APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF MEDICINE

MYFENOTIL 250 (Capsules)

WARNING 1:

CONTRAINDICTIONS

MYFENOTIL 250 is contraindicated in pregnancy and lactation, and in women intending to become pregnant (see Section 4.3 and Section 4.8).

WARNING 2:

IMMUNOSUPPRESSION - RISK OF INFECTIONS AND MALIGNANCY

Immunosuppression caused by MYFENOTIL 250 may result in an increased susceptibility to infection and the development of lymphoma and other malignancies, especially of the skin. Only medical practitioners experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should prescribe MYFENOTIL 250. Patients receiving MYFENOTIL 250 should be managed in facilities equipped with adequate laboratory and supportive medical resources. The medical practitioner responsible for maintenance therapy should have complete information as required for the follow-up of the patient.

WARNING 3:

TERATOGENICITY

MYFENOTIL 250 is a potent teratogenic and mutagenic medicine. Congenital malformations and spontaneous abortions have been reported with the use of MYFENOTIL 250 in pregnancy. Women of childbearing potential must have two negative medical practitioner or laboratory supervised serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL (IU/L); and the second test should be performed 8-10 days after the first one and 24 hours before MYFENOTIL 250 therapy is initiated. Repeat pregnancy tests should be performed during routine follow-up visits. Women of childbearing potential should use two reliable forms of contraception simultaneously, including at least one highly effective method, before MYFENOTIL 250 therapy is initiated, during therapy, and for 90 days following discontinuation of therapy; unless abstinence is the chosen method of contraception. Sexually active men are recommended to use condoms during treatment and for 90 days after cessation of treatment. Condom use applies both for reproductively competent and vasectomised men, because the risk associated with the transfer of seminal fluid also apply to men who have had a vasectomy. Female partners of male patients are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of MYFENOTIL 250.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg mycophenolate mofetil.

Sugar free.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules.

White to off white blend of mycophenolate mofetil filled in size 1 hard gelatine capsules with ivory cap and ivory body printed "SAL" on cap and "726" on body in black.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MYFENOTIL 250 is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, hepatic or cardiac transplants. MYFENOTIL 250 should be used concomitantly with ciclosporin and corticosteroids.

4.2 Posology and method of administration

Posology

The initial dose of MYFENOTIL 250 should be given as soon as possible following renal, cardiac or hepatic transplantation.

Dosage for prophylaxis of renal rejection

Adults

The recommended dose is 1 g, administered orally or intravenously (over NO LESS THAN 2 HOURS) twice a day (daily dose of 2 g) is recommended for 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 MYFENOTIL 250, demonstrated an overall better safety profile than patients receiving 3 g/day.

Children aged 3 months to 18 years

Patients with a body surface area of 1,25 to 1,5 m^2 may be prescribed MYFENOTIL 250 capsules at a dose of 750 mg twice daily (1,5 g daily dose). Patients with a body surface area > 1,5 m^2 may be prescribed 500 mg mycophenolate mofetil capsules at a dose of 1 g twice daily (2 g daily dose).

Standard dosage for prophylaxis of cardiac rejection

Adults

A dose of 1,5 g administered orally or intravenously (over NO LESS THAN 2 HOURS), twice a day (daily dose of 3 g), is recommended for use in cardiac transplant patients.

Standard dosage for prophylaxis of hepatic rejection

Adults

A dose of 1 g administered intravenously (over NO LESS THAN 2 HOURS) twice a day (daily dose of 2 g), or 1,5 g administered orally, twice a day (daily dose of 3 g), is recommended for use in hepatic transplant patients.

Standard dosage for treatment of first or refractory renal rejection

Adults

A dose of 1,5 g administered orally or intravenously (over NO LESS THAN 2 HOURS) twice a day (daily dose of 3 g) is recommended for management of first or refractory rejection.

Special Populations

Renal impairment

In patients with severe chronic renal impairment (glomerular filtration rate < 25 mL/min/1,73 m^2), outside of 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 data are available for cardiac or hepatic transplant patients with severe chronic renal impairment. No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively.

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.

Elderly

The recommended dose of 1 g, administered twice a day for renal transplant patients and 1,5 g, twice a day for cardiac and hepatic transplant patients, is appropriate for elderly patients (see Section 4.4).

Patients with neutropenia

If neutropenia develops (absolute neutrophil count <1,3 x $10^9/\ell$), dosing with MYFENOTIL 250 should be interrupted or the dose reduced.

Paediatric population

No data available on the use of this medicine in paediatric transplant patients for cardiac or hepatic transplants, or for the treatment of first or refractory rejection in paediatric renal or other transplant settings

Method of administration

For oral administration.

