

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Myclausen 500 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg mycophenolate mofetil.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet

White round film-coated tablets.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Myclausen is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

### 4.2 Posology and method of administration

Treatment should be initiated and maintained by appropriately qualified transplant specialists.

#### Posology

##### Use in renal transplant

###### *Adults*

Treatment should be initiated within 72 hours following transplantation. The recommended dose in renal transplant patients is 1 g administered twice daily (2 g daily dose).

###### *Paediatric population aged 2 to 18 years*

The recommended dose of mycophenolate mofetil is 600 mg/m<sup>2</sup> administered orally twice daily (up to a maximum of 2 g daily). Tablets should only be prescribed to patients with a body surface area greater than 1.5 m<sup>2</sup>, at a dose of 1 g twice daily (2 g daily dose). As some adverse reactions occur with greater frequency in this age group (see section 4.8) compared with adults, temporary dose reduction or interruption may be required; these will need to take into account relevant clinical factors including severity of reaction.

###### *Paediatric population < 2 years*

There are limited safety and efficacy data in children below the age of 2 years. These are insufficient to make dosage recommendations and therefore use in this age group is not recommended.

##### Use in cardiac transplant

###### *Adults*

Treatment should be initiated within 5 days following transplantation. The recommended dose in cardiac transplant patients is 1.5 g administered twice daily (3 g daily dose).

###### *Paediatric population*

No data are available for paediatric cardiac transplant patients.

#### Use in hepatic transplant

##### *Adults*

Intravenous (IV) mycophenolate mofetil should be administered for the first 4 days following hepatic transplant, with oral Myclausen initiated as soon after this as it can be tolerated. The recommended oral dose in hepatic transplant patients is 1.5 g administered twice daily (3 g daily dose).

##### *Paediatric population*

No data are available for paediatric hepatic transplant patients.

#### Use in special populations

##### *Elderly*

The recommended dose of 1 g administered twice a day for renal transplant patients and 1.5 g twice a day for cardiac or hepatic transplant patients is appropriate for the elderly.

##### *Renal impairment*

In renal transplant patients with severe chronic renal impairment (glomerular filtration rate  $< 25$  mL/min/1.73 m<sup>2</sup>), outside the immediate post-transplant period, doses greater than 1 g administered twice a day should be avoided. These patients should also be carefully observed. No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively (see section 5.2). No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

##### *Severe hepatic impairment*

No dose adjustments are needed for renal transplant patients with severe hepatic parenchymal disease. No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

##### *Treatment during rejection episodes*

Mycophenolic acid (MPA) is the active metabolite of mycophenolate mofetil. Renal transplant rejection does not lead to changes in MPA pharmacokinetics; dosage reduction or interruption of Myclausen is not required. There is no basis for Myclausen dose adjustment following cardiac transplant rejection. No pharmacokinetic data are available during hepatic transplant rejection.

##### *Paediatric population*

No data are available for treatment of first or refractory rejection in paediatric transplant patients.

#### Method of administration

For oral use. The film-coated tablets should be swallowed whole with a glass of water.

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

Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits, film-coated tablets should not be broken or crushed.

### **4.3 Contraindications**

- Myclausen should not be given to patients with hypersensitivity to mycophenolate mofetil, mycophenolic acid or to any of the excipients listed in section 6.1. Hypersensitivity reactions to mycophenolate mofetil have been observed (see section 4.8).
- Myclausen should not be given to women of childbearing potential who are not using highly effective contraception (see section 4.6).
- Myclausen treatment should not be initiated in women of child bearing potential without

providing a pregnancy test result to rule out unintended use in pregnancy (see section 4.6).

- Myclausen should not be used during pregnancy unless there is no suitable alternative treatment to prevent transplant rejection (see section 4.6).
- Myclausen should not be given to women who are breast-feeding (see section 4.6).

#### **4.4 Special warnings and precautions for use**

##### Neoplasms

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including Myclausen, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.8). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As general advice to minimise the risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

##### Infections

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

There have been reports of hypogammaglobulinaemia in association with recurrent infections in patients receiving mycophenolate mofetil in combination with other immunosuppressants. In some of these cases switching mycophenolate mofetil to an alternative immunosuppressant resulted in serum IgG levels returning to normal. Patients on Myclausen who develop recurrent infections should have their serum immunoglobulins measured. In cases of sustained, clinically relevant hypogammaglobulinaemia, appropriate clinical action should be considered taking into account the potent cytostatic effects that mycophenolic acid has on T- and B-lymphocytes.

There have been published reports of bronchiectasis in adults and children who received mycophenolate mofetil in combination with other immunosuppressants. In some of these cases switching mycophenolate mofetil to another immunosuppressant resulted in improvement in respiratory symptoms. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect on the lung. There have also been isolated reports of interstitial lung disease and pulmonary fibrosis, some of which were fatal (see section 4.8). It is recommended that patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, are investigated.

##### Blood and immune system

Patients receiving Myclausen should be monitored for neutropenia, which may be related to Myclausen itself, concomitant medications, viral infections, or some combination of these causes. Patients taking Myclausen 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  $< 1.3 \times 10^3/\mu\text{l}$ ), it may be appropriate to interrupt or discontinue Myclausen.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil in combination with other immunosuppressants. The mechanism for mycophenolate mofetil induced PRCA is unknown. PRCA may resolve with dose reduction or cessation of Myclausen therapy. Changes to Myclausen 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 Myclausen 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 Myclausen, vaccinations may be less effective, and the use of live attenuated vaccines should be avoided (see section 4.5). Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

### Gastro-intestinal

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

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

### Interactions

Caution should be exercised when switching combination therapy from regimens containing immunosuppressants, which interfere with MPA enterohepatic recirculation, e.g. ciclosporin, to others devoid of this effect, e.g. tacrolimus, sirolimus, belatacept, or vice versa, as this might result in changes of MPA exposure. Drugs which interfere with MPA's enterohepatic cycle (e.g. cholestyramine, antibiotics) should be used with caution due to their potential to reduce the plasma level and efficacy of Myclausen (see also section 4.5). Therapeutic drug monitoring of MPA may be appropriate when switching combination therapy (e.g. from ciclosporin to tacrolimus or vice versa) or to ensure adequate immunosuppression in patients with high immunological risk (e.g. risk of rejection, treatment with antibiotics, addition or removal of an interacting medication).

It is recommended that Myclausen 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 also section 4.5).

### Special populations

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

### Teratogenic effects

Mycophenolate is a powerful human teratogen. Spontaneous abortion (rate of 45% to 49%) and congenital malformations (estimated rate of 23% to 27%) have been reported following MMF exposure during pregnancy. Therefore Myclausen 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 Myclausen. Physicians should ensure that women taking mycophenolate understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult their physician if there is a possibility of pregnancy.

#### Contraception (see section 4.6)

Because of robust clinical evidence showing a high risk of abortion and congenital malformations when mycophenolate mofetil is used in pregnancy, every effort to avoid pregnancy during treatment should be taken. Therefore, women with childbearing potential must use at least one form of reliable contraception (see section 4.3) before starting Myclausen therapy, during therapy, and for six weeks after stopping the therapy, unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred to minimise the potential for contraceptive failure and unintended pregnancy.

For contraception advice for men see section 4.6.

#### Educational materials

In order to assist patients in avoiding foetal exposure to mycophenolate and to provide additional important safety information, the Marketing Authorisation holder will provide educational materials to healthcare professionals. The educational materials will reinforce the warnings about the teratogenicity of mycophenolate, provide advice on contraception before therapy is started and guidance on the need for pregnancy testing. Full patient information about the teratogenic risk and the pregnancy prevention measures should be given by the physician to women of childbearing potential and, as appropriate, to male patients.

#### Additional precautions

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

#### Sodium contents

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

### **4.5 Interaction with other medicinal products and other forms of interaction**

#### Aciclovir

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

#### Antacids and proton pump inhibitors (PPIs)

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

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

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

#### 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 Myclausen.

#### Ciclosporin A

Ciclosporin A (CsA) pharmacokinetics are unaffected by mycophenolate mofetil. In contrast, if concomitant CsA treatment is stopped, an increase in MPA AUC of around 30 % should be expected. CsA interferes with MPA enterohepatic recycling, resulting in reduced MPA exposures by 30 - 50 % in renal transplant patients treated with mycophenolate mofetil and CsA compared with patients receiving sirolimus or belatacept and similar doses of mycophenolate mofetil (see also section 4.4). Conversely, changes of MPA exposure should be expected when switching patients from CsA to one of the immunosuppressants which does not interfere with MPA's enterohepatic cycle.

Antibiotics eliminating  $\beta$ -glucuronidase-producing bacteria in the intestine (e.g. aminoglycoside, cephalosporin, fluoroquinolone, and penicillin classes of antibiotics) may interfere with MPAG/MPA enterohepatic recirculation, thus leading to reduced systemic MPA exposure. Information concerning the following antibiotics is available:

#### Ciprofloxacin or amoxicillin plus clavulanic acid

Reductions in pre-dose (trough) MPA concentrations of about 50% have been reported in renal transplant recipients in the days immediately following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. This effect tended to diminish with continued antibiotic use and to cease within a few days of antibiotic discontinuation. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of Myclausen should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

#### Norfloxacin and metronidazole

In healthy volunteers, no significant interaction was observed when mycophenolate mofetil was concomitantly administered with norfloxacin or metronidazole separately. However, norfloxacin and metronidazole combined reduced the MPA exposure by approximately 30% following a single dose of mycophenolate mofetil.

