice daily intravenous mycophenolate mofetil at the recommended infusion rate to renal patients in the immediate post-transplant phase are comparable to those observed following oral dosing. In hepatic transplant patients, administration of 1 g twice daily intravenous mycophenolate mofetil followed by 1.5 g twice daily oral mycophenolate mofetil resulted in MPA AUC values similar to those found in renal transplant patients administered 1 g mycophenolate mofetil twice daily.

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

<u>Equivalence of oral dosage forms</u>

Bioequivalence of mycophenolate mofetil oral dosage forms have been evaluated. Two 500 mg tablets

have been shown to be bioequivalent to four 250 mg capsules. Likewise, 1 g/5 mL of mycophenolate mofetil constituted powder for oral suspension has been shown to be bioequivalent to four 250 mg capsules

Distribution
Secondary increases in plasma MPA concentrations are usually observed at approximately 6-12 hours postdose, consistent with enterohepatic recirculation. A reduction of approximately 40% in the AUC of MPA is associated with coadministration of cholestyramine (4 g three times daily), consistent with interruption of enterohepatic recirculation.

At clinically relevant concentrations, MPA is 97% bound to plasma albumin. This value is dependent on renal function; changes in albumin binding after initiating therapy may explain the non-stationarity in the pharmacokinetics of MPA.

Metabolism
MPA is conjugated primarily by glucuronyltransferase (isoform UGT1A9) to form the inactive phenolic glucuronide of MPA (MPAG). In vivo, MPAG is converted 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
Oral administration of radiolabelled mycophenolate mofetil resulted in complete recovery of the administered dose, with 93% of the dose recovered in the urine and 6% recovered in the feces. Most (about 87%) of a dose is excreted in the urine as MPAG. A negligible amount of drug (<1% of dose) is excreted as MPA in the urine.

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 and why plasma concentrations tend to increase over time compared to what is observed immediately after transplantation.

At clinically encountered concentrations, MPA and MPAG are not removed by haemodialysis. However, at high MPAG concentrations (>100 μg/ml), small amounts of MPAG are removed. By interfering with enterohepatic circulation 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.

Pharmacokinetics In Special Populations
Renal impairment
The mean single-dose MPAG AUC was 3- to 6-fold higher in subjects with severe renal impairment than in subjects with mild renal impairment and 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.

Patients with delayed renal graft function post-transplant
In patients with delayed renal graft function post-transplant, mean MPA AUC_{0-12} was comparable to that seen in post-transplant patients without delayed renal 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. Mean plasma MPAG AUC_{0-12} was 2- to 3-fold higher than in post-transplant patients without delayed renal graft function.

In patients with primary non-functioning graft following renal transplantation, plasma concentrations of MPAG accumulated; accumulation of MPA, if any, was much smaller.

Hepatic impairment
Overall, the pharmacokinetics of MPA and MPAG were relatively unaffected by hepatic parenchymal disease in volunteers with alcoholic cirrhosis dosed with oral or intravenous MMF. 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.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core:

Microcrystalline Cellulose, Povidone, Croscarmellose Sodium, Magnesium Stearate

Film coat:

Opadry Complete Film Coating System Y-5R-10272-A Lavender (250mg and 500mg)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

Please refer to the expiry date on the product labels.

6.4 Special Precautions for Storage

Store below 30°C. Store in original container to protect from light and moisture.

6.5 Nature and Content of Container

Mynotil 250mg Film Coated Tablets: Alu/Alu blister of 1x10's, 3x10's, 5x10's, 6x10's, 10x10's, 50x10's, 100x10's, 1x8's, 5x8's, 10x8's, 15x8's, 50x8's and 100x8's tablets packed in the outer carton. Not all pack size will be marketed.

Mynotil 500mg Film Coated Tablets: Alu/Alu blister of 1x10's, 3x10's, 5x10's, 6x10's, 10x10's, 50x10's, 100x10's, 1x8's, 5x8's, 10x8's, 15x8's, 50x8's and 100x8's tablets packed in the outer

carton. Not all pack size will be marketed.

6.6 Special precautions for disposal and other handling

Mycophenolate mofetil has demonstrated teratogenic effects, therefore Mynotil should not be crushed or opened. Patients should also avoid inhalation or contact of the skin or mucous membranes with the powder contained in Mynotil. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.

7 MANUFACTURER

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8 DATE OF REVISION

12/11/2024

Package insert is drafted in Times New Roman with font size of 11, subject to change based on any other legible font and font size.