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

4.3 Contraindications

MYFENOTIL 250 is contraindicated in:

- Hypersensitivity to mycophenolate mofetil, mycophenolic acid or to any of the excipients listed in section 6.1. Allergic reactions to MYFENOTIL 250 have been observed.
- Pregnancy and breastfeeding (see section 4.6).
- Women of childbearing potential not using highly effective methods of contraception (see section 4.6).
- MYFENOTIL 250 is an IMPDH (inosine monophosphate dehydrogenase) inhibitor; and it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmillar syndrome.

4.4 Special warnings and precautions for use

Neoplasms

Patients receiving immunosuppressive regimens involving combinations of medicines, including MYFENOTIL 250, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.8). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific medicine (see BOXED WARNING). 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

The use of immunosuppressive agents, including MYFENOTIL 250, has been associated with an increased risk of opportunistic infections (bacterial, fungal, viral, and protozoal). These may involve the reactivation of latent viruses such as hepatitis B and hepatitis C, and infections linked to polyomaviruses, notably BK virus-associated nephropathy and progressive multifocal leukoencephalopathy (PML) caused by JC virus. Serious life-threatening infections such as

meningitis and infectious endocarditis have been reported and there is evidence of a higher frequency of certain types of infections such as tuberculosis and atypical mycobacterial infection. Patients treated with immunosuppressants, including mycophenolate mofetil as in MYFENOTIL 250, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis (see Section 4.8). Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation and infections caused by polyomaviruses (BK virus associated nephropathy, JC virus associated progressive multifocal leukoencephalopathy PML). Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that medical practitioners should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. Mycophenolic acid has a cytostatic effect on B- and T-lymphocytes, therefore an increased severity of COVID-19 may occur, and appropriate clinical action should be considered.

There have been reports of hypogammaglobulinaemia in association with recurrent infections in patients receiving mycophenolate mofetil as in MYFENOTIL 250 in combination with other immunosuppressants. In some of these cases, switching MYFENOTIL 250 to an alternative immunosuppressant resulted in serum IgG levels returning to normal. Patients on MYFENOTIL 250 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 as in MYFENOTIL 250 in combination with other immunosuppressants. In some of these cases, switching mycophenolate mofetil to another immunosuppressant resulted in

improvement in respiratory symptoms. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect on the lung. There have also been isolated reports of interstitial lung disease and pulmonary fibrosis, some of which were fatal (see Section 4.8). It is recommended that patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, are investigated.

Blood and immune system

Patients receiving MYFENOTIL 250 should be monitored for neutropenia, which may be related to MYFENOTIL 250 itself, concomitant medications, viral infections, or some combination of these causes. Patients taking MYFENOTIL 250 should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If neutropenia develops (absolute neutrophil count < 1,3 x 10^3/µl), it may be appropriate to interrupt or reduce the dose of MYFENOTIL 250 and these patients should be carefully observed.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil as in MYFENOTIL 250 in combination with other immunosuppressants. The mechanism for mycophenolate mofetil induced PRCA is unknown. PRCA may resolve with dose reduction or cessation of MYFENOTIL 250 therapy. Changes to MYFENOTIL 250 therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimise the risk of graft rejection (see section 4.8).

Patients receiving MYFENOTIL 250 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 MYFENOTIL 250, vaccinations may be less effective, and the use of live attenuated vaccines should be avoided (see section 4.5).

Influenza vaccination with killed virus may be of value. Medical practitioners should refer to national guidelines for influenza vaccination.

Gastrointestinal

Mycophenolate mofetil has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, haemorrhage and perforation. MYFENOTIL 250 should be administered with caution in patients with active serious digestive system disease.

MYFENOTIL 250 is an IMPDH (inosine monophosphate dehydrogenase) inhibitor. Therefore, it should not be given to patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome (see section 4.3).

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. Medicines which interfere with MPA's enterohepatic cycle (e.g., cholestyramine, antibiotics) should be used with caution due to their potential to reduce the plasma levels and efficacy of MYFENOTIL 250 (see section 4.5). Therapeutic drug monitoring of MPA may be appropriate when switching combination therapy (e.g., from ciclosporin to tacrolimus or vice versa) or to ensure adequate immunosuppression in patients with high immunological risk (e.g., risk of rejection, treatment with antibiotics, addition, or removal of an interacting medication).

It is recommended that MYFENOTIL 250 should not be administered concomitantly with azathioprine because such concomitant administration has not been studied.

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

Special populations

Administration of doses greater than 1 g twice a day to renal transplant patients with severe chronic renal impairment should be avoided and these patients should be carefully observed. No data is available for cardiac transplant patients with severe chronic renal impairment. In patients with delayed renal graft function post-transplant, mean MPA AUC_{0-12} was comparable, but MPAG AUC_{0-12} was 2 to 3 fold higher, compared to that seen in post-transplant patients without delayed renal graft function. No dose adjustment is recommended for these patients; however, they should be carefully observed (see Section 5.2).

