

# Data Sheet

## **MYACCORD**

Mycophenolate mofetil  
Immunosuppressant; inosine monophosphate dehydrogenase (IMPDH)  
inhibitor

## **Pharmaceutical Form**

### **Oral administration**

Myaccord is supplied as capsules and tablets.

## **Qualitative and Quantitative Composition**

### **Active ingredient**

Mycophenolate mofetil.

### ***Oral administration***

Each capsule contains 250 mg mycophenolate mofetil.

Each tablet contains 500 mg mycophenolate mofetil. Do not halve tablet.

Dose equivalence when the tablet is divided has not been established.

## **Appearance**

*Myaccord capsules 250 mg:* Light blue/peach, hard gelatin capsules with two bar lines on cap and body containing white to off white powder.

*Myaccord tablets 500 mg:* Purple coloured, capsule shaped, biconvex, film coated tablets engraved 'AHI' on one side and '500' on the other side.

## **Clinical Particulars**

### **Therapeutic Indications**

Myaccord is indicated for the prophylaxis of acute organ rejection in patients receiving allogeneic renal transplants.

Myaccord is indicated for the prophylaxis of acute organ rejection in patients receiving allogeneic cardiac transplants. In the treated population, MMF improved survival in the first year after transplantation.

Myaccord is indicated for the prophylaxis of acute organ rejection in patients receiving allogeneic hepatic transplants.

Myaccord should be used concomitantly with ciclosporin and corticosteroids.

## **Dosage and Method of Administration**

Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

## **Standard Dosage**

### ***Standard dosage for prophylaxis of renal rejection***

#### *Adults*

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/day of mycophenolate mofetil demonstrated an overall better safety profile compared to patients receiving 3g/day of mycophenolate mofetil.

#### *Children (aged 3 months to 18 years)*

Patients with a body surface area of 1.25 to 1.5 m<sup>2</sup> may be prescribed Myaccord capsules at a dose of 750 mg twice daily (1.5 g daily dose). Patients with a body surface area > 1.5 m<sup>2</sup> may be prescribed Myaccord tablets at a dose of 1g twice daily (2 g daily dose).

### ***Standard dosage for prophylaxis of cardiac rejection***

#### *Adults*

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

#### *Children*

No data are available for paediatric cardiac transplant patients.

### ***Standard dosage for prophylaxis of hepatic rejection***

#### *Adults*

A dose of 1.5 g orally twice a day (daily dose of 3 g) is recommended for use in hepatic transplant patients.

#### *Children*

No data are available for paediatric hepatic transplant patients.

### ***Oral administration (see Bioequivalence)***

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

## **Special Dosage Instructions**

### ***Patients with neutropenia***

If neutropenia develops (absolute neutrophil count <1.3 x 10<sup>3</sup>/μl), dosing with Myaccord should be interrupted or the dose reduced (See Warnings and Precautions).

## **Contraindications**

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

## **Warnings and Precautions**

Female patients of childbearing potential must use effective contraception for four weeks before, during and for six weeks after receiving Myaccord. The use of Myaccord is not recommended during pregnancy and should be reserved for cases where no suitable alternate treatment is available. Myaccord should be used in pregnant women only if the potential benefits outweigh the potential risks to the foetus (see Pregnancy and Nursing mothers).

As in all patients receiving immunosuppressive regimens involving combinations of medicines, patients receiving Myaccord as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see Undesirable Effects). 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.

Patients receiving Myaccord should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

Oversuppression of the immune system can also increase susceptibility to infection including opportunistic infections, fatal infections and sepsis (see Undesirable Effects).

Such infections included latent viral reactivation, such as by polyomaviruses. Cases of Progressive Multifocal Leukoencephalopathy (PML), associated with JC virus, sometimes fatal, have been reported in mycophenolate mofetil-treated patients. The reported cases generally had risk factors for PML, including concomitant immunosuppressant therapies and impaired immune function. In immunosuppressed patients reporting neurological symptoms, physicians should consider PML in the differential diagnosis and consult with a Neurologist 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. Reduction in immunosuppression should be considered for patients who develop evidence of BK virus-associated nephropathy.

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 should be advised that during treatment with Myaccord vaccinations may be less effective and the use of live attenuated vaccines should be avoided (See Interactions with other Medicinal Products and other Forms of Interaction). Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

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

Because Myaccord is an inosine monophosphate dehydrogenase (IMPDH) inhibitor, on theoretical grounds it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

It is recommended that Myaccord 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.

In view of the significant reduction in the AUC of MPA by cholestyramine, caution should be used in the concomitant administration of Myaccord with medicines that interfere with enterohepatic recirculation because of their potential to reduce the efficacy of Myaccord (see Interactions with other Medicinal Products and other Forms of Interaction).

Administration of doses greater than 1 g bid to renal patients with severe chronic renal impairment should be avoided (see Pharmacokinetic Properties and Special Dosage Instructions).

No dose adjustment is recommended for post-transplant patients with delayed renal graft function but patients should be carefully monitored (see Pharmacokinetic Properties and Special Dosage Instructions). No data are available for cardiac or hepatic transplant patients with severe renal impairment.

Elderly patients may be at an increased risk of adverse events compared with younger individuals (see Undesirable Effects).

### **Laboratory monitoring**

Patients on Myaccord 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 Myaccord should be monitored for neutropenia. The development of neutropenia may be

related to Myaccord, concomitant medications, viral infection or some combination of these causes (see Special Dosage Instructions). If neutropenia develops (absolute neutrophil count  $<1.3 \times 10^3/\mu\text{l}$ ), dosing with Myaccord should be interrupted or the dose reduced and the patient should be carefully observed (see Special Dosage Instructions).