#### Trimethoprim/sulfamethoxazole

No effect on the bioavailability of MPA was observed.

#### Medicinal products that affect glucuronidation (e.g. isavuconazole, telmisartan)

Concomitant administration of drugs affecting glucuronidation of MPA may change MPA exposure. Caution is therefore recommended when administering these drugs concomitantly with Myclausen.

#### Isavuconazole

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

#### Telmisartan

Concomitant administration of telmisartan and mycophenolate mofetil resulted in an approximately 30 % decrease of MPA concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression, which in turn results in an enhanced uridine diphosphate 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 mycophenolate mofetil (see section 4.2) and ganciclovir, it is anticipated that co-administration of these agents (which compete for mechanisms of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics is anticipated and Myclausen dose adjustment is not required. In patients with renal impairment in whom Myclausen 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 coadministration of mycophenolate mofetil (see also section 5.2).

### Rifampicin

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

### Sevelamer

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

### Tacrolimus

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

### Live vaccines

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

### Paediatric population

Interaction studies have only been performed in adults.

### Potential interaction

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

## **4.6 Fertility, pregnancy and lactation**

### Women of childbearing potential

Pregnancy whilst taking mycophenolate must be avoided. Therefore, women of childbearing potential must use at least one form of reliable contraception (see section 4.3) before starting Myclausen therapy, during therapy, and for six weeks after stopping the therapy, unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred.



## Pregnancy

Myclausen is contraindicated during pregnancy unless there is no suitable alternative treatment to prevent transplant rejection. Treatment should not be initiated without providing a negative pregnancy test result to rule out unintended use in pregnancy (see section 4.3).

Female patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations at the beginning of the treatment and must be counselled regarding pregnancy prevention and planning.

Before starting Myclausen treatment, women of child bearing potential should have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL in order to exclude unintended exposure of an embryo to mycophenolate. It is recommended that the second test should be performed 8 – 10 days after the first test. For transplants from deceased donors, if it is not possible to perform two tests 8 – 10 days apart before treatment starts (because of the timing of transplant organ availability), a pregnancy test must be performed immediately before starting treatment and a further test 8 – 10 days later. Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported). Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.

Mycophenolate is a powerful human teratogen, with an increased risk of spontaneous abortions and congenital malformations in case of exposure during pregnancy;

- Spontaneous abortions have been reported in 45 to 49% of pregnant women exposed to mycophenolate mofetil, compared to a reported rate of between 12 and 33% in solid organ transplant patients treated with immunosuppressants other than mycophenolate mofetil.
- Based on literature reports, malformations occurred in 23 to 27% of live births in women exposed to mycophenolate mofetil during pregnancy (compared to 2 to 3 % of live births in the overall population and approximately 4 to 5% of live births in solid organ transplant recipients treated with immunosuppressants other than mycophenolate mofetil).

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

- Abnormalities of the ear (e.g. abnormally formed or absent external ear), external auditory canal atresia (middle ear);
- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;
- Abnormalities of the eye (e.g. coloboma);
- Congenital heart disease such as atrial and ventricular septal defects;
- Malformations of the fingers (e.g. polydactyly, syndactyly);
- Tracheo-oesophageal malformations (e.g. oesophageal atresia);
- Nervous system malformations such as spina bifida;
- Renal abnormalities.

In addition, there have been isolated reports of the following malformations:

- Microphthalmia;
- congenital choroid plexus cyst;
- septum pellucidum agenesis;
- olfactory nerve agenesis.

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

## Breast-feeding

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

## Men

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

MPA is a powerful teratogen. It is not known if MPA is present in semen. Calculations based on animal data show that the maximum amount of MPA that could potentially be transferred to woman is so low that it would be unlikely to have an effect. Mycophenolate has been shown to be genotoxic in animal studies at concentrations exceeding the human therapeutic exposures only by small margins such that the risk of genotoxic effects on sperm cells cannot completely be excluded.

Therefore, the following precautionary measures are recommended: sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 90 days after cessation of mycophenolate mofetil. Male patients of reproductive potential should be made aware of and discuss with a qualified healthcare professional the potential risk of fathering a child.

## Fertility

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

### **4.7 Effects on ability to drive and use machines**

Mycophenolate mofetil has a moderate influence on the ability to drive and use machines. Mycophenolate mofetil may cause somnolence, confusion, dizziness, tremor or hypotension, and therefore patients are advised to use caution when driving or using machines.

### **4.8 Undesirable effects**

#### *Summary of the safety profile*

Diarrhoea (up to 52.6%), leukopenia (up to 45.8%), bacterial infections (up to 39.9%) and vomiting (up to 39.1%) were among the most common and/or serious adverse drug reactions associated with the administration of mycophenolate mofetil in combination with ciclosporin and corticosteroids. There is evidence of a higher frequency of certain types of infections (see section 4.4).

#### *Tabulated list of adverse reactions*

The adverse reactions from clinical trials and post-marketing experience are listed in Table 1, by MedDRA system organ class (SOC) along with their frequencies. The corresponding frequency category for each adverse reaction is based on the following convention: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ ). Due to the large differences observed in the frequency of certain adverse reactions across the different transplant indications, the frequency is presented separately for renal, hepatic and cardiac transplant patients.

### **Table 1 Adverse reactions**

<b>Adverse reaction (MedDRA) System Organ Class</b>	<b>Renal transplant</b>	<b>Hepatic transplant</b>	<b>Cardiac transplant</b>
	Frequency	Frequency	Frequency
<b>Infections and infestations</b>			
Bacterial infections	Very common	Very common	Very common
Fungal infections	Common	Very common	Very common
Protozoal infections	Uncommon	Uncommon	Uncommon
Viral infections	Very common	Very common	Very common
<b>Neoplasms benign, malignant and unspecified (including cysts and polyps)</b>			
Benign neoplasm of skin	Common	Common	Common
Lymphoma	Uncommon	Uncommon	Uncommon
Lymphoproliferative disorder	Uncommon	Uncommon	Uncommon
Neoplasm	Common	Common	Common
Skin cancer	Common	Uncommon	Common
<b>Blood and lymphatic system disorders</b>			
Anemia	Very common	Very common	Very common
Aplasia pure red cell	Uncommon	Uncommon	Uncommon
Bone marrow failure	Uncommon	Uncommon	Uncommon
Ecchymosis	Common	Common	Very common
Leukocytosis	Common	Very common	Very common
Leukopenia	Very common	Very common	Very common
Pancytopenia	Common	Common	Uncommon
Pseudolymphoma	Uncommon	Uncommon	Common
Thrombocytopenia	Common	Very common	Very common
<b>Metabolism and nutrition disorders</b>			
Acidosis	Common	Common	Very common
Hypercholesterolemia	Very common	Common	Very common
Hyperglycemia	Common	Very common	Very common
Hyperkalemia	Common	Very common	Very common
Hyperlipidemia	Common	Common	Very common
Hypocalcemia	Common	Very common	Common
Hypokalemia	Common	Very common	Very common
Hypomagnesemia	Common	Very common	Very common
Hypophosphatemia	Very common	Very common	Common
Hyperuricaemia	Common	Common	Very common
Gout	Common	Common	Very common
Weight decreased	Common	Common	Common
<b>Psychiatric disorders</b>			
Confusional state	Common	Very common	Very common
Depression	Common	Very common	Very common
Insomnia	Common	Very common	Very common
Agitation	Uncommon	Common	Very common
Anxiety	Common	Very common	Very common
Thinking abnormal	Uncommon	Common	Common
<b>Nervous system disorders</b>			
Dizziness	Common	Very common	Very common
Headache	Very common	Very common	Very common
Hypertonia	Common	Common	Very common
Paresthesia	Common	Very common	Very common
Somnolence	Common	Common	Very common
Tremor	Common	Very common	Very common
Convulsion	Common	Common	Common