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

Teratogenic effects

Mycophenolate is a powerful human teratogen. Spontaneous abortion (rate of 45 % to 49 %) and congenital malformations (estimated rate of 23 % to 27 %) have been reported following MMF exposure during pregnancy. Therefore, MYFENOTIL 250 is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejection. Female patients of childbearing potential should be made aware of the risks and follow the recommendations provided in section 4.6 (e.g., contraceptive methods, pregnancy testing) prior to, during, and after therapy with MYFENOTIL 250. Medical practitioners 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 medical practitioner if there is a possibility of pregnancy. It is

recommended that MYFENOTIL 250 therapy should not be initiated until a negative pregnancy test has been obtained (see section 4.6).

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 two forms of reliable contraception (see section 4.3 and boxed warning) before starting MYFENOTIL 250 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.

Additional precautions

Patients should not donate blood during therapy or for at least 6 weeks following discontinuation of mycophenolate. Men should not donate semen during therapy or for 90 days following discontinuation of MYFENOTIL 250.

4.5 Interaction with other medicines 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 medicines may occur.

Antacids and proton pump inhibitors (PPIs)

Decreased mycophenolic acid exposure has been observed when antacids, such as magnesium and aluminium hydroxides, and PPIs, including lansoprazole and pantoprazole, were administered with mycophenolate mofetil as in MYFENOTIL 250. 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 as in MYFENOTIL 250 was co-administered with PPIs.

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

Caution should be used with medicines that interfere with enterohepatic recirculation because of their potential to reduce the efficacy of MYFENOTIL 250:

Cholestyramine

Following single dose administration of 1,5 g of mycophenolate mofetil to normal healthy subjects pre-treated with 4 g TID of cholestyramine for 4 days, there was a 40 % reduction in the AUC of MPA (see section 4.4, and section 5.2). Caution should be used during concomitant administration because of the potential to reduce efficacy of MYFENOTIL 250.

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 as in MYFENOTIL 250 and CsA compared with patients receiving sirolimus or belatacept and similar doses of mycophenolate mofetil (see also section 4.4). Conversely, changes of MPA exposure should be

expected when switching patients from CsA to one of the immunosuppressants which does not interfere with MPA's enterohepatic cycle.

Antibiotics

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 first 7 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 MYFENOTIL 250 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 MYFENOTIL 250 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.

Medicines that affect glucuronidation (e.g., isavuconazole, telmisartan)

Concomitant administration of medicines affecting glucuronidation of MPA may change MPA exposure. Caution is therefore recommended when administering these medicines concomitantly with MYFENOTIL 250.

Isavuconazole

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

Telmisartan

Concomitant administration of telmisartan and mycophenolate mofetil

as in MYFENOTIL 250 resulted in an approximately 30 % decrease of MPA concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression, which in turn results in an enhanced uridine diphosphate glucuronyltransferase isoform 1A9 (UGT1A9) expression and activity. When comparing rates of transplant rejection, rates of graft loss or adverse event profiles between mycophenolate mofetil patients with and without concomitant telmisartan medication, no clinical consequences of the pharmacokinetic drug-drug interaction were seen.

Ganciclovir

Based on the results of a single dose administration study of recommended doses of oral mycophenolate and IV ganciclovir and the known effects of renal impairment on the pharmacokinetics of MYFENOTIL 250 and ganciclovir, it is anticipated that co-administration of these medicines (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 MYFENOTIL 250 dose adjustment is not required. In patients with renal impairment in whom MYFENOTIL 250 and ganciclovir or its prodrugs, e.g., valganciclovir, are co-administered, the dose recommendations for ganciclovir should be observed and patients should be monitored carefully.

Oral contraceptives

The pharmacodynamics and pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by co-administration of mycophenolate mofetil as in MYFENOTIL 250 (see also section 5.2).

Rifampicin

In patients not also taking ciclosporin, concomitant administration of mycophenolate mofetil and rifampicin resulted in a decrease in MPA exposure (AUC_{0-12h}) of 18 % to 70 %. It is recommended to monitor MPA exposure levels and to adjust MYFENOTIL 250 doses accordingly to maintain clinical efficacy when rifampicin is administered concomitantly.

Sevelamer

Decrease in MPA C_{max} and AUC_{0-12h} by 30 % and 25 %, respectively, were observed when mycophenolate mofetil was concomitantly administered with sevelamer without any clinical consequences (i.e., graft rejection). It is recommended that sevelamer should be given 2 hours after MYFENOTIL 250 to minimise the impact on the absorption of MPA. There are no data on MYFENOTIL 250 with phosphate binders other than sevelamer.

Tacrolimus

In hepatic transplant patients initiated on mycophenolate mofetil as in MYFENOTIL 250 and tacrolimus, the AUC and C_{max} of MPA, the active metabolite of MYFENOTIL 250, 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 MYFENOTIL 250 (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 MYFENOTIL 250 (see also section 4.4).