## **Interactions with other Medical Products and other Forms of Interaction**

### ***Aciclovir***

Higher MPAG (the phenolic glucuronide of MPA) and aciclovir plasma concentrations were observed when mycophenolate mofetil was administered with aciclovir than when the medicines were administered alone. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are aciclovir concentrations, the potential exists for mycophenolate and aciclovir or its prodrugs e.g. valaciclovir to compete for tubular secretion, further increasing the concentrations of both substances.

### ***Antacids with magnesium and aluminium hydroxides***

Absorption of mycophenolate mofetil was decreased when it was administered with antacids.

### ***Cholestyramine***

Following single-dose administration of 1.5 g of mycophenolate mofetil to normal healthy subjects pretreated with 4 g tid of cholestyramine for 4 days, there was a 40% reduction in the AUC of MPA. Caution should be used during concomitant administration or with medicines that interfere with enterohepatic circulation (see Special Warnings and Special Precautions for Use).

### ***Ciclosporin A (CsA)***

CsA pharmacokinetics were unaffected by mycophenolate mofetil. However, in renal transplant patients concomitant administration of mycophenolate mofetil and CsA resulted in reduced MPA exposures by 30-50% compared with patients receiving the combination of sirolimus and similar doses of mycophenolate Mofetil.

### ***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 MMF (see Pharmacokinetic Properties and Warnings and Precautions) 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 which MMF and ganciclovir or its prodrugs e.g. valganciclovir are co-administered, patients should be monitored carefully.

### ***Oral contraceptives***

The pharmacokinetics of oral contraceptives were unaffected by coadministration of mycophenolate mofetil. A study of co-administration of mycophenolate mofetil (1 g bid) 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 - 0.10mg) 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. Although the long-term effect of mycophenolate mofetil dosing on the pharmacokinetics of oral contraceptives is not known, the free concentration of MPA remains relatively constant over time. Therefore, it is unlikely the efficacy of oral contraceptives would be adversely affected (see Pregnancy and Nursing mothers).

### ***Rifampicin***

After correction for dose, a 70% decrease in MPA exposure ( $AUC_{0-12\text{ h}}$ ) 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 Myaccord doses accordingly to maintain clinical efficacy when the medicines are administered concomitantly.

### ***Tacrolimus***

Exposure to tacrolimus concomitantly administered with mycophenolate mofetil had no effect on the AUC or  $C_{\text{max}}$  of MPA in liver transplant recipients. A similar finding was observed in a recent study in kidney 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 of approximately 20% in tacrolimus AUC when multiple doses of mycophenolate mofetil (1.5 g bid) were administered to patients taking tacrolimus.

### ***Trimethoprim/sulphamethoxazole***

No effect on the bioavailability of MPA was observed.

### ***Norfloxacin and Metronidazole***

No effect on the systemic exposure of MPA was observed when mycophenolate mofetil was concomitantly administered with any antibiotic separately. In contrast, the combination of norfloxacin and metronidazole reduced the MPA  $AUC_{0-48}$  by 30% following a single dose of mycophenolate mofetil.

### ***Ciprofloxacin and 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, the clinical relevance of these observations is unclear.

### ***Other interactions***

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

Concomitant administration of sevelamer and mycophenolate mofetil in adults and paediatric patients decreased the MPA C<sub>max</sub> and AUC<sub>0-12</sub> by 30% and 25%, respectively. This data suggest that sevelamer and other calcium free phosphate binders preferentially should be given 2 hours after Myaccord intake to minimise the impact on the absorption of MPA.

### ***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 Warnings and Precautions).

### **Use in Special Populations**

#### **Pregnancy**

Pregnancy Category D.

Adverse effects on foetal development (including malformations) occurred when pregnant rats and rabbits were dosed during organogenesis. These responses occurred at doses lower than those associated with maternal toxicity, and at doses below the recommended clinical dose for renal, cardiac or hepatic transplantation.

There are no adequate and well-controlled studies in pregnant women conducted with mycophenolate mofetil. However, post-marketing data from the US National Transplant Pregnancy Registry (NTPR) indicated that use of mycophenolate mofetil is associated with an increased risk of congenital malformations. Therefore, Myaccord should be avoided in pregnant women unless the potential benefits outweigh the potential risks to the foetus. Congenital malformations, including ear malformations i.e. abnormally formed or absent external/middle ear, have been reported in children of patients exposed to mycophenolate mofetil in combination with other immunosuppressant agents during pregnancy.

Women of childbearing potential should have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 1 week prior to beginning therapy. It is recommended that Myaccord therapy should not be

initiated by the physician until a report of a negative pregnancy test has been obtained.

Mycophenolate mofetil may slightly reduce the blood levels of oral contraceptives; however, there is no clinically relevant alteration in serum progesterone, LH and FSH levels. This suggests that efficacy of the oral contraceptives are unlikely to be reduced (see Interactions with other Medicinal Products and other Forms of Interaction).

Effective contraception must be used for four weeks before beginning Myaccord therapy, during therapy, and for 6 weeks following discontinuation of therapy, even where there has been a history of infertility, unless due to hysterectomy. Two reliable forms of contraception must be used simultaneously unless abstinence is the chosen method (see Interactions with other Medicinal Products and other Forms of Interaction). If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy.

### **Nursing mothers**

Studies in rats have shown mycophenolate mofetil to be excreted in milk. It is not known whether it is excreted in human milk. Because many medicines are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from mycophenolate mofetil, a decision should be made whether to discontinue nursing or to discontinue the medicine, taking into account the importance of mycophenolate mofetil to the mother.

### **Geriatric use**

The recommended oral doses of 1 g bid for renal transplant patients and 1.5 g bid for cardiac or hepatic transplant patients are appropriate for elderly patients (see Warnings and Precautions).