<b>Adverse reaction (MedDRA) System Organ Class</b>	<b>Renal transplant</b>	<b>Hepatic transplant</b>	<b>Cardiac transplant</b>
	Frequency	Frequency	Frequency
Dysgeusia	Uncommon	Uncommon	Common
<b>Cardiac disorders</b>			
Tachycardia	Common	Very common	Very common
<b>Vascular disorders</b>			
Hypertension	Very common	Very common	Very common
Hypotension	Common	Very common	Very common
Lymphocele	Uncommon	Uncommon	Uncommon
Venous thrombosis	Common	Common	Common
Vasodilatation	Common	Common	Very common
<b>Respiratory, thoracic and mediastinal disorders</b>			
Bronchiectasis	Uncommon	Uncommon	Uncommon
Cough	Very common	Very common	Very common
Dyspnea	Very common	Very common	Very common
Interstitial lung disease	Uncommon	Very rare	Very rare
Pleural effusion	Common	Very common	Very common
Pulmonary fibrosis	Very rare	Uncommon	Uncommon
<b>Gastrointestinal disorders</b>			
Abdominal distension	Common	Very common	Common
Abdominal pain	Very common	Very common	Very common
Colitis	Common	Common	Common
Constipation	Very common	Very common	Very common
Decreased appetite	Common	Very common	Very common
Diarrhea	Very common	Very common	Very common
Dyspepsia	Very common	Very common	Very common
Esophagitis	Common	Common	Common
Eructation	Uncommon	Uncommon	Common
Flatulence	Common	Very common	Very common
Gastritis	Common	Common	Common
Gastrointestinal hemorrhage	Common	Common	Common
Gastrointestinal ulcer	Common	Common	Common
Gingival hyperplasia	Common	Common	Common
Ileus	Common	Common	Common
Mouth ulceration	Common	Common	Common
Nausea	Very common	Very common	Very common
Pancreatitis	Uncommon	Common	Uncommon
Stomatitis	Common	Common	Common
Vomiting	Very common	Very common	Very common
<b>Immune system disorders</b>			
Hypersensitivity	Uncommon	Common	Common
Hypogammaglobulinaemia	Uncommon	Very rare	Very rare
<b>Hepatobiliary disorders</b>			
Blood alkaline phosphatase increased	Common	Common	Common
Blood lactate dehydrogenase increased	Common	Uncommon	Very common
Hepatic enzyme increased	Common	Very common	Very common
Hepatitis	Common	Very common	Uncommon
Hyperbilirubinaemia	Common	Very common	Very common
Jaundice	Uncommon	Common	Common
<b>Skin and subcutaneous tissue disorders</b>			
Acne	Common	Common	Very common

<b>Adverse reaction (MedDRA) System Organ Class</b>	<b>Renal transplant</b>	<b>Hepatic transplant</b>	<b>Cardiac transplant</b>
	Frequency	Frequency	Frequency
Alopecia	Common	Common	Common
Rash	Common	Very common	Very common
Skin hypertrophy	Common	Common	Very common
<b>Musculoskeletal and connective tissue disorders</b>			
Arthralgia	Common	Common	Very common
Muscular weakness	Common	Common	Very common
<b>Renal and urinary disorders</b>			
Blood creatinine increased	Common	Very common	Very common
Blood urea increased	Uncommon	Very common	Very common
Hematuria	Very common	Common	Common
Renal impairment	Common	Very common	Very common
<b>General disorders and administration site conditions</b>			
Asthenia	Very common	Very common	Very common
Chills	Common	Very common	Very common
Oedema	Very common	Very common	Very common
Hernia	Common	Very common	Very common
Malaise	Common	Common	Common
Pain	Common	Very common	Very common
Pyrexia	Very common	Very common	Very common
De novo purine synthesis inhibitors associated acute inflammatory syndrome	Uncommon	Uncommon	Uncommon

#### *Description of selected adverse reactions*

##### *Malignancies*

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

##### *Infections*

All patients treated with immunosuppressants are at increased risk of bacterial, viral and fungal infections (some of which may lead to a fatal outcome), including those caused by opportunistic agents and latent viral reactivation. The risk increases with total immunosuppressive load (see section 4.4). The most serious infections were sepsis, peritonitis, meningitis, endocarditis, tuberculosis and atypical mycobacterial infection. The most common opportunistic infections in patients receiving mycophenolate mofetil (2 g or 3 g daily) with other immunosuppressants in controlled clinical trials in renal, cardiac and hepatic transplant patients followed for at least 1 year were candida mucocutaneous, CMV viraemia/syndrome and Herpes simplex. The proportion of patients with CMV viraemia/syndrome was 13.5%. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including mycophenolate mofetil.

##### *Blood and lymphatic disorders*

Cytopenias, including leukopenia, anemia, thrombocytopenia and pancytopenia, are known risks associated with mycophenolate mofetil and may lead or contribute to the occurrence of infections and hemorrhages (see section 4.4). Agranulocytosis and neutropenia have been reported; therefore, regular monitoring of patients taking mycophenolate mofetil is advised (see section 4.4). There have been reports of aplastic anaemia and bone marrow failure in patients treated with mycophenolate mofetil, some of which have been fatal. Cases of pure red cell aplasia (PRCA) have been reported in patients

treated with mycophenolate mofetil (see section 4.4).

Isolated cases of abnormal neutrophil morphology, including the acquired Pelger-Huet anomaly, have been observed in patients treated with mycophenolate mofetil. These changes are not associated with impaired neutrophil function. These changes may suggest a 'left shift' in the maturity of neutrophils in haematological investigations, which may be mistakenly interpreted as a sign of infection in immunosuppressed patients such as those that receive mycophenolate mofetil.

#### *Gastrointestinal disorders*

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

#### *Hypersensitivity*

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

#### *Pregnancy, puerperium and perinatal conditions*

Cases of spontaneous 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, see section 4.6.

#### *Respiratory, thoracic and mediastinal disorders*

There have been isolated reports of interstitial lung disease and pulmonary fibrosis in patients treated with mycophenolate mofetil in combination with other immunosuppressants, some of which have been fatal. There have also been reports of bronchiectasis in children and adults.

#### *Immune system disorders*

Hypogammaglobulinaemia has been reported in patients receiving mycophenolate mofetil in combination with other immunosuppressants.

#### *General disorders and administration site conditions*

Oedema, including peripheral, face and scrotal edema, was reported very commonly during the pivotal trials. Musculoskeletal pain such as myalgia, and neck and back pain were also very commonly reported.

De novo purine synthesis inhibitors-associated acute inflammatory syndrome has been described from post-marketing experience as a paradoxical proinflammatory reaction associated with mycophenolate mofetil and mycophenolic acid, characterised by fever, arthralgia, arthritis, muscle pain and elevated inflammatory markers. Literature case reports showed rapid improvement following discontinuation of the medicinal product.

#### *Special populations*

##### *Paediatric population*

The type and frequency of adverse reactions in a clinical study, which recruited 92 paediatric patients aged 2 to 18 years who were given 600 mg/m<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 were more frequent in the paediatric population, particularly in children under 6 years of age, when compared to adults: diarrhoea, sepsis, leukopenia, anaemia and infection.

### *Elderly*

Elderly patients ( $\geq 65$  years) may generally be at increased risk of adverse reactions due to immunosuppression. Elderly patients receiving mycophenolate mofetil as part of a combination immunosuppressive regimen, may be at increased risk of certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared to younger individuals.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

## **4.9 Overdose**

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

It is expected that an overdose of mycophenolate mofetil could possibly result in oversuppression of the immune system and increase susceptibility to infections and bone marrow suppression (see section 4.4). If neutropenia develops, dosing with Myclausen should be interrupted or the dose reduced (see section 4.4).

Haemodialysis would not be expected to remove clinically significant amounts of MPA or MPAG. Bile acid sequestrants, such as cholestyramine, can remove MPA by decreasing the enterohepatic recirculation of the drug (see section 5.2).

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: immunosuppressive agents, ATC code: L04AA06

#### Mechanism of action

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

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

### **5.2 Pharmacokinetic properties**

#### Absorption

Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, MPA. As evidenced by suppression of acute rejection following renal transplantation, the immunosuppressant activity of mycophenolate

mofetil is correlated with MPA concentration. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94 % relative to IV mycophenolate mofetil. Food had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g BID to renal transplant patients. However, MPA C<sub>max</sub> was decreased by 40 % in the presence of food. Mycophenolate mofetil is not measurable systemically in plasma following oral administration.

### Distribution

As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed at approximately 6-12 hours post-dose. A reduction in the AUC of MPA of approximately 40 % is associated with the co-administration of cholestyramine (4 g TID), indicating that there is a significant amount of enterohepatic recirculation.

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

In the early post-transplant period (< 40 days post-transplant), renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30% lower and C<sub>max</sub> 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, leukopenia).

### 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 potentially interact with renal organic anion transporters.

Enterohepatic recirculation interferes with accurate determination of MPA's disposition parameters; only apparent values can be indicated. In healthy volunteers and patients with autoimmune disease approximate clearance values of 10.6 L/h and 8.27 L/h respectively and half-life values of 17 h were observed. In transplant patients mean clearance values were higher (range 11.9-34.9 L/h) and mean half-life values shorter (5-11 h) with little difference between renal, hepatic or cardiac transplant patients. In the individual patients, these elimination parameters vary based on type of co-treatment with other immunosuppressants, time post-transplantation, plasma albumin concentration and renal function. These factors explain why reduced exposure is seen when mycophenolate mofetil is co-administered with cyclosporine (see section 4.5) and why plasma concentrations tend to increase over time compared to what is observed immediately after transplantation.

### Special populations



### *Renal impairment*

In a single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate < 25 mL/min/1.73 m<sup>2</sup>) 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<sub>0-12 h</sub> was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC<sub>0-12 h</sub> was 2-3-fold higher than in post-transplant patients without delayed graft function. There may be a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of Myclausen does not appear to be necessary.

### *Hepatic impairment*

In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease. Effects of hepatic disease on these processes probably depend on the particular disease. Hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.

### *Paediatric population*

Pharmacokinetic parameters were evaluated in 49 paediatric renal transplant patients (aged 2 to 18 years) given 600 mg/m<sup>2</sup> 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 posttransplant period. MPA AUC values across age groups were similar in the early and late post-transplant period.