Live vaccines

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

Other interactions

Medicines known to undergo renal tubular secretion e.g., probenecid, may compete with MPAG and thereby raise plasma concentrations of MPAG, or the other compound undergoing tubular secretion. Concomitant administration of sevelamer and mycophenolate mofetil as in adults and paediatric patients decreased the MPA C_{max} and AUC_{0-12} by 30 % and 25 % respectively. The data suggests that sevelamer and other calcium free phosphate binders preferentially should be given 2 hours after MYFENOTIL 250 intake to minimise the impact on the absorption of MPA.

4.6 Fertility, pregnancy and lactation

MYFENOTIL 250 is teratogenic and mutagenic. Congenital abnormalities and spontaneous abortions have been reported with the use of MYFENOTIL 250 during pregnancy (see BOXED WARNING).

The following malformations were 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)

4.7 Effects on ability to drive and use machines

MYFENOTIL 250 has moderate influence on the ability to drive and use machines. MYFENOTIL 250 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

a. Tabulated summary of adverse reactions

System Organ Class	**Renal Transplant**	**Hepatic Transplant**	**Cardiac Transplant**
	Frequency		
General disorders and administration site conditions			
Asthenia	Frequent	Frequent	Frequent
Fever	Frequent	Frequent	Frequent
Headache	Frequent	Frequent	Frequent
Infection	Frequent	Frequent	Frequent
Pain (includes abdominal, back, and chest)	Frequent	Frequent	Frequent
Oedema	Frequent	Frequent	Frequent
Sepsis	Frequent	Frequent	Frequent
Chills	-	Frequent	Frequent
Ascites	-	Frequent	-
Enlarged abdomen	Less frequent	Frequent	Less frequent
Hernia	Less frequent	Frequent	Less frequent
Peritonitis	-	Frequent	-

Cysts (including lymphocele and hydrocele)	Less frequent	Less frequent	Less frequent
Facial oedema	Less frequent	-	Less frequent
Flu syndrome	Less frequent	Less frequent	Less frequent
Haemorrhage	Less frequent	Less frequent	Less frequent
Malaise	Less frequent	Less frequent	Less frequent
Pelvic pain	Less frequent	-	Less frequent
Cellulitis	-	Less frequent	Less frequent
Neck pain	-	Less frequent	Less frequent
Pallor	-	-	Less frequent
Abscess	-	Less frequent	-
De novo purine synthesis inhibitors associated acute inflammatory syndrome	Less frequent	Less frequent	Less frequent
Infections and infestations			
Bacterial infections	Frequent	Frequent	Frequent
Fungal infections	Frequent	Frequent	Frequent
Protozoal infections	Less Frequent	Less Frequent	Less Frequent
Viral infections	Frequent	Frequent	Frequent

Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Benign neoplasm of skin	Frequent	Frequent	Frequent
Neoplasm	Frequent	Frequent	Frequent
Skin cancer	Frequent	Less Frequent	Frequent
Lymphoma	Less Frequent	Less Frequent	Less Frequent
Lymphoproliferative disorder	Less Frequent	Less Frequent	Less Frequent
Blood and lymphatic system disorders			
Anaemia (including hypochromic anaemia)	Frequent	Frequent	Frequent
Leucocytosis	Frequent	Frequent	Frequent
Leucopenia	Frequent	Frequent	Frequent
Thrombocytopenia	Frequent	Frequent	Frequent
Ecchymosis	Less frequent	Less frequent	Frequent
Aplasia pure red cell	Less frequent	Less frequent	Less frequent
Bone marrow failure	Less frequent	Less frequent	Less frequent
Polycythaemia	Less frequent	-	-
Petechia	-	-	Less frequent
Prothrombin time increased	-	Less frequent	Less frequent
Thromboplastin time increased	-	-	Less frequent

Pancytopenia	-	Less frequent	-
Pseudolyphoma	Less frequent	Less frequent	Frequent
Metabolism and nutrition disorders			
Hypercholesterolaemia	Frequent	Less frequent	Frequent
Hyperglycaemia	Frequent	Frequent	Frequent
Hyperkalaemia	Frequent	Frequent	Frequent
Hypokalaemia	Frequent	Frequent	Frequent
Hypophosphataemia	Frequent	Frequent	Less frequent
Acidosis (metabolic or respiratory)	Less frequent	Less frequent	Frequent
Alkalosis	-	-	Less frequent
Bilirubinaemia	-	Frequent	Frequent
Elevated blood urea	-	Frequent	Frequent
Elevated creatinine	Less frequent	Frequent	Frequent
Elevated enzyme levels (lactic dehydrogenase, AST and ALT)	Less frequent	Less frequent	Frequent
Hyperlipaemia	Less frequent	Less frequent	Frequent
Hyperuricaemia	Less frequent	-	Frequent
Hypervolaemia	Less frequent	-	Frequent
Hypomagnesaemia	-	Frequent	Frequent