### **Renal impairment**

#### **Patients with severe renal impairment**

In renal transplant patients with severe chronic renal impairment (glomerular filtration rate  $<25$  ml/min/1.73m<sup>2</sup>) outside of the immediate post-transplant period or after treatment of acute rejection, doses greater than 1 g administered twice a day should be avoided (see Warnings and Precautions).

No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

#### **Patients with delayed renal graft function post-transplant**

No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively (see Pharmacokinetic Properties).

## **Hepatic impairment**

### **Patients with severe hepatic impairment**

No dose adjustments are needed for renal patients with severe hepatic parenchymal disease (see Pharmacokinetic Properties).

No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

### **Undesirable Effects**

The adverse event profile associated with the use of immunosuppressive medicines is often difficult to establish owing to the presence of underlying diseases and the concurrent use of many other medications.

### **Clinical Trials**

The principal adverse reactions associated with the administration of mycophenolate mofetil in the prevention of renal, cardiac and hepatic transplant rejection in combination with ciclosporin and corticosteroids include diarrhoea, leucopenia, sepsis and vomiting, and there is evidence of a higher frequency of certain types of infection, e.g. opportunistic infections (see Warnings and Precautions).

The safety profile of mycophenolate mofetil in patients treated for refractory renal transplant rejection was similar to that observed in three controlled trials for prevention of renal rejection at doses of 3 g per day. Diarrhoea and leucopenia, followed by anaemia, nausea, abdominal pain, sepsis, nausea and vomiting, and dyspepsia were the predominant adverse events reported in patients receiving mycophenolate mofetil in comparison to patients receiving IV corticosteroids.

### ***Malignancies***

As in patients receiving immunosuppressive regimes involving combinations of medicines, patients receiving mycophenolate mofetil as part of an immunosuppressive regime are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see Warnings and Precautions).

Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving mycophenolate mofetil (2 g or 3 g daily) in combination with other immunosuppressants in controlled clinical trials of renal, cardiac and hepatic transplant patients followed for at least 1 year. Non-melanoma skin carcinoma occurred in 1.6% to 4.2% of patients; other types of malignancy occurred in 0.7% to 2.1% of patients. Three-year safety data in renal and cardiac transplant patients did not reveal any unexpected changes in the incidence of malignancy compared to the 1-year data. Hepatic transplant patients were followed for at least 1 year, but less than 3 years.

In controlled trials of treatment of refractory renal rejection, the lymphoma rate was 3.9% at an average follow-up of 42 months.

### **Opportunistic infections**

All transplant patients are at increased risk of opportunistic infections. The risk increased with total immunosuppressive load (see Warnings and Precautions). The most common opportunistic infections in patients receiving mycophenolate mofetil (2 g or 3 g daily) with other immunosuppressants in controlled clinical trials of renal (2 g data), 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%.

### **Children (aged 3-months to 18 years)**

The type and frequency of adverse reactions in a clinical study of 100 paediatric patients aged 3 months to 18 years given 600 mg/m<sup>2</sup> 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 occurred with a frequency of  $\geq 10\%$  in children and were more frequent in the paediatric population, particularly in children under 6 years of age, when the frequency of treatment-related adverse events were compared to adults: diarrhoea, leucopenia, sepsis, infection, anaemia.

### **Elderly patients ( $\geq 65$ years)**

Elderly patients, particularly those who are receiving Myaccord as part of a combination immunosuppressive regimen, may be at greater increased risk of certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared to younger individuals (see Warnings and Precautions).

### **Safety profile of Mycophenolate Mofetil following oral administration**

Adverse events reported in  $\geq 10\%$  and in 3 to  $< 10\%$  of patients treated with mycophenolate mofetil in controlled trials for prevention of renal transplant rejection (3 trials, 2 g and 3 g data), one controlled cardiac transplant trial, and one controlled hepatic transplant trial are listed in the table below.

### **Adverse Events Reported in $\geq 10\%$ and in 3% to $< 10\%$ of Patients Treated with Mycophenolate Mofetil in Clinical Trials in Adults when Used in Combination with Ciclosporin and Corticosteroids**

Body System		Adverse Events Reported in Renal Transplant Patients (n = 991) *	Adverse Events Reported in Cardiac Transplant Patients (n = 289) **	Adverse Events Reported in Hepatic Transplant Patients (n = 277) ***
Body as a whole	$\geq 10\%$	asthenia, fever, headache, infection, pain (includes abdominal, back, and chest), oedema, sepsis	asthenia, fever, chills, headache, infection, pain (includes abdominal, back, and chest), oedema, sepsis	ascites, asthenia, chills, enlarged abdomen, fever, headache, hernia, infection, pain

Body System		Adverse Events Reported in Renal Transplant Patients (n = 991) *	Adverse Events Reported in Cardiac Transplant Patients (n = 289) **	Adverse Events Reported in Hepatic Transplant Patients (n = 277) ***
				(includes abdominal, back and chest), oedema, peritonitis, sepsis
	3 - < 10%	cysts (including lymphocele and hydrocele), enlarged abdomen, facial oedema, flu syndrome, haemorrhage, hernia, malaise, pelvic pain	cellulitis, cysts (including lymphocele and hydrocele), enlarged abdomen, facial oedema, flu syndrome, haemorrhage, hernia, malaise, neck pain, pallor, pelvic pain	abscess, cellulitis, cyst (including lymphocele and hydrocele), flu syndrome, haemorrhage, malaise, neck pain
Blood and lymphatic	≥ 10%	anaemia (including hypochromic anaemia), leucocytosis, leucopenia, thrombocytopenia	anaemia (including hypochromic anaemia), ecchymosis, leucocytosis, leucopenia, thrombocytopenia	anaemia (including hypochromic anaemia), leucocytosis, leucopenia, thrombocytopenia
	3 - < 10%	ecchymosis, polycythaemia	petechia, prothrombin time increased, thromboplastin time increased	ecchymosis, pancytopenia, prothrombin time increased
Urogenital	≥ 10%	haematuria, renal tubular necrosis, urinary tract infection	abnormal kidney function (decrease in renal function, elevated serum creatinine), oliguria, urinary tract infection	abnormal kidney function (decrease in renal function, elevated serum creatinine), oliguria, urinary tract infection
	3 - < 10%	albuminuria, dysuria, hydronephrosis, impotence, pyelonephritis, urinary frequency	dysuria, haematuria, impotence, nocturia, renal failure, urinary frequency, urinary incontinence, urinary retention	acute renal failure, dysuria, haematuria renal failure, scrotal oedema, urinary frequency, urinary incontinence
Cardio-vascular	≥ 10%	hypertension	arrhythmia, bradycardia, cardiac failure, hypertension, hypotension, pericardial effusion	hypertension, hypotension, tachycardia
	3 - < 10%	angina pectoris, atrial fibrillation,	angina pectoris, arrhythmias (including	arterial thrombosis, atrial fibrillation,