### *Elderly*

The pharmacokinetic of mycophenolate mofetil and its metabolites have not been found to be altered in the elderly patients (≥ 65 years) when compared to younger transplant patients.

### *Patients taking oral contraceptives*

A study of the co-administration of mycophenolate mofetil (1 g BID ) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) conducted in 18 non-transplant women (not taking other immunosuppressants) over 3 consecutive menstrual cycles showed no clinically relevant influence of mycophenolate mofetil on the ovulation suppressing action of the oral contraceptives. Serum levels of LH, FSH and progesterone were not significantly affected. The pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by co-administration of mycophenolate mofetil (see also section 4.5).

## **5.3 Preclinical safety data**

In experimental models, mycophenolate mofetil was not tumourigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2-3 times the systemic exposure (AUC or C<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 (*in vitro* mouse lymphoma assay and *in vivo* mouse bone marrow micronucleus test) showed a potential of mycophenolate mofetil to cause chromosomal aberrations. These effects can be related to the pharmacodynamic mode of action, i.e. inhibition of nucleotide synthesis in sensitive cells. Other *in vitro* tests for detection of gene mutation did not demonstrate genotoxic activity.

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

The haematopoietic and lymphoid systems were the primary organs affected in toxicology studies conducted with mycophenolate mofetil in the rat, mouse, dog and monkey. These effects occurred at systemic exposure levels that are equivalent to or less than the clinical exposure at the recommended dose of 2 g/day for renal transplant recipients. Gastrointestinal effects were observed in the dog at systemic exposure levels equivalent to or less than the clinical exposure at the recommended dose. Gastrointestinal and renal effects consistent with dehydration were also observed in the monkey at the highest dose (systemic exposure levels equivalent to or greater than clinical exposure). The nonclinical toxicity profile of mycophenolate mofetil appears to be consistent with adverse events observed in human clinical trials which now provide safety data of more relevance to the patient population (see section 4.8).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core

Microcrystalline cellulose  
Povidone (K-30)  
Croscarmellose sodium  
Magnesium stearate

#### Tablet coating

Polyvinyl alcohol (partially hydrolysed)  
Titanium dioxide (E 171)  
Macrogol 3000  
Talc

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

PVC-aluminium blisters containing 10 film-coated tablets.

Each carton contains either 50 or 150 film-coated tablets.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**

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

## **7. MARKETING AUTHORISATION HOLDER**

Passauer Pharma GmbH  
Eiderstedter Weg 3  
14129 Berlin  
Germany  
Tel.: 0049 (0)30 744 60 12  
Fax: 0049 (0)30 744 60 41

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/10/647/001-002

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

Date of first authorisation: 7 October 2010  
Date of latest renewal: 27 May 2015

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **1. NAME OF THE MEDICINAL PRODUCT**

Myclausen 250 mg hard capsules

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each hard capsule contains 250 mg mycophenolate mofetil.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Capsule, hard.

Oblong, white capsules.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Myclausen is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

### **4.2 Posology and method of administration**

Treatment should be initiated and maintained by appropriately qualified transplant specialists.

#### Posology

##### Use in renal transplant

###### *Adults*

Treatment should be initiated within 72 hours following transplantation. The recommended dose in renal transplant patients is 1 g administered twice daily (2 g daily dose).

###### *Paediatric population aged 2 to 18 years*

The recommended dose of mycophenolate mofetil is 600 mg/m<sup>2</sup> administered orally twice daily (up to a maximum of 2 g daily). Capsules should only be prescribed to patients with a body surface area of at least 1.25 m<sup>2</sup>. Patients with a body surface area of 1.25 to 1.5 m<sup>2</sup> may be prescribed mycophenolate mofetil capsules at a dose of 750 mg twice daily (1.5 g daily dose). Patients with a body surface area greater than 1.5 m<sup>2</sup> may be prescribed mycophenolate mofetil capsules at a dose of 1 g twice daily (2 g daily dose). As some adverse reactions occur with greater frequency in this age group (see section 4.8) compared with adults, temporary dose reduction or interruption may be required; these will need to take into account relevant clinical factors including severity of reaction.

###### *Paediatric population < 2 years*

There are limited safety and efficacy data in children below the age of 2 years. These are insufficient to make dosage recommendations and therefore use in this age group is not recommended.

##### Use in cardiac transplant

###### *Adults*

Treatment should be initiated within 5 days following transplantation. The recommended dose in cardiac transplant patients is 1.5 g administered twice daily (3 g daily dose).

#### *Paediatric population*

No data are available for paediatric cardiac transplant patients.

#### *Use in hepatic transplant*

##### *Adults*

Intravenous (IV) mycophenolate mofetil should be administered for the first 4 days following hepatic transplant, with oral Myclausen initiated as soon after this as it can be tolerated. The recommended oral dose in hepatic transplant patients is 1.5 g administered twice daily (3 g daily dose).

##### *Paediatric population*

No data are available for paediatric hepatic transplant patients.

#### *Use in special populations*

##### *Elderly*

The recommended dose of 1 g administered twice a day for renal transplant patients and 1.5 g twice a day for cardiac or hepatic transplant patients is appropriate for the elderly.

##### *Renal impairment*

In renal transplant patients with severe chronic renal impairment (glomerular filtration rate < 25 mL/min/1.73 m<sup>2</sup>), outside the immediate post-transplant period, doses greater than 1 g administered twice a day should be avoided. These patients should also be carefully observed. No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively (see section 5.2). No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

##### *Severe hepatic impairment*

No dose adjustments are needed for renal transplant patients with severe hepatic parenchymal disease. No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

##### *Treatment during rejection episodes*

Mycophenolic acid (MPA) is the active metabolite of mycophenolate mofetil. Renal transplant rejection does not lead to changes in MPA pharmacokinetics; dosage reduction or interruption of Myclausen is not required. There is no basis for Myclausen dose adjustment following cardiac transplant rejection. No pharmacokinetic data are available during hepatic transplant rejection.

##### *Paediatric population*

No data are available for treatment of first or refractory rejection in paediatric transplant patients.

#### Method of administration

For oral use. The hard capsules should be swallowed whole with a glass of water. They should not be opened or crushed.

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

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**

- Myclausen should not be given to patients with hypersensitivity to mycophenolate mofetil, mycophenolic acid or to any of the excipients listed in section 6.1. Hypersensitivity reactions to mycophenolate mofetil have been observed (see section 4.8).

- Myclausen should not be given to women of childbearing potential who are not using highly effective contraception (see section 4.6).
- Myclausen treatment should not be initiated in women of child bearing potential without providing a pregnancy test result to rule out unintended use in pregnancy (see section 4.6).
- Myclausen should not be used in pregnancy unless there is no suitable alternative treatment to prevent transplant rejection (see section 4.6).
- Myclausen should not be given to women who are breastfeeding (see section 4.6).

#### **4.4 Special warnings and precautions for use**

##### Neoplasms

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including Myclausen, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.8). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As general advice to minimise the risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

##### Infections

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

There have been reports of hypogammaglobulinaemia in association with recurrent infections in patients receiving mycophenolate mofetil in combination with other immunosuppressants. In some of these cases, switching mycophenolate mofetil to an alternative immunosuppressant resulted in serum IgG levels returning to normal. Patients on Myclausen who develop recurrent infections should have their serum immunoglobulins measured. In cases of sustained, clinically relevant hypogammaglobulinaemia, appropriate clinical action should be considered taking into account the potent cytostatic effects that mycophenolic acid has on T- and B-lymphocytes.

There have been published reports of bronchiectasis in adults and children who received mycophenolate mofetil in combination with other immunosuppressants. In some of these cases switching mycophenolate mofetil to another immunosuppressant resulted in improvement in respiratory symptoms. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect on the lung. There have also been isolated reports of interstitial lung disease and pulmonary fibrosis, some of which were fatal (see section 4.8). It is recommended that patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, are investigated.

##### Blood and immune system

Patients receiving Myclausen should be monitored for neutropenia, which may be related to Myclausen itself, concomitant medications, viral infections, or some combination of these causes. Patients taking Myclausen 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  $< 1.3 \times 10^3/\mu\text{l}$ ), it may be appropriate to interrupt or discontinue Myclausen.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil in combination with other immunosuppressants. The mechanism for mycophenolate mofetil induced PRCA is unknown. PRCA may resolve with dose reduction or cessation of Myclausen therapy. Changes to Myclausen 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 Myclausen 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 Myclausen, vaccinations may be less effective and the use of live attenuated vaccines should be avoided (see section 4.5). Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

### Gastro-intestinal

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

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

### Interactions

Caution should be exercised when switching combination therapy from regimens containing immunosuppressants, which interfere with MPA enterohepatic recirculation, e.g. ciclosporin, to others devoid of this effect, e.g. tacrolimus, sirolimus, belatacept, or vice versa, as this might result in changes of MPA exposure. Drugs which interfere with MPA's enterohepatic cycle (e.g. cholestyramine, antibiotics) should be used with caution due to their potential to reduce the plasma levels and efficacy of Myclausen (see also section 4.5). Therapeutic drug monitoring of MPA may be appropriate when switching combination therapy (e.g. from ciclosporin to tacrolimus or vice versa) or to ensure adequate immunosuppression in patients with high immunological risk (e.g. risk of rejection, treatment with antibiotics, addition or removal of an interacting medication).