Hyponatraemia	-	Less frequent	Frequent
Weight gain	Less frequent	Less frequent	Frequent
Abnormal healing	-	Frequent	Less frequent
Hypocalcaemia	Less frequent	Frequent	Less frequent
Hypoglycaemia	Less frequent	Frequent	Less frequent
Alkaline phosphatase increased	Less frequent	Less frequent	Less frequent
Dehydration	Less frequent	Less frequent	Less frequent
Elevated enzyme levels (gamma glutamyl transpeptidase)	Less frequent	-	-
Elevated creatinine	Less frequent	Frequent	Frequent
Hypercalcaemia	Less frequent	-	-
Hypovolaemia	-	Less frequent	Less frequent
Hypochloraemia	-	-	Less frequent
Hypoproteinaemia	Less frequent	Frequent	Less frequent
Thirst	-	-	Less frequent

Weight Loss	-	-	Less frequent
Gout	-	-	Less frequent
Hypoxia	-	Less frequent	Less frequent
Hyperphosphataemia	-	Less frequent	-
Hypercholesteraemia	-	Less frequent	-
Psychiatric disorders			
Insomnia	Frequent	Frequent	Frequent
Anxiety	Less frequent	Frequent	Frequent
Depression	Less frequent	Frequent	Frequent
Somnolence	Less frequent	Less frequent	Frequent
Emotional lability	-	-	Less frequent
Hallucinations	-	-	Less frequent
Abnormal thinking	-	Less frequent	Less frequent
Delirium	-	Less frequent	-
Psychosis	-	Less frequent	-
Confusional state	Frequent	Frequent	Frequent
Agitation	Less frequent	Frequent	Frequent
Nervous system disorders			
Dizziness	Frequent	Frequent	Frequent

Tremor	Frequent	Frequent	Frequent
Agitation	-		Frequent
Confusion	-	Frequent	Frequent
Hypertonia	Less frequent	-	Frequent
Paraesthesia	Less frequent	Frequent	Frequent
Convulsion	-	-	Less frequent
Neuropathy	-	-	Less frequent
Vertigo	-	-	Less frequent
Agitation	-	Less frequent	-
Convulsion	-	Less frequent	-
Dry mouth	-	Less frequent	-
Hyperaesthesia	-	Less frequent	-
Neuropathy	-	Less frequent	-
Cardiac disorders			
Hypertension	Frequent	Frequent	Frequent
Dysrhythmia	-	Less frequent	Frequent
Bradycardia	-	Less frequent	Frequent
Cardiac failure	-	-	Frequent

Hypotension	Less frequent	Frequent	Frequent
Pericardial effusion	-	-	Frequent
Tachycardia	Less frequent	Frequent	-
Angina pectoris	Less frequent	-	Less frequent
Atrial fibrillation	Less frequent	Less frequent	Less frequent
Postural hypotension	Less frequent	-	Less frequent
Thrombosis	Less frequent	-	-
Vasodilatation	Less frequent	Less frequent	-
Dysrhythmias (including supraventricular and ventricular extrasystoles)	-	Less frequent	Less frequent
Atrial flutter	-	-	Less frequent
Supraventricular and ventricular tachycardias)	-	-	Less frequent
Arterial thrombosis	-	Less frequent	-
Atrial fibrillation	-	Less frequent	-
Syncope	-	Less frequent	Less frequent
Cardiac arrest	-	-	Less frequent
Congestive heart failure	-	-	Less frequent
Postural hypotension	-	-	Less frequent

Pulmonary hypertension	-	-	Less frequent
Vasospasm	-	-	Less frequent
Venous pressure increased	-	-	Less frequent
Lymphocele	Less frequent	Less frequent	Less frequent
Vascular disorders			
Hypertension	Frequent	Frequent	Frequent
Hypotension	Frequent	Frequent	Frequent
Venous thrombosis	Frequent	Frequent	Frequent
Vasodilatation	Frequent	Frequent	Frequent
Lymphocele	Less frequent	Less frequent	Less frequent
Respiratory, thoracic and mediastinal disorders			
Cough increased	Frequent	Frequent	Frequent
Dyspnoea	Frequent	Frequent	Frequent
Pharyngitis	Frequent	Frequent	Frequent
Pneumonia	Frequent	Frequent	Frequent
Bronchiectasis	Frequent	Frequent	Frequent
Bronchitis	Frequent	Less frequent	Less frequent
Asthma	Less frequent	Less frequent	Frequent
Pleural effusion	Less frequent	Frequent	Frequent
Rhinitis	Less frequent	Less frequent	Frequent
Sinusitis	Less frequent	Frequent	Frequent