Body System		Adverse Events Reported in Renal Transplant Patients (n = 991) *	Adverse Events Reported in Cardiac Transplant Patients (n = 289) **	Adverse Events Reported in Hepatic Transplant Patients (n = 277) ***
		hypotension, postural hypotension, tachycardia, thrombosis, vasodilatation	supraventricular and ventricular extrasystoles, atrial flutter, supraventricular and ventricular tachycardias), atrial fibrillation, cardiac arrest, congestive heart failure, postural hypotension, pulmonary hypertension, syncope, vasospasm, venous pressure increased	arrhythmia, bradycardia, vasodilatation, syncope
Metabolic/ Nutritional	≥ 10%	hypercholesterolaemia, hyperglycaemia, hyperkalaemia, hypokalaemia, hypophosphataemia	Acidosis (metabolic or respiratory), bilirubinaemia, elevated BUN, elevated creatinine, elevated enzyme levels (lactic dehydrogenase, SGOT and SGPT), hypercholesterolaemia, hyperglycaemia, hyperkalaemia, hyperlipaemia, hyperuricaemia, hypervolaemia, hypokalaemia, hypomagnesaemia, hyponatraemia, weight gain	bilirubinaemia, elevated BUN, elevated creatinine, healing abnormal, hyperglycaemia, hyperkalaemia, hypocalcaemia, hypokalaemia, hypoglycaemia, hypomagnesaemia, hypophosphataemia, hypoproteinaemia,
	3 - < 10%	acidosis (metabolic or respiratory), alkaline phosphatase increased, dehydration, elevated enzyme levels (gamma glutamyl transpeptidase, lactic dehydrogenase, SGOT and SGPT), elevated creatinine,	abnormal healing, alkaline phosphatase increased, alkalosis, dehydration, gout, hypocalcaemia, hypochloraemia, hypoglycaemia, hypoproteinaemia, hypophosphataemia, hypovolaemia, hypoxia, respiratory	acidosis (metabolic or respiratory), alkaline phosphatase increased, dehydration, elevated enzyme levels (SGOT and SGPT), hypercholesterolaemia, hyperlipaemia, hyperphosphataemia, hypervolaemia,

Body System		Adverse Events Reported in Renal Transplant Patients (n = 991) *	Adverse Events Reported in Cardiac Transplant Patients (n = 289) **	Adverse Events Reported in Hepatic Transplant Patients (n = 277) ***
		hypercalcaemia, hyperlipaemia, hypervolaemia, hypocalcaemia, hypoglycaemia, hypoproteinaemia, hyperuricaemia, weight gain	acidosis, thirst, weight loss	hyponatraemia, hypoxia, hypovolaemia, weight gain, weight loss
Gastro-intestinal	≥10%	constipation, diarrhoea, dyspepsia, nausea and vomiting, oral moniliasis	constipation, diarrhoea, dyspepsia, flatulence, nausea and vomiting, oral moniliasis	elevated liver function tests (incl. AST, ALT), anorexia, cholangitis, cholestatic jaundice constipation, diarrhoea, dyspepsia, flatulence, hepatitis, nausea and vomiting, oral moniliasis
	3 - < 10%	elevated liver function tests (incl. AST, ALT), anorexia, flatulence, gastroenteritis, gastrointestinal haemorrhage, gastrointestinal moniliasis, gingivitis, gum hyperplasia, hepatitis, ileus, oesophagitis, stomatitis	elevated liver function tests (incl. AST, ALT), anorexia, dysphagia, gastroenteritis, gingivitis, gum hyperplasia, jaundice, melaena, oesophagitis, stomatitis	dysphagia, gastritis, gastrointestinal haemorrhage, ileus, jaundice, melaena, mouth ulceration, oesophagitis, rectal disorder, stomach ulcer
Respiratory	≥ 10%	cough increased, dyspnoea, pharyngitis, pneumonia, bronchitis	asthma, cough increased, dyspnoea, pharyngitis, pleural effusion, pneumonia, rhinitis, sinusitis	atelectasis, cough increased, dyspnoea, pharyngitis, pleural effusion, pneumonia, sinusitis
	3 - < 10%	asthma, pleural effusion, pulmonary oedema, rhinitis, sinusitis	apnoea, atelectasis, bronchitis, epistaxis, haemoptysis, hiccough, neoplasm, pneumothorax, pulmonary oedema, sputum increased, voice alteration	asthma, bronchitis, epistaxis, hyperventilation, pneumothorax, pulmonary oedema, respiratory moniliasis, rhinitis