It is recommended that Myclausen 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 also section 4.5).

### Special populations

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

### Teratogenic effects

Mycophenolate is a powerful human teratogen. Spontaneous abortion (rate of 45% to 49%) and congenital malformations (estimated rate of 23% to 27%) have been reported following MMF exposure during pregnancy. Therefore Myclausen 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 Myclausen. Physicians should ensure that women taking mycophenolate understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult their physician if there is a possibility of pregnancy.

#### Contraception (see section 4.6)

Because of robust clinical evidence showing a high risk of abortion and congenital malformations when mycophenolate mofetil is used in pregnancy, every effort to avoid pregnancy during treatment should be taken. Therefore, women with childbearing potential must use at least one form of reliable contraception (see section 4.3) before starting Myclausen therapy, during therapy, and for six weeks after stopping the therapy; unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred to minimise the potential for contraceptive failure and unintended pregnancy.

For contraception advice for men see section 4.6.

#### Educational materials

In order to assist patients in avoiding foetal exposure to mycophenolate and to provide additional important safety information, the Marketing Authorisation holder will provide educational materials to healthcare professionals. The educational materials will reinforce the warnings about the teratogenicity of mycophenolate, provide advice on contraception before therapy is started and guidance on the need for pregnancy testing. Full patient information about the teratogenic risk and the pregnancy prevention measures should be given by the physician to women of childbearing potential and, as appropriate, to male patients.

#### Additional precautions

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

#### Sodium contents

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

### **4.5 Interaction with other medicinal products and other forms of interaction**

#### Aciclovir

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

#### Antacids and proton pump inhibitors (PPIs)

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

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



### antibiotics)

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

### 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 Myclausen.

### Ciclosporin A

Ciclosporin A (CsA) pharmacokinetics are unaffected by mycophenolate mofetil. In contrast, if concomitant CsA treatment is stopped, an increase in MPA AUC of around 30 % should be expected. CsA interferes with MPA enterohepatic recycling, resulting in reduced MPA exposures by 30-50 % in renal transplant patients treated with mycophenolate mofetil and CsA compared with patients receiving sirolimus or belatacept and similar doses of mycophenolate mofetil (see also section 4.4). Conversely, changes of MPA exposure should be expected when switching patients from CsA to one of the immunosuppressants which does not interfere with MPA's enterohepatic cycle.

Antibiotics eliminating  $\beta$ -glucuronidase-producing bacteria in the intestine (e.g. aminoglycoside, cephalosporin, fluoroquinolone, and penicillin classes of antibiotics) may interfere with MPAG/MPA enterohepatic recirculation, thus leading to reduced systemic MPA exposure. Information concerning the following antibiotics is available:

### Ciprofloxacin or amoxicillin plus clavulanic acid

Reductions in pre-dose (trough) MPA concentrations of about 50% have been reported in renal transplant recipients in the days immediately following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. This effect tended to diminish with continued antibiotic use and to cease within a few days of antibiotic discontinuation. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of Myclausen should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

### Norfloxacin and metronidazole

In healthy volunteers, no significant interaction was observed when mycophenolate mofetil was concomitantly administered with norfloxacin or metronidazole separately. However, norfloxacin and metronidazole combined reduced the MPA exposure by approximately 30% following a single dose of mycophenolate mofetil.

### Trimethoprim/sulfamethoxazole

No effect on the bioavailability of MPA was observed.

### Medicinal products that affect glucuronidation (e.g. isavuconazole, telmisartan)

Concomitant administration of drugs affecting glucuronidation of MPA may change MPA exposure. Caution is therefore recommended when administering these drugs concomitantly with Myclausen.

### Isavuconazole

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

### Telmisartan

Concomitant administration of telmisartan and mycophenolate mofetil resulted in an approximately 30 % decrease of MPA concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression, which in turn results in an enhanced uridine diphosphate glucuryltransferase isoform 1A9 (UGT1A9) expression and activity. When comparing rates of transplant rejection, rates of graft loss or adverse event profiles

between mycophenolate mofetil patients with and without concomitant telmisartan medication, no clinical consequences of the pharmacokinetic drug-drug interaction were seen.

#### Ganciclovir

Based on the results of a single dose administration study of recommended doses of oral mycophenolate and IV ganciclovir and the known effects of renal impairment on the pharmacokinetics of mycophenolate mofetil (see section 4.2) and ganciclovir, it is anticipated that co-administration of these agents (which compete for mechanisms of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics is anticipated and Myclausen dose adjustment is not required. In patients with renal impairment in whom Myclausen 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 coadministration of mycophenolate mofetil (see also section 5.2).

#### Rifampicin

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

#### Sevelamer

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

#### Tacrolimus

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

#### Live vaccines

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

#### Paediatric population

Interaction studies have only been performed in adults.

#### Potential interactions

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

## **4.6 Fertility, pregnancy and lactation**

#### Women of childbearing potential

Pregnancy whilst taking mycophenolate must be avoided. Therefore women of childbearing potential must use at least one form of reliable contraception (see section 4.3) before starting Myclausen

therapy, during therapy, and for six weeks after stopping the therapy, unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred.

### Pregnancy

Myclausen is contraindicated during pregnancy unless there is no suitable alternative treatment to prevent transplant rejection. Treatment should not be initiated without providing a negative pregnancy test result to rule out unintended use in pregnancy.

Female patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations at the beginning of the treatment and must be counselled regarding pregnancy prevention and planning.

Before starting Myclausen treatment, women of child bearing potential should have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL in order to exclude unintended exposure of an embryo to mycophenolate. It is recommended that the second test should be performed 8 – 10 days after the first test. For transplants from deceased donors, if it is not possible to perform two tests 8 – 10 days apart before treatment starts (because of the timing of transplant organ availability), a pregnancy test must be performed immediately before starting treatment and a further test 8 – 10 days later. Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported). Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.

Mycophenolate is a powerful human teratogen, with an increased risk of spontaneous abortions and congenital malformations in case of exposure during pregnancy;

- Spontaneous abortions have been reported in 45 to 49% of pregnant women exposed to mycophenolate mofetil, compared to a reported rate of between 12 and 33% in solid organ transplant patients treated with immunosuppressants other than mycophenolate mofetil.
- Based on literature reports, malformations occurred in 23 to 27% of live births in women exposed to mycophenolate mofetil during pregnancy (compared to 2 to 3 % of live births in the overall population and approximately 4 to 5% of live births in solid organ transplant recipients treated with immunosuppressants other than mycophenolate mofetil).

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

- Abnormalities of the ear (e.g. abnormally formed or absent external ear), external auditory canal atresia (middle ear);
- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;
- Abnormalities of the eye (e.g. coloboma);
- Congenital heart disease such as atrial and ventricular septal defects;
- Malformations of the fingers (e.g. polydactyly, syndactyly);
- Tracheo-oesophageal malformations (e.g. oesophageal atresia);
- Nervous system malformations such as spina bifida;
- Renal abnormalities.

In addition, there have been isolated reports of the following malformations:

- Microphthalmia;
- congenital choroid plexus cyst;
- septum pellucidum agenesis;
- olfactory nerve agenesis.

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

### Breast-feeding

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

### Men

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

MPA is a powerful teratogen. It is not known if MPA is present in semen. Calculations based on animal data show that the maximum amount of MPA that could potentially be transferred to woman is so low that it would be unlikely to have an effect. Mycophenolate has been shown to be genotoxic in animal studies at concentrations exceeding the human therapeutic exposures only by small margins, such that the risk of genotoxic effects on sperm cells cannot completely be excluded.

Therefore, the following precautionary measures are recommended: sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 90 days after cessation of mycophenolate mofetil. Male patients of reproductive potential should be made aware of and discuss with a qualified health-care professional the potential risks of fathering a child.

### Fertility

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

## **4.7 Effects on ability to drive and use machines**

Myclausen has moderate influence on the ability to drive and use machines. Myclausen may cause somnolence, confusion, dizziness, tremor or hypotension, and therefore patients are advised to use caution when driving or using machines.

## **4.8 Undesirable effects**

### *Summary of the safety profile*

Diarrhoea (up to 52.6%), leukopenia (up to 45.8%), bacterial infections (up to 39.9%) and vomiting (up to 39.1%) were among the most common and/or serious adverse drug reactions associated with the administration of mycophenolate mofetil in combination with ciclosporin and corticosteroids. There is also evidence of a higher frequency of certain types of infections (see section 4.4).

### *Tabulated list of adverse reactions*

The adverse reactions from clinical trials and post-marketing experience are listed in Table 1, by MedDRA system organ class (SOC) along with their frequencies. The corresponding frequency category for each adverse reaction is based on the following convention: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) and very rare ( $< 1/10,000$ ). Due to the large differences observed in the frequency of certain adverse reactions across the different transplant indications, the frequency is presented separately for renal, hepatic and cardiac transplant patients.