Apnoea	-	Less frequent	Less frequent
Atelectasis	Less frequent	Frequent	Less frequent
Interstitial lung disease	Less frequent	Less frequent	Less frequent
Pulmonary fibrosis	Less frequent	Less frequent	Less frequent
Epistaxis	-	Less frequent	Less frequent
Haemoptysis	-	-	Less frequent
Hiccough	-	-	Less frequent
Neoplasm	-	-	Less frequent
Pneumothorax	-	-	Less frequent
Pulmonary oedema	-	Less frequent	Less frequent
Sputum increased	-	-	Less frequent
Voice alteration	-	-	Less frequent
Hyperventilation	-	Less frequent	-
Respiratory moniliasis	-	Less frequent	-
Gastrointestinal disorders			
Constipation	Frequent	Frequent	Frequent
Diarrhoea	Frequent	Frequent	Frequent
Dyspepsia	Frequent	Frequent	Frequent

Nausea	Frequent	Frequent	Frequent
Vomiting	Frequent	Frequent	Frequent
Decreased appetite	Frequent	Less frequent	Less frequent
Abdominal distention	Frequent	Frequent	Frequent
Oral moniliasis	Frequent	Frequent	Frequent
Flatulence	Less frequent	Frequent	Frequent
Elevated liver function tests (incl. AST, ALT)	Less frequent	Frequent	Less frequent
Anorexia	Less frequent	Frequent	Less frequent
Cholangitis	Less frequent	Frequent	Less frequent
Cholestatic jaundice	Less frequent	Frequent	Less frequent
Hepatitis	Less frequent	Frequent	-
Dysphagia	-	-	Less frequent
Gastroenteritis	Less frequent	-	Less frequent
Gastrointestinal haemorrhage	Less frequent	Less frequent	-
Gastrointestinal moniliasis	Less frequent	-	-
Gingivitis	Less frequent	-	Less frequent
Gum hyperplasia	-	-	Less frequent
Jaundice	-	-	Less frequent

Ileus	Less frequent	Less frequent	-
Melaena	-	Less frequent	Less frequent
Oesophagitis	Less frequent	Less frequent	Less frequent
Stomatitis	Less frequent	-	Less frequent
Stomach ulcer	-	-	Less frequent
Mouth ulceration	-	Less frequent	-
Gastritis	-	Less frequent	-
Rectal disorder	-	Less frequent	-
Pancreatitis	Less frequent	Frequent	Less frequent
Eructation	Less frequent	Less frequent	Less frequent
Immune system disorders			
Hypersensitivity	Less Frequent	Frequent	Frequent
Hypogammaglobulinaemia	Less Frequent	Less Frequent	Less Frequent
Hepatobiliary disorders			
Blood alkaline phosphatase increased	Frequent	Frequent	Frequent
Blood lactate dehydrogenase increased	Frequent	Less Frequent	Frequent
Hepatic enzyme increased	Frequent	Frequent	Frequent
Hepatitis	Frequent	Frequent	Less Frequent
Hyperbilirubinaemia	Frequent	Frequent	Frequent

Jaundice	Less Frequent	Frequent	Frequent
Skin and subcutaneous tissue disorders			
Acne	Frequent	Less frequent	Frequent
Herpes simplex	Frequent	Less frequent	Frequent
Herpes zoster	Less frequent	Less frequent	Frequent
Rash	Less frequent	Frequent	Frequent
Pruritus	Less frequent	Frequent	Less frequent
Sweating	Less frequent	Frequent	Less frequent
Alopecia	Less frequent	-	-
Benign neoplasm of skin	Less frequent	Less frequent	Less frequent
Fungal dermatitis	Less frequent	Less frequent	Less frequent
Hirsutism	Less frequent	Less frequent	-
Skin carcinoma	Less frequent	-	Less frequent
Skin hypertrophy (incl. Actinic keratosis)	Less frequent	-	Less frequent
Skin ulcer	Less frequent	Less frequent	Less frequent
Haemorrhage	-	Less frequent	Less frequent
Skin hypertrophy	-	-	-
Hirsutism	-	-	-
Vesiculobullous rash	-	Less frequent	-

Musculoskeletal and connective tissue disorders			
Leg cramps	Less frequent	Less frequent	Frequent
Myalgia	Less frequent	Less frequent	Frequent
Myasthenia	Less frequent	Less frequent	Frequent
Arthralgia	Less frequent	Less frequent	Less frequent
Muscle weakness	Frequent	Frequent	Less frequent
Osteoporosis	-	Less frequent	-
Renal and urinary disorders			
Haematuria	Frequent	Less frequent	Less frequent
Renal tubular necrosis	Frequent	-	-
Urinary tract infection	Frequent	-	-
Abnormal kidney function (decrease in renal function, elevated serum creatinine)	-	Frequent	Frequent
Oliguria	-	Frequent	Frequent
Urinary tract infection	Frequent	Frequent	Frequent
Albuminuria	Less frequent	-	-
Dysuria	Less frequent	Less frequent	Less frequent
Hydronephrosis	Less frequent	-	-
Impotence	Less frequent	-	Less frequent
Pyelonephritis	Less frequent	-	-