<b>Body System</b>		<b>Adverse Events Reported in Renal Transplant Patients (n = 991) *</b>	<b>Adverse Events Reported in Cardiac Transplant Patients (n = 289) **</b>	<b>Adverse Events Reported in Hepatic Transplant Patients (n = 277) ***</b>
Skin and Appendages	≥ 10%	acne, herpes simplex	acne, herpes simplex, herpes zoster, rash	pruritus, rash, sweating
	3 - < 10%	alopecia, benign neoplasm of skin, fungal dermatitis, herpes zoster, hirsutism, pruritus, skin carcinoma, skin hypertrophy (incl. actinic keratosis), sweating, skin ulcer, rash	benign neoplasm of skin, fungal dermatitis, haemorrhage, pruritus, skin carcinoma, skin hypertrophy, skin ulcer, sweating	acne, fungal dermatitis, haemorrhage, herpes simplex, herpes zoster, hirsutism, skin benign neoplasm, skin ulcer, vesiculobullous rash
Nervous	≥ 10%	dizziness, insomnia, tremor	agitation, anxiety, confusion, depression, dizziness, hypertonia, insomnia, paraesthesia, somnolence, tremor	anxiety, confusion, depression, dizziness, insomnia, paraesthesia, tremor
	3 - < 10%	anxiety, depression, hypertonia, paraesthesia, somnolence	convulsion, emotional lability, hallucinations, neuropathy, thinking abnormal, vertigo	agitation, convulsion, delirium, dry mouth, hypertonia, hypesthesia, neuropathy, psychosis, somnolence, thinking abnormal
Musculo-skeletal	≥ 10%	-	leg cramps, myalgia, myasthenia	-
	3 - < 10%	arthralgia, leg cramps, myalgia, myasthenia	arthralgia	arthralgia, leg cramps, myalgia, myasthenia osteoporosis
Special Senses	≥ 10%	-	amblyopia	-
	3 - < 10%	amblyopia, cataract, conjunctivitis	abnormal vision, conjunctivitis, deafness, ear pain, eye haemorrhage, tinnitus	abnormal vision, amblyopia, conjunctivitis, deafness
Endocrine	≥ 10%	-	-	-
	3 - < 10%	diabetes mellitus, parathyroid disorder	diabetes mellitus, Cushing's syndrome,	diabetes mellitus

Body System	Adverse Events Reported in Renal Transplant Patients (n = 991) *	Adverse Events Reported in Cardiac Transplant Patients (n = 289) **	Adverse Events Reported in Hepatic Transplant Patients (n = 277) ***
	(elevated PTH level)	hypothyroidism	

\*(total n=1,483) \*\* (total n=578) \*\*\* (total n=564)

In the three controlled trials for prevention of renal transplant rejection, patients receiving 2 g per day of mycophenolate mofetil demonstrated an overall better safety profile than did patients receiving 3 g mycophenolate mofetil.

### Post-Marketing Experience

*Gastro-intestinal:* colitis (sometimes caused by cytomegalovirus), pancreatitis, isolated cases of intestinal villous atrophy.

*Disorders of immunosuppression:* Serious life-threatening infections such as meningitis and infectious endocarditis have been reported occasionally and there is evidence of a higher frequency of certain types of infections such as tuberculosis and atypical mycobacterial infection.

Cases of Progressive Multifocal Leukoencephalopathy (PML), sometimes fatal, have been reported in mycophenolate mofetil-treated patients. The reported cases generally had risk factors for PML, including concomitant immunosuppressant therapies and impaired immune function.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil in combination with other immunosuppressive agents.

BK virus-associated nephropathy has been observed in patients treated with mycophenolate mofetil. This infection can be associated with serious outcomes, sometimes leading to renal graft loss.

*Congenital disorders:* The use of mycophenolate mofetil in combination with other immunosuppressant agents during pregnancy is associated with an increased risk of congenital malformations, especially: external ear abnormalities, facial abnormalities (including cleft lip and palate) and abnormalities of the distal limbs, heart, oesophagus and kidney.

Other adverse reactions during post-marketing experience with mycophenolate mofetil are similar to those seen in the controlled renal, cardiac and hepatic transplant studies.

### Overdose

Reports of overdoses with mycophenolate mofetil have been received from clinical trials and during post-marketing experience. In many of these cases no adverse events were reported. In those overdose cases in which adverse events were reported, the events fall within the known safety profile of the 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 (see Warnings and Precautions). If neutropenia develops, dosing with Myaccord should be interrupted or the dose reduced (see Warnings and Precautions).

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 medicine (see Pharmacokinetic Properties).

## **Pharmacological Properties & Effects**

### **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. 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.

#### **Efficacy / Clinical Studies**

Mycophenolate mofetil has been administered in combination with the following agents in clinical trials for the prevention of renal, cardiac and hepatic rejection episodes: antithymocyte globulin, OKT3, ciclosporin and corticosteroids. Prior to treatment with mycophenolate mofetil, patients may have also received antilymphocyte globulin, antithymocyte globulin and OKT3. Mycophenolate mofetil has further been used in clinical trials together with daclizumab and tacrolimus.

#### ***Prevention of organ rejection***

##### ***Adults***

The safety and efficacy of mycophenolate mofetil in combination with corticosteroids and ciclosporin for the prevention of organ rejection were assessed in renal transplant patients in three randomised, double-blind, multicentre trials, in cardiac patients in one randomised double-blind, multicentre trial, and in hepatic patients in one randomised, double-blind, multicentre trial.

## Children

The safety, pharmacokinetics and efficacy of mycophenolate mofetil in combination with corticosteroids and ciclosporin for the prevention of organ rejection in paediatric renal transplant patients were assessed in an open-label, multicentre study in 100 patients (aged 3-months to 18 years).

## **Renal transplant**

### *Adults*

The three studies compared two dose levels of oral mycophenolate mofetil (1 g bid and 1.5 g bid) with azathioprine (2 studies) or placebo (1 study) when administered in combination with ciclosporin and corticosteroids to prevent acute rejection episodes.