**Table 1 Adverse reactions**

<b>Adverse reaction (MedDRA) System Organ Class</b>	<b>Renal transplant</b>	<b>Hepatic transplant</b>	<b>Cardiac transplant</b>
	Frequency	Frequency	Frequency
<b>Infections and infestations</b>			
Bacterial infections	Very common	Very common	Very common
Fungal infections	Common	Very common	Very common
Protozoal infections	Uncommon	Uncommon	Uncommon
Viral infections	Very common	Very common	Very common
<b>Neoplasms benign, malignant and unspecified (including cysts and polyps)</b>			
Benign neoplasm of skin	Common	Common	Common
Lymphoma	Uncommon	Uncommon	Uncommon
Lymphoproliferative disorder	Uncommon	Uncommon	Uncommon
Neoplasm	Common	Common	Common
Skin cancer	Common	Uncommon	Common
<b>Blood and lymphatic system disorders</b>			
Anemia	Very common	Very common	Very common
Aplasia pure red cell	Uncommon	Uncommon	Uncommon
Bone marrow failure	Uncommon	Uncommon	Uncommon
Ecchymosis	Common	Common	Very common
Leukocytosis	Common	Very common	Very common
Leukopenia	Very common	Very common	Very common
Pancytopenia	Common	Common	Uncommon
Pseudolymphoma	Uncommon	Uncommon	Common
Thrombocytopenia	Common	Very common	Very common
<b>Metabolism and nutrition disorders</b>			
Acidosis	Common	Common	Very common
Hypercholesterolemia	Very common	Common	Very common
Hyperglycemia	Common	Very common	Very common
Hyperkalemia	Common	Very common	Very common
Hyperlipidemia	Common	Common	Very common
Hypocalcemia	Common	Very common	Common
Hypokalemia	Common	Very common	Very common
Hypomagnesemia	Common	Very common	Very common
Hypophosphatemia	Very common	Very common	Common
Hyperuricaemia	Common	Common	Very common
Gout	Common	Common	Very common
Weight decreased	Common	Common	Common
<b>Psychiatric disorders</b>			
Confusional state	Common	Very common	Very common
Depression	Common	Very common	Very common
Insomnia	Common	Very common	Very common
Agitation	Uncommon	Common	Very common
Anxiety	Common	Very common	Very common
Thinking abnormal	Uncommon	Common	Common
<b>Nervous system disorders</b>			
Dizziness	Common	Very common	Very common
Headache	Very common	Very common	Very common
Hypertonia	Common	Common	Very common
Paresthesia	Common	Very common	Very common
Somnolence	Common	Common	Very common
Tremor	Common	Very common	Very common

<b>Adverse reaction (MedDRA) System Organ Class</b>	<b>Renal transplant</b>	<b>Hepatic transplant</b>	<b>Cardiac transplant</b>
	Frequency	Frequency	Frequency
Convulsion	Common	Common	Common
Dysgeusia	Uncommon	Uncommon	Common
<b>Cardiac disorders</b>			
Tachycardia	Common	Very common	Very common
<b>Vascular disorders</b>			
Hypertension	Very common	Very common	Very common
Hypotension	Common	Very common	Very common
Lymphocele	Uncommon	Uncommon	Uncommon
Venous thrombosis	Common	Common	Common
Vasodilatation	Common	Common	Very common
<b>Respiratory, thoracic and mediastinal disorders</b>			
Bronchiectasis	Uncommon	Uncommon	Uncommon
Cough	Very common	Very common	Very common
Dyspnea	Very common	Very common	Very common
Interstitial lung disease	Uncommon	Very rare	Very rare
Pleural effusion	Common	Very common	Very common
Pulmonary fibrosis	Very rare	Uncommon	Uncommon
<b>Gastrointestinal disorders</b>			
Abdominal distension	Common	Very common	Common
Abdominal pain	Very common	Very common	Very common
Colitis	Common	Common	Common
Constipation	Very common	Very common	Very common
Decreased appetite	Common	Very common	Very common
Diarrhea	Very common	Very common	Very common
Dyspepsia	Very common	Very common	Very common
Esophagitis	Common	Common	Common
Eructation	Uncommon	Uncommon	Common
Flatulence	Common	Very common	Very common
Gastritis	Common	Common	Common
Gastrointestinal hemorrhage	Common	Common	Common
Gastrointestinal ulcer	Common	Common	Common
Gingival hyperplasia	Common	Common	Common
Ileus	Common	Common	Common
Mouth ulceration	Common	Common	Common
Nausea	Very common	Very common	Very common
Pancreatitis	Uncommon	Common	Uncommon
Stomatitis	Common	Common	Common
Vomiting	Very common	Very common	Very common
<b>Immune system disorders</b>			
Hypersensitivity	Uncommon	Common	Common
Hypogammaglobulinaemia	Uncommon	Very rare	Very rare
<b>Hepatobiliary disorders</b>			
Blood alkaline phosphatase increased	Common	Common	Common
Blood lactate dehydrogenase increased	Common	Uncommon	Very common
Hepatic enzyme increased	Common	Very common	Very common
Hepatitis	Common	Very common	Uncommon
Hyperbilirubinaemia	Common	Very common	Very common
Jaundice	Uncommon	Common	Common
<b>Skin and subcutaneous tissue disorders</b>			

<b>Adverse reaction (MedDRA) System Organ Class</b>	<b>Renal transplant</b>	<b>Hepatic transplant</b>	<b>Cardiac transplant</b>
	Frequency	Frequency	Frequency
Acne	Common	Common	Very common
Alopecia	Common	Common	Common
Rash	Common	Very common	Very common
Skin hypertrophy	Common	Common	Very common
<b>Musculoskeletal and connective tissue disorders</b>			
Arthralgia	Common	Common	Very common
Muscular weakness	Common	Common	Very common
<b>Renal and urinary disorders</b>			
Blood creatinine increased	Common	Very common	Very common
Blood urea increased	Uncommon	Very common	Very common
Hematuria	Very common	Common	Common
Renal impairment	Common	Very common	Very common
<b>General disorders and administration site conditions</b>			
Asthenia	Very common	Very common	Very common
Chills	Common	Very common	Very common
Oedema	Very common	Very common	Very common
Hernia	Common	Very common	Very common
Malaise	Common	Common	Common
Pain	Common	Very common	Very common
Pyrexia	Very common	Very common	Very common
De novo purine synthesis inhibitors associated acute inflammatory syndrome	Uncommon	Uncommon	Uncommon

#### *Description of selected adverse reactions*

##### *Malignancies*

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

##### *Infections*

All patients treated with immunosuppressants are at increased risk of bacterial, viral and fungal infections (some of which may lead to a fatal outcome), including those caused by opportunistic agents and latent viral reactivation. The risk increases with total immunosuppressive load (see section 4.4). The most serious infections were sepsis, peritonitis, meningitis, endocarditis, tuberculosis and atypical mycobacterial infection. The most common opportunistic infections in patients receiving mycophenolate mofetil (2 g or 3 g daily) with other immunosuppressants in controlled clinical trials in renal, cardiac and hepatic transplant patients followed for at least 1 year were candida mucocutaneous, CMV viraemia/syndrome and Herpes simplex. The proportion of patients with CMV viraemia/syndrome was 13.5%. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including mycophenolate mofetil.

##### *Blood and lymphatic disorders*

Cytopenias, including leukopenia, anemia, thrombocytopenia and pancytopenia, are known risks associated with mycophenolate mofetil and may lead or contribute to the occurrence of infections and hemorrhages (see section 4.4). Agranulocytosis and neutropenia have been reported; therefore, regular monitoring of patients taking mycophenolate mofetil is advised (see section 4.4). There have been reports of aplastic anaemia and bone marrow failure in patients treated with mycophenolate mofetil,

some of which have been fatal. Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil (see section 4.4).

Isolated cases of abnormal neutrophil morphology, including the acquired Pelger-Huet anomaly, have been observed in patients treated with mycophenolate mofetil. These changes are not associated with impaired neutrophil function. These changes may suggest a 'left shift' in the maturity of neutrophils in haematological investigations, which may be mistakenly interpreted as a sign of infection in immunosuppressed patients such as those that receive mycophenolate mofetil.

#### *Gastrointestinal disorders*

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

#### *Hypersensitivity*

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

#### *Pregnancy, puerperium and perinatal conditions*

Cases of spontaneous 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, see section 4.6.

#### *Respiratory, thoracic and mediastinal disorders*

There have been isolated reports of interstitial lung disease and pulmonary fibrosis in patients treated with mycophenolate mofetil in combination with other immunosuppressants, some of which have been fatal. There have also been reports of bronchiectasis in children and adults.

#### *Immune system disorders*

Hypogammaglobulinaemia has been reported in patients receiving mycophenolate mofetil in combination with other immunosuppressants.

#### *General disorders and administration site conditions*

Oedema, including peripheral, face and scrotal edema, was reported very commonly during the pivotal trials. Musculoskeletal pain such as myalgia, and neck and back pain were also very commonly reported.

De novo purine synthesis inhibitors-associated acute inflammatory syndrome has been described from post-marketing experience as a paradoxical proinflammatory reaction associated with mycophenolate mofetil and mycophenolic acid, characterised by fever, arthralgia, arthritis, muscle pain and elevated inflammatory markers. Literature case reports showed rapid improvement following discontinuation of the medicinal product.