Nocturia	-	-	Less frequent
Renal failure	-	Less frequent	Less frequent
Urinary frequency	Less frequent	Less frequent	Less frequent
Urinary incontinence	-	Less frequent	Less frequent
Urinary retention	-	-	Less frequent
Acute renal failure	-	Less frequent	-
Scrotal oedema	-	Less frequent	-
Endocrine disorders			
Diabetes mellitus	Less frequent	Less frequent	Less frequent
Parathyroid disorder (elevated PTH level)	Less frequent	-	-
Cushing's syndrome	-	Less frequent	-
Hypothyroidism	-	Less frequent	-
Eye disorders			
Amblyopia (lazy eye)	Less frequent	-	Frequent
Cataract	Less frequent	-	-
Conjunctivitis	Less frequent	Less frequent	Less frequent
Abnormal vision	-	Less frequent	Less frequent
Eye haemorrhage	-	-	Less frequent

Ear and labyrinth disorders			
Deafness	-	Less frequent	Less frequent
Ear pain	-	-	Less frequent
Tinnitus	-	-	Less frequent

c. Description of selected adverse reactions

Malignancies

Patients receiving immunosuppressive regimens involving combinations of medicines, including MYFENOTIL 250, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.4). Three-year safety data in renal and cardiac transplant patients did not reveal any unexpected changes in incidence of malignancy compared to the 1-year data. Hepatic transplant patients were followed for at least 1 year, but less than 3 years.

Infections

All patients treated with immunosuppressants are at increased risk of bacterial, viral and fungal infections (some of which may lead to a fatal outcome), including those caused by opportunistic agents and latent viral reactivation. The risk increases with total immunosuppressive load (see section 4.4). The most serious infections were sepsis, peritonitis, meningitis, endocarditis, tuberculosis and atypical mycobacterial infection. The most common opportunistic infections in patients receiving mycophenolate (2 g or 3 g daily) with other immunosuppressants in controlled clinical trials in renal, cardiac and hepatic transplant patients followed for at least 1 year were candida mucocutaneous, CMV viraemia/syndrome and Herpes simplex. The proportion of patients with CMV viraemia/syndrome was 13,5 %. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including MYFENOTIL 250.

Blood and lymphatic disorders

Cytopenia's, including leucopenia, anaemia, thrombocytopenia and pancytopenia, are known risks associated with mycophenolate mofetil and may lead or contribute to the occurrence of infections and haemorrhages (see section 4.4). Agranulocytosis and neutropenia have been reported; therefore, regular monitoring of patients taking MYFENOTIL 250 is advised (see section 4.4). There have been reports of aplastic anaemia and bone marrow failure in patients treated with mycophenolate, some of which have been fatal. Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil (see section 4.4). Isolated cases of abnormal neutrophil morphology, including the acquired Pelger-Huet anomaly, have been observed in patients treated with mycophenolate mofetil. These changes are not associated with impaired neutrophil function. These changes may suggest a 'left shift' in the maturity of neutrophils in haematological investigations, which may be mistakenly interpreted as a sign of infection in immunosuppressed patients such as those that receive MYFENOTIL 250.

Gastrointestinal disorders

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

Hypersensitivity

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

Pregnancy, puerperium and perinatal conditions

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

Congenital disorders

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

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 frequently during the pivotal trials. Musculoskeletal pain such as myalgia, and neck and back pain were also frequently 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 mycophenolate mofetil treatment.

Special populations

Paediatric population

The type and frequency of adverse reactions in a clinical study, which recruited 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 MYFENOTIL 250 as part of a combination immunosuppressive regimen may be at increased risk of certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared to younger individuals.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In cases of overdose, side effects would be exacerbated and exaggerated (see section 4.6). Reports of overdose with mycophenolate mofetil have been received from clinical trials and during post-marketing experience. Overdose of mycophenolate mofetil may result in oversuppression of the immune system and could increase susceptibility to infections and bone marrow suppression.

If neutropenia develops, dosing with MYFENOTIL 250 should be interrupted or the dose reduced. MPA cannot be removed by haemodialysis. However, at high MPAG plasma concentrations (> 100 mg/mL) small amounts of MPAG are removed. By increasing excretion of the medicine, MPA can be removed by bile acid sequestrants, such as cholestyramine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A. 34 Immuno-suppressants - Other

Pharmacotherapeutic group: Immunosuppressive Agents

ATC Code: L04AA06

Mechanism of action

Mycophenolate mofetil is the 2-morpholinoethyl ester of MPA. MPA is a selective, uncompetitive and reversible inhibitor of IMPDH, and therefore inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. 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. 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 utilise salvage pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells.

In addition to its inhibition of IMPDH and the resulting deprivation of lymphocytes, MPA also influences cellular checkpoints responsible for metabolic programming of lymphocytes. It has been shown, using human CD4+ T-cells, that MPA shifts transcriptional activities in lymphocytes from a

proliferative state to catabolic processes relevant to metabolism and survival leading to an anergic state of T-cells, whereby the cells become unresponsive to their specific antigen.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, MPA. As evidenced by suppression of acute rejection following renal transplantation, the immunosuppressant activity of mycophenolate mofetil is correlated with MPA concentration. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94 % relative to IV mycophenolate mofetil. Food had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1,5 g BID to renal transplant patients. However, MPA C_{max} was decreased by 40 % in the presence of food. Mycophenolate mofetil can be measured during intravenous infusion; however, after oral administration it is below the limit of quantification (0,4 µg/mL).