The primary efficacy endpoint was the proportion of patients in each treatment group who experienced treatment failure within the first 6 months after transplantation (defined as biopsy-proven acute rejection on treatment or the occurrence of death, graft loss or early termination from the study for any reason without prior biopsy-proven rejection). Mycophenolate mofetil was studied in the following three therapeutic regimens: (1) antithymocyte globulin induction/MMF or azathioprine/ciclosporin/corticosteroids, (2) MMF or azathioprine/ciclosporin/corticosteroids, and (3) MMF or placebo/ciclosporin/corticosteroids.

Mycophenolate mofetil, in combination with corticosteroids and ciclosporin reduced (statistically significant at the  $< 0.05$  level) the incidence of treatment failure within the first 6 months following transplantation. The following tables summarise the results of these studies. Patients who prematurely discontinued treatment were followed for the occurrence of death or graft loss, and the cumulative incidence of graft loss and patient death are summarised separately. Patients who prematurely discontinued treatment were not followed for the occurrence of acute rejection after termination. More patients receiving mycophenolate mofetil discontinued (without prior biopsy-proven rejection, death or graft loss) than discontinued in the control groups, with the highest rate in the mycophenolate mofetil 3 g/day group. Therefore, the acute rejection rates may be underestimates, particularly in the mycophenolate mofetil 3 g/day group.

### **Renal Transplant Studies Incidence of Treatment Failure (Biopsy-proven Rejection or Early Termination for Any Reason)**

<b>USA Study* (N=499 patients)</b>	<b>Mycophenolate Mofetil 2 g/day (n=167 patients)</b>	<b>Mycophenolate Mofetil 3 g/day (n=166 patients)</b>	<b>Azathioprine 1 to 2 mg/kg/day (n=166 patients)</b>
All treatment failures	31.1%	31.3%	47.6%

<b>USA Study* (N=499 patients)</b>	<b>Mycophenolate Mofetil 2 g/day (n=167 patients)</b>	<b>Mycophenolate Mofetil 3 g/day (n=166 patients)</b>	<b>Azathioprine 1 to 2 mg/kg/day (n=166 patients)</b>
Early termination without prior acute rejection**	9.6%	12.7%	6.0%
Biopsy-proven rejection episode on treatment	19.8%	17.5%	38.0%

\* antithymocyte globulin induction/MMF or azathioprine/ciclosporin/corticosteroids

<b>Europe/Canada/Australia Study* (N=503 patients)</b>	<b>Mycophenolate Mofetil 2 g/day (n=173 patients)</b>	<b>Mycophenolate Mofetil 3 g/day (n=164 patients)</b>	<b>Azathioprine 100 to 150 mg/day (n=166 patients)</b>
All treatment failures	38.2%	34.8%	50.0%
Early termination without prior acute rejection**	13.9%	15.2%	10.2%
Biopsy-proven rejection episode on treatment	19.7%	15.9%	35.5%

\* MMF or azathioprine/ciclosporin/corticosteroids

<b>Europe Study* (N=491 patients)</b>	<b>Mycophenolate Mofetil 2 g/day (n=165 patients)</b>	<b>Mycophenolate Mofetil 3 g/day (n=160 patients)</b>	<b>Placebo (n=166 patients)</b>
All treatment failures	30.3%	38.8%	56.0%
Early termination without prior acute rejection**	11.5%	22.5%	7.2%
Biopsy-proven rejection episode on treatment	17.0%	13.8%	46.4%

\* MMF or placebo/ciclosporin/corticosteroids

\*\* Does not include death and graft loss as reason for early termination.

Cumulative incidence of 12-month graft loss and patient death are presented below. No advantage of mycophenolate mofetil with respect to graft loss and patient death was established. Numerically, patients receiving mycophenolate mofetil 2 g/day and 3 g/day experienced a better outcome than controls in all three studies; patients receiving mycophenolate mofetil 2 g/day experienced a better outcome than mycophenolate mofetil 3 g/day in two of the three

studies. Patients in all treatment groups who terminated treatment early were found to have a poor outcome with respect to graft loss and patient death at 1 year.

**Renal Transplant Studies  
Cumulative Incidence of Combined Graft Loss  
and Patient Death at 12 Months**

<b>Study</b>	<b>Mycophenolate Mofetil 2 g/day</b>	<b>Mycophenolate Mofetil 3 g/day</b>	<b>Control (Azathioprine or Placebo)</b>
USA	8.5%	11.5%	12.2%
Europe/Canada/Australia	11.7%	11.0%	13.6%
Europe	8.5%	10.0%	11.5%

*Children (aged 3 months to 18 years)*

One open-label, safety, pharmacokinetics and efficacy study of mycophenolate mofetil in another dose form (powder for oral suspension) in combination with ciclosporin and corticosteroids for the prevention of renal allograft rejection was performed in 100 paediatric patients (aged 3 months to 18 years) at centres in the US (9), Europe (5) and Australia (1). Mycophenolate mofetil was dosed at 600 mg/m<sup>2</sup> bid (up to 1 g bid) in all age groups.

The primary efficacy endpoint was the proportion of patients experiencing an acute rejection episode in the first 6 months post transplant. The rate of biopsy-proven rejection was similar across the age groups (3 months to < 6 years, 6 years to < 12 years, 12 years to 18 years). The overall biopsy-proven rejection rate at 6 months was comparable to adults. The combined incidence of graft loss (5%) and patient death (2%) at 12 months post-transplant was similar to that observed in adult renal transplant patients.