#### *Special populations*

##### *Paediatric population*

The type and frequency of adverse reactions in a clinical study, which recruited 92 paediatric patients aged 2 to 18 years who were given 600 mg/m<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 were more frequent in the paediatric population, particularly in children under 6 years of age, when compared to adults: diarrhoea, sepsis,



leukopenia, anaemia and infection.

#### *Elderly*

Elderly patients ( $\geq 65$  years) may generally be at increased risk of adverse reactions due to immunosuppression. Elderly patients receiving mycophenolate mofetil as part of a combination immunosuppressive regimen, may be at increased risk of certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared to younger individuals.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

### **4.9 Overdose**

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

It is expected that an overdose of mycophenolate mofetil could possibly result in oversuppression of the immune system and increase susceptibility to infections and bone marrow suppression (see section 4.4). If neutropenia develops, dosing with Myclausen should be interrupted or the dose reduced (see section 4.4).

Haemodialysis would not be expected to remove clinically significant amounts of MPA or MPAG. Bile acid sequestrants, such as cholestyramine, can remove MPA by decreasing the enterohepatic recirculation of the drug (see section 5.2).

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: immunosuppressive agents, ATC code L04AA06

#### Mechanism of action

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

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

### **5.2 Pharmacokinetic properties**

#### Absorption

Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, MPA. As evidenced by suppression of

acute rejection following renal transplantation, the immunosuppressant activity of mycophenolate mofetil is correlated with MPA concentration. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94 % relative to IV mycophenolate mofetil. Food had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g BID to renal transplant patients. However, MPA C<sub>max</sub> was decreased by 40 % in the presence of food. Mycophenolate mofetil is not measurable systemically in plasma following oral administration.

### Distribution

As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed at approximately 6-12 hours post-dose. A reduction in the AUC of MPA of approximately 40 % is associated with the co-administration of cholestyramine (4 g TID), indicating that there is a significant amount of enterohepatic recirculation.

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

In the early post-transplant period (< 40 days post-transplant), renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30% lower and C<sub>max</sub> 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 mycophenolate mofetil's side effects (diarrhoea, leukopenia).

### 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 potentially interact with renal organic anion transporters.

Enterohepatic recirculation interferes with accurate determination of MPA's disposition parameters; only apparent values can be indicated. In healthy volunteers and patients with autoimmune disease approximate clearance values of 10.6 L/h and 8.27 L/h respectively and half-life values of 17 h were observed. In transplant patients mean clearance values were higher (range 11.9-34.9 L/h) and mean half-life values shorter (5-11 h) with little difference between renal, hepatic or cardiac transplant patients. In the individual patients, these elimination parameters vary based on type of co-treatment with other immunosuppressants, time post-transplantation, plasma albumin concentration and renal function. These factors explain why reduced exposure is seen when mycophenolate mofetil is co-administered with cyclosporine (see section 4.5) and why plasma concentrations tend to increase over time compared to what is observed immediately after transplantation.

### Special populations

### *Renal impairment*

In a single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate < 25 mL•min<sup>-1</sup>•1.73 m<sup>-2</sup>) 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<sub>0-12 h</sub> was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC<sub>0-12 h</sub> was 2-3-fold higher than in post-transplant patients without delayed graft function. There may be a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of Myclausen does not appear to be necessary.

### *Hepatic impairment*

In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease. Effects of hepatic disease on these processes probably depend on the particular disease. Hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.

### *Paediatric population*

Pharmacokinetic parameters were evaluated in 49 paediatric renal transplant patients (aged 2 to 18 years) given 600 mg/m<sup>2</sup> mycophenolate mofetil orally twice daily. This dose achieved MPA AUC values similar to those seen in adult renal transplant patients receiving mycophenolate mofetil at a dose of 1 g BID in the early and late post-transplant period. MPA AUC values across age groups were similar in the early and late post-transplant period.

### *Elderly*

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

### *Patients taking oral contraceptives*

A study of the co-administration of mycophenolate mofetil (1 g BID) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) conducted in 18 non-transplant women (not taking other immunosuppressants) over 3 consecutive menstrual cycles showed no clinically relevant influence of mycophenolate mofetil on the ovulation suppressing action of the oral contraceptives. Serum levels of LH, FSH and progesterone were not significantly affected. The pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by co-administration of mycophenolate mofetil (see also section 4.5).

## **5.3 Preclinical safety data**

In experimental models, mycophenolate mofetil was not tumourigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2-3 times the systemic exposure (AUC or C<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 (*in vitro* mouse lymphoma assay and *in vivo* mouse bone marrow micronucleus test) showed a potential of mycophenolate mofetil to cause chromosomal aberrations. These effects can be related to the pharmacodynamic mode of action, i.e. inhibition of nucleotide synthesis in sensitive cells. Other *in vitro* tests for detection of gene mutation did not demonstrate

genotoxic activity.

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

The haematopoietic and lymphoid systems were the primary organs affected in toxicology studies conducted with mycophenolate mofetil in the rat, mouse, dog and monkey. These effects occurred at systemic exposure levels that are equivalent to or less than the clinical exposure at the recommended dose of 2 g/day for renal transplant recipients. Gastrointestinal effects were observed in the dog at systemic exposure levels equivalent to or less than the clinical exposure at the recommended dose. Gastrointestinal and renal effects consistent with dehydration were also observed in the monkey at the highest dose (systemic exposure levels equivalent to or greater than clinical exposure). The nonclinical toxicity profile of mycophenolate mofetil appears to be consistent with adverse events observed in human clinical trials which now provide safety data of more relevance to the patient population (see section 4.8).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule content

Pregelatinised starch (maize)  
Croscarmellose sodium  
Povidone (K-30)  
Magnesium stearate

#### Capsule shells

Gelatine  
Titanium dioxide (E 171)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

Store below 30 °C.

### **6.5 Nature and contents of container**

PVC-aluminium blisters containing 10 hard capsules.

Each carton contains either 100 or 300 hard capsules.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**

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

## **7. MARKETING AUTHORISATION HOLDER**

Passauer Pharma GmbH  
Eiderstedter Weg 3  
14129 Berlin  
Germany  
Tel.: 0049 (0)30 744 60 12  
Fax: 0049 (0)30 744 60 41

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/10/647/003-004

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

Date of first authorisation: 7 October 2010  
Date of latest renewal: 27 May 2015

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer responsible for batch release

Passauer Pharma GmbH  
Eiderstedter Weg 3  
14129 Berlin  
Germany

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

### **• Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

### **• Risk Management Plan (RMP)**

Not applicable.

### **• Additional risk minimisation measures**

Prior to the use of Myclausen in each Member State (MS) the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme and a follow-up pregnancy questionnaire, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at ensuring that the health professionals and patients are aware of the teratogenicity and mutagenicity, the need for pregnancy tests before starting therapy with mycophenolate mofetil, the contraceptive requirements for both male and female patients and what to do in case of pregnancy during treatment with Myclausen.

The MAH shall ensure that in each MS where Myclausen is marketed, all healthcare professionals and patients who are expected to prescribe, dispense or use Myclausen are provided with the following educational package:

- Physician educational material
- Patient information pack

The health professional educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals

The patient information pack should contain:

- The Package Leaflet
- Guide for patients

The educational materials should be implemented within four months after completion of this procedure and shall contain the following key elements:

Separate guides for healthcare professionals and patients should be provided. For patients, the text should be appropriately separated for men and women. The following areas should be covered in these guides:

- An introduction in each guide will inform the reader that the purpose of the guide is to tell them that a foetal exposure must be avoided and how to minimize the risk of birth defects and miscarriage associated with mycophenolate mofetil. It will explain that although this guide is very important it does not provide full information on mycophenolate mofetil and that the SmPC (healthcare professionals) and package leaflet (patients) supplied with the medicine must also be read carefully.
- Background information on mycophenolate mofetil teratogenicity and mutagenicity in humans. This section will provide important background information concerning the teratogenicity and mutagenicity of mycophenolate mofetil. It will provide details about the nature and magnitude of the risk, in line with the information provided in the SmPC. The information provided in this section will facilitate a correct understanding of the risk and explain the rationale for the following pregnancy prevention measures. Guides should also mention that patients should not to give this drug to any other person.
- Counselling of patients: This section will emphasise the importance of a thorough, informative and ongoing dialogue between patient and healthcare professional about the pregnancy risks associated with mycophenolate mofetil and the relevant minimisation strategies including alternative treatment choices, if applicable. The need to plan a pregnancy will be highlighted.
- The need to avoid foetal exposure: Contraceptive requirements for patients of reproductive potential prior to, during and after treatment with mycophenolate mofetil. Contraceptive requirements for sexually active male patients (including vasectomised men) and female patients of childbearing potential will be explained. The need for contraception prior to, during and after treatment with mycophenolate mofetil, including details of the duration of time for which contraception must be continued after cessation of therapy, will be clearly stated.

In addition, the text relating to women should explain the pregnancy test requirements prior to and during therapy with mycophenolate mofetil; including the advice for two negative pregnancy tests prior to starting therapy and the importance of the timing of these tests. The need for subsequent pregnancy tests during treatment will also be explained.