Distribution

As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed at approximately 6 – 12 hours post-dose. A reduction in the AUC of MPA of approximately 40 % is associated with the co-administration of cholestyramine (4 g TID), indicating that there is a significant amount of enterohepatic recirculation. MPA at clinically relevant concentrations is 97 % bound to plasma albumin. In the early post-transplant period (< 40 days post-transplant), renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30 % lower and C_{max} approximately 40 % lower compared to the late post-transplant period (3 - 6 months post-transplant).

Biotransformation

MPA is metabolised principally by glucuronyl transferase (isoform UGT1A9) to form the inactive phenolic glucuronide of MPA (MPAG). *In vivo*, MPAG is converted back to free MPA via enterohepatic recirculation. A minor acylglucuronide (AcMPAG) is also formed. AcMPAG is pharmacologically active and is suspected to be responsible for some of MMF's side effects (diarrhoea, leucopenia).

Elimination

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

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

MPA's disposition depends on several transporters. Organic anion-transporting polypeptides (OATPs) and multidrug resistance-associated protein 2 (MRP2) are involved in MPA's disposition; OATP isoforms, MRP2 and breast cancer resistance protein (BCRP) are transporters associated with the glucuronides' biliary excretion. Multidrug resistance protein 1 (MDR1) is also able to transport MPA, but its contribution seems to be confined to the absorption process. In the kidney, MPA and its metabolites potently interact with renal organic anion transporters.

Enterohepatic recirculation interferes with accurate determination of MPA's disposition parameters; only apparent values can be indicated. In healthy volunteers and patients with autoimmune disease approximate clearance values of 10,6 L/h and 8,27 L/h respectively and half-life values of 17 h were observed. In transplant patients mean clearance values were higher (range 11,9 – 34,9 L/h) and mean half-life values shorter (5 - 11 h) with little difference between renal, hepatic or cardiac transplant patients. In the individual patients, these elimination parameters vary based on type of co-treatment with other immunosuppressants, time post-transplantation, plasma albumin concentration and renal function. These factors explain why reduced exposure is seen when mycophenolate mofetil is co-administered with cyclosporine (see section 4.5) and why plasma concentrations tend to increase over time compared to what is observed immediately after transplantation.

Special populations

Renal impairment

In a single dose study, mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate <25 mL/min/1,73 m^2) were 28 – 75 % higher relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. The mean single dose MPAG AUC was 3 – 6-fold higher in subjects with severe renal impairment than in subjects with mild renal impairment or normal healthy subjects, consistent with the known renal elimination of MPAG. Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Delayed renal graft function

In patients with delayed renal graft function post-transplant, mean MPA

AUC_{0-12h} was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC_{0-12h} was 2 – 3-fold higher than in post-transplant patients without delayed

graft function. In patients with primary renal non-functioning graft following renal transplantation, plasma concentrations of MPAG accumulated; accumulation of MPA, if any, was much smaller. 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 paediatric renal transplant patients (aged 2 to 18 years) given 600 mg/m^2 mycophenolate mofetil orally twice daily. This dose achieved MPA AUC values similar to those seen in adult renal transplant patients receiving mycophenolate mofetil at a dose of 1 g BID in the early and late post-transplant period. MPA AUC values across age groups were similar in the early and late post-transplant period.

Elderly

The pharmacokinetics of mycophenolate mofetil and its metabolites have not been found to be altered in the elderly patients (≥ 65 years) when compared to younger 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 non-transplant women (not taking other immunosuppressants) over 3 consecutive menstrual cycles showed no clinically relevant influence of mycophenolate mofetil on the ovulation-suppressing action of the oral contraceptives. Serum levels of LH, FSH and progesterone were not significantly affected. The pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by co-administration of mycophenolate mofetil (see also section 4.5).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Filling

Microcrystalline cellulose (Avicel-PH 101)

Croscarmellose sodium (AC-DI-SOL)

Povidone (K-30)

Magnesium stearate

Capsule (Cap and Body)

Gelatine

Titanium dioxide (E171)

Iron oxide yellow (E172)

FD & C Red 3 (E127)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original container in order to protect form light and moisture.

6.5 Nature and contents of container

MYFENOTIL 250 is packed in white opaque HDPE containers with ribbed screw white opaque polypropylene closures.

Pack sizes: 100, 120 or 500.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDERS OF CERTIFICATE OF REGISTRATION

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2031

8 REGISTRATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

23 June 2026

10 DATE OF REVISION OF THE TEXT