***Cardiac transplant***

A double-blind, randomised, comparative, parallel-group, multicentre study was performed in primary cardiac transplant recipients. The total number of patients enrolled was 650; 72 never received the study medicine and 578 received the study medicine. Patients received mycophenolate mofetil 1.5 g bid (n=289) or azathioprine 1.5 to 3 mg/kg/day (n=289), in combination with ciclosporin and corticosteroids as maintenance immunosuppressive therapy. The two primary efficacy endpoints were: (1) the proportion of patients who, after transplantation, had at least one endomyocardial biopsy-proven rejection with haemodynamic compromise, or were retransplanted or died, within the first 6 months, and (2) the proportion of patients who died or were transplanted during the first 12 months following transplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection for up to 6 months and for the occurrence of death for 1 year.

1. *Rejection*: No difference was established between mycophenolate mofetil and azathioprine (AZA) with respect to biopsy-proven rejection with haemodynamic compromise, as presented below.

	Rejection at 6 Months			
	All Patients		Treated Patients	
	AZA N = 323	Mycophenolate Mofetil N = 327	AZA N = 289	Mycophenolate Mofetil N = 289
Biopsy-proven rejection with haemodynamic compromise*	121 (38%)	120 (37%)	100 (35%)	92 (32%)

2. \* Haemodynamic compromise occurred if any of the following criteria were met: pulmonary capillary wedge pressure  $\geq 20$ mm or a 25% increase; cardiac index  $< 2.0$  l/min/m<sup>2</sup> or a 25% decrease; ejection fraction  $\leq 30\%$ ; pulmonary artery oxygen saturation  $\leq 60\%$  or a 25% decrease; presence of new S<sub>3</sub> gallop; fractional shortening was  $\leq 20\%$  or a 25% decrease; inotropic support required to manage the clinical condition.

3. *Survival*: In the enrolled patients, there were no statistically significant differences between patients randomised to MMF and patients randomised to AZA for death and retransplantation. In patients who received study medicine, the lower limit of the 97.5% confidence interval of the difference of death and retransplantation was 0.9 at 1 year, indicating that MMF was superior to AZA in these patients, as presented below.

	Death or Retransplantation at 1 Year			
	All Patients		Treated Patients	
	AZA N = 323	Mycophenolate Mofetil N = 327	AZA N = 289	Mycophenolate Mofetil N = 289
Death or Retransplantation	49 (15.2%)	42 (12.8%)	33 (11.4%)	18 (6.2%)
Weighted Treatment Difference	2.6%		5.3%	
Lower Limit of 97.5% one-sided Confidence Interval	-2.5%		+0.9%	

### ***Hepatic transplant***

A double-blind, randomised, comparative, parallel-group, multicentre study in primary hepatic transplant recipients was performed at 16 centres in the United States, 2 in Canada, 4 in Europe and 1 in Australia. The total number of patients enrolled was 565 and 564 received study medicine. Patients either received mycophenolate mofetil 1 g bid intravenously for up to 14 days followed by mycophenolate mofetil 1.5 g bid orally or azathioprine 1 mg - 2 mg/kg/day intravenously followed by azathioprine 1 mg - 2 mg/kg/day orally, in combination with ciclosporin and corticosteroids as maintenance immunosuppressive therapy. The two primary endpoints were: (1) the proportion of patients who experienced, in the first 6 months post transplantation, one or more episodes of biopsy-proven and treated rejection or death/retransplantation, and (2) the proportion of patients who experienced graft loss (death/retransplantation) during the first 12 months post-transplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection and for the occurrence of graft loss (death/retransplantation) for 1 year. Results: In the primary (intent-to-treat) analyses mycophenolate mofetil in combination with corticosteroids and ciclosporin was superior to azathioprine for prevention of acute rejection ( $p = 0.025$ ) and equivalent to azathioprine for survival.

	<b>Rejection at 6 Months / Death or Retransplantation at 1 Year</b>	
	<b>AZA N = 287</b>	<b>Mycophenolate Mofetil N = 278</b>
Biopsy proven, treated rejection at 6 months	137 (47.7%)	107 (38.5%)
Death or retransplantation at 1 year	42 (14.6%)	41 (14.7%)

### ***Treatment of refractory organ rejection***

A randomised, open-label comparison study of MMF 3 g per day against intravenous corticosteroids was conducted in 150 renal transplant recipients with refractory, acute, cellular allograft rejection. The primary endpoint was the proportion of patients who were still alive with a functioning graft at 6 months after study entry.

Results: The incidence of graft loss in the control group was unexpectedly low and the primary analysis, based on the sequential probability ratio test showed a trend toward improved graft survival in the MMF group ( $p = 0.081$ ). A secondary analysis, using the Cochran-Mantel-Haenzel test (not adjusted for sequential monitoring) suggested a 45% reduction in the incidence of graft loss or death at 6 months after study entry in the MMF arm ( $p = 0.062$ ).

	<b>Graft Loss or Death at 6 Months</b>	
	<b>IV Steroids N = 73</b>	<b>Mycophenolate Mofetil N = 77</b>
Graft Loss or death at 6 months	19 (26.0%)	11 (14.3%)

## **Pharmacokinetic Properties**

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

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 IV MMF dose have similar MPA levels compared to renal transplant patients receiving 1 g oral or IV MMF.

### **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 IV mycophenolate mofetil. Mycophenolate mofetil can be measured systemically during intravenous infusion; however, after oral administration it is below the limit of quantitation (0.4 mcg/ml).

Immediately post-transplant (< 40 days) renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30% lower and C<sub>max</sub> approximately 40% lower compared to the late transplant period (3 to 6 months post-transplant). MPA AUC values obtained following administration of 1 g bid 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 bid intravenous mycophenolate mofetil followed by 1.5 g bid oral mycophenolate mofetil resulted in MPA AUC values similar to those found in renal transplant patients administered 1 g mycophenolate mofetil bid.

Food had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil administered at doses of 1.5 g bid to renal transplant patients. However, MPA C<sub>max</sub> was decreased by 40% in the presence of food.

### **Distribution**

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

At clinically relevant concentrations, MPA is 97% bound to plasma albumin.

### **Metabolism**

MPA is conjugated primarily with glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG), which is not pharmacologically active. *In vivo*, MPAG is converted to free MPA via enterohepatic recirculation.

### **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 faeces. Most (about 87%) of a dose is excreted in the urine as MPAG. A negligible amount of medicine (< 1% of dose) is excreted as MPA in the urine.

At clinically encountered concentrations, MPA and MPAG are not removed by haemodialysis. However, at high MPAG concentrations (> 100 mcg/mL), small amounts of MPAG are removed. By interfering with enterohepatic circulation of the medicine, bile acid sequestrants, such as cholestyramine, reduce MPA AUC (see Overdose).

### **Bioequivalence**

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.

### **Pharmacokinetics in Special Populations**

#### ***Patients with severe renal impairment***

In a single-dose study (6 subjects per group), mean plasma MPA AUCs observed after oral dosing in subjects with severe chronic renal impairment (glomerular filtration rate < 25 ml/min/1.73m<sup>2</sup>) were 28 to 75% higher than those observed in normal healthy subjects or subjects with lesser degrees of renal impairment. However, 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<sub>0-12</sub> 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 (see Special Dosage Instructions). Mean plasma MPAG AUC<sub>0-12</sub> 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.

#### ***Patients with 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.

### ***Children (aged ≤ 18 years)***

Pharmacokinetic parameters were evaluated in 55 paediatric renal transplant patients (ranging from 1 to 18 years of age) given 600 mg/m<sup>2</sup> mycophenolate mofetil orally twice daily (up to a maximum of 1 g 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 twice daily 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 (≥ 65 years)***

Pharmacokinetics in the elderly has not been formally evaluated.

### **Preclinical Safety**

The haematopoietic and lymphoid systems were the primary organs affected in toxicology studies conducted with mycophenolate mofetil in the rat, mouse, dog and monkey. These effects occurred at systemic exposure levels that are equivalent to or less than the clinical exposure at the recommended dose of 2 g/day for renal transplant recipients. Gastrointestinal effects were observed in the dog at systemic exposure levels equivalent to or less than the clinical exposure at the recommended doses. Gastrointestinal and renal effects consistent with dehydration were also observed in the monkey at the highest dose (systemic exposure levels equivalent to or greater than clinical exposure). The nonclinical toxicity profile of mycophenolate mofetil appears to be consistent with adverse events observed in human clinical trials which now provide safety data of more relevance to the patient population (see Undesirable Effects).

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. The systemic exposure at this dose represents 2 to 3 times the clinical exposure at the recommended clinical dose of 2 g/day in renal transplant patients and 1.3 to 2 times the clinical exposure at the recommended clinical dose of 3 g/day in cardiac transplant patients. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (including anophthalmia, agnathia, and hydrocephaly) in the first generation offspring in the absence of maternal toxicity. The systemic exposure at this dose was approximately 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

In teratology studies in rats and rabbits, foetal resorptions and malformations occurred in rats at 6 mg/kg/day (including anophthalmia, agnathia, and hydrocephaly) and in rabbits at 90 mg/kg/day (including cardiovascular and renal anomalies, such as ectopia cordis and ectopic kidneys, and diaphragmatic and umbilical hernia), in the absence of maternal toxicity. The

systemic exposure at these levels are approximately equivalent to or less than 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients (see Pregnancy and Nursing mothers).

In experimental models, mycophenolate mofetil was not tumourigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2 - 3 times the systemic exposure (AUC or C<sub>max</sub>) observed in renal transplant patients at the recommended clinical dose of 2 g/day and 1.3 - 2 times the systemic exposure (AUC or C<sub>max</sub>) observed in cardiac transplant patients at the recommended clinical dose of 3 g/day. Two genotoxicity assays (the mouse lymphoma/thymidine kinase assay and the mouse micronucleus aberration assay) indicated a potential of mycophenolate mofetil to cause chromosomal instability at severely cytotoxic dose levels. Other genotoxicity tests (the bacterial mutation assay, the yeast mitotic gene conversion assay or the Chinese hamster ovary cell chromosomal aberration assay) did not demonstrate mutagenic activity.

## ***Pharmaceutical Particulars***

### **List of Excipients**

*Myaccord capsules 250 mg*: contains the excipients cellulose microcrystalline (Avicel PH 101), hydroxyl propyl cellulose, povidone K-90, croscarmellose sodium, talc, magnesium stearate and purified water. The capsule shells contain gelatin, FD & C blue, iron oxide yellow, iron oxide red, titanium dioxide, sodium lauryl sulphate and purified water. The printing ink contains black iron oxide, potassium hydroxide, shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution and purified water.

*Myaccord tablets 500 mg*: contains the excipients microcrystalline cellulose, croscarmellose sodium, povidone, talc, magnesium stearate, hydroxypropyl cellulose, opadry 03B50110 purple and purified water.

### **Stability**

This medicine should not be used after the expiry date shown on the pack.

### **Special Remarks**

#### **Special Precautions for Storage**

*Myaccord capsules*: Store below 25°C, store in the original package.

*Myaccord tablets*: Store below 25°C, store in the original container.

### **Instructions for Use, Handling and Disposal**

#### ***Myaccord oral administration***

Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits (see Pregnancy and Nursing mothers), *Myaccord* tablets should not be crushed or divided, and *Myaccord* capsules should not be opened or

crushed. Avoid inhalation or direct contact with skin or mucous membranes of the powder contained in Myaccord capsules. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.

***Packs***

*Myaccord 250 mg capsules:* Packs of 30, 90 and 100.

*Myaccord 500 mg tablets:* Packs of 50 and 100.

***Medicine Classification***

Prescription Medicine

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***Date of Preparation***

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