- Advice that patients should not donate blood during therapy or for at least 6 weeks following discontinuation of mycophenolate. Furthermore, men should not donate semen during therapy or for 90 days following discontinuation of mycophenolate.
- Advice on action if a pregnancy occurs or is suspected during or shortly after being treated with mycophenolate mofetil. Patients will be informed that they should not stop taking mycophenolate mofetil but must contact their doctor immediately. It will be explained that the correct course of action, based on an assessment of the individual benefit-risk, will be determined on a case by case basis through a discussion between the treating physician and the patient.

In addition, a pregnancy follow-up questionnaire including details of exposure during pregnancy, including timing and dose; duration of therapy, before and during pregnancy; concomitant drugs; known teratogenic risks and full details of congenital malformations should be agreed to with the national competent authorities and implemented within four months after completion of this procedure.



**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Myclausen 500 mg film-coated tablets  
Mycophenolate mofetil

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 500 mg mycophenolate mofetil.

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

50 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
For oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Myclausen film-coated tablets should be handled with care.  
Do not break or crush the tablets.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Passauer Pharma GmbH  
Eiderstedter Weg 3  
14129 Berlin  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/10/647/001

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Myclausen 500 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC: {number} [product code]

SN: {number} [serial number]

NN: {number} [national reimbursement number or other national number identifying the medicinal product]

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Myclausen 500 mg film-coated tablets  
Mycophenolate mofetil

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 500 mg mycophenolate mofetil.

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

150 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
For oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Myclausen film-coated tablets should be handled with care.  
Do not break or crush the tablets.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Passauer Pharma GmbH  
Eiderstedter Weg 3  
14129 Berlin  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/10/647/002

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Myclausen 500 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC: {number} [product code]

SN: {number} [serial number]

NN: {number} [national reimbursement number or other national number identifying the medicinal product]

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

**1. NAME OF THE MEDICINAL PRODUCT**

Myclausen 500 mg film-coated tablets  
Mycophenolate mofetil

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Passauer Pharma GmbH

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

Myclausen 250 mg hard capsules  
Mycophenolate mofetil

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each capsule contains 250 mg mycophenolate mofetil.

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

100 hard capsules  
300 hard capsules

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
For oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Myclausen capsules should be handled with care.  
Do not open or crush the capsules and breathe the powder inside the capsules or allow it to touch your skin.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store below 30 °C.



**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Passauer Pharma GmbH  
Eiderstedter Weg 3  
14129 Berlin  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/10/647/003 (100 hard capsules)  
EU/1/10/647/004 (300 hard capsules)

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Myclausen 250 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC: {number} [product code]  
SN: {number} [serial number]  
NN: {number} [national reimbursement number or other national number identifying the medicinal product]

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

**1. NAME OF THE MEDICINAL PRODUCT**

Myclausen 250 mg hard capsules  
Mycophenolate mofetil

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Passauer Pharma GmbH

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the patient

### Myclausen 500 mg film-coated tablets Mycophenolate mofetil

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### What is in this leaflet

1. What Myclausen is and what it is used for
2. What you need to know before you take Myclausen
3. How to take Myclausen
4. Possible side effects
5. How to store Myclausen
6. Contents of the pack and other information

#### 1. What Myclausen is and what it is used for

Myclausen contains mycophenolate mofetil.

- This belongs to a group of medicines called “immunosuppressants”.

Myclausen is used to prevent your body rejecting a transplanted organ.

- A kidney, heart or liver.

Myclausen should be used together with other medicines:

- Ciclosporin and corticosteroids.

#### 2. What you need to know before you take Myclausen

##### WARNING

Mycophenolate causes birth defects and miscarriage. If you are a woman who could become pregnant, you must provide a negative pregnancy test before starting treatment and must follow the contraception advice given to you by your doctor.

Your doctor will speak to you and give you written information, particularly on the effects of mycophenolate on unborn babies. Read the information carefully and follow the instructions. If you do not fully understand these instructions, please ask your doctor to explain them again before you take mycophenolate. See also further information in this section under “Warnings and precautions” and “Pregnancy and breast-feeding”.

##### Do not take Myclausen

- If you are allergic to mycophenolate mofetil, mycophenolic acid or any of the other ingredients of this medicine (listed in section 6).
- If you are a woman who could be pregnant and you have not provided a negative pregnancy test before your first prescription, as mycophenolate causes birth defects and miscarriage.
- If you are pregnant or planning to become pregnant or think you may be pregnant
- If you are not using effective contraception (see Pregnancy, contraception and breast-feeding).
- If you are breast-feeding.

Do not take this medicine if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Myclausen.

### **Warnings and precautions**

Talk to your doctor straight away before starting treatment with Myclausen

- If you are older than 65 years as you may have an increased risk of developing adverse events such as certain viral infections, gastrointestinal bleeding and pulmonary oedema when compared to younger patients
- If you have a sign of infection such as a fever or sore throat
- If you have any unexpected bruising or bleeding
- If you have ever had a problem with your digestive system such as a stomach ulcer
- If you are planning to become pregnant or if you get pregnant while you or your partner are taking Myclausen.
- If you have a hereditary enzyme deficiency such as Lesch-Nyhan and Kelley-Seegmiller syndrome

If any of the above apply to you (or you are not sure), talk to your doctor straight away before starting treatment with Myclausen.

### **The effect of sunlight**

Myclausen reduces your body's defences. As a result, there is an increased risk of skin cancer. Limit the amount of sunlight and UV light you get. Do this by:

- wearing protective clothing that also covers your head, neck, arms and legs
- using a sunscreen with a high protection factor.

### **Children**

Do not give this medicine to children younger than 2 years because based on the limited safety and efficacy data for this age group no dose recommendations can be made.

### **Other medicines and Myclausen**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, including herbal medicines. This is because Myclausen can affect the way some other medicines work. Also other medicines can affect the way Myclausen works.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines before you start Myclausen:

- azathioprine or other medicines that suppress your immune system (given after a transplant operation)
- cholestyramine (used to treat high cholesterol)
- rifampicin (an antibiotic used to prevent and treat infections such as tuberculosis (TB))
- antacids or proton pump inhibitors (used for acid problems in your stomach such as indigestion)
- phosphate binders (used by people with chronic kidney failure to reduce how much phosphate gets absorbed into their blood).
- antibiotics (used to treat bacterial infections)
- isavuconazole (used to treat fungal infections)
- telmisartan (used to treat high blood pressure)

### **Vaccines**

If you need to have a vaccination (a live vaccine) while taking Myclausen, talk to your doctor or pharmacist first. Your doctor will have to advise you on what vaccines you can have.

You must not donate blood during treatment with Myclausen and for at least 6 weeks after stopping treatment. Men must not donate semen during treatment with Myclausen and for at least 90 days after stopping treatment.

### **Myclausen with food and drink**

Taking food and drink has no effect on your treatment with Myclausen.

### **Contraception in women taking Myclausen**

If you are a woman who could become pregnant you must use an effective method of contraception with Myclausen. This includes:

- Before you start taking Myclausen
- During your entire treatment with Myclausen
- For 6 weeks after you stop taking Myclausen.

Talk to your doctor about the most suitable contraception for you. This will depend on your individual situation. Two forms of contraception are preferable as this will reduce the risk of unintended pregnancy. **Contact your doctor as soon as possible, if you think your contraception may not have been effective or if you have forgotten to take your contraceptive pill.**

You cannot become pregnant if any of the following conditions applies to you:

- You are post-menopausal, i.e. at least 50 years old and your last period was more than a year ago (if your periods have stopped because you have had treatment for cancer, then there is still a chance you could become pregnant)
- Your fallopian tubes and both ovaries have been removed by surgery (bilateral salpingo-oophorectomy)
- Your womb (uterus) has been removed by surgery (hysterectomy)
- Your ovaries no longer work (premature ovarian failure, which has been confirmed by a specialist gynaecologist)
- You were born with one of the following rare conditions that make pregnancy impossible: the XY genotype, Turner's syndrome or uterine agenesis
- You are a child or teenager who has not started having periods.

### **Contraception in men taking Myclausen**

The available evidence does not indicate an increased risk of malformations or miscarriage if the father takes mycophenolate. However, a risk cannot be completely excluded. As a precaution you or your female partner are recommended to use reliable contraception during treatment and for 90 days after you stop taking Myclausen.

If you are planning to have a child, talk to your doctor about the potential risks and alternative therapies.

### **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will talk to you about the risks in case of pregnancy and the alternatives you can take to prevent rejection of your transplant organ if:

- You plan to become pregnant.
- You miss or think you have missed a period, or you have unusual menstrual bleeding, or suspect you are pregnant.
- You have sex without using effective methods of contraception.

If you do become pregnant during the treatment with mycophenolate, you must inform your doctor immediately. However, keep taking Myclausen until you see him or her.

### **Pregnancy**

Mycophenolate causes a very high frequency of miscarriage (50%) and of severe birth defects (23 - 27%) in the unborn baby. Birth defects which have been reported include anomalies of ears, of eyes, of face (cleft lip/palate), of development of fingers, of heart, oesophagus (tube that connects the throat with the stomach), kidneys and nervous system (for example spina bifida (where the bones of the spine are not properly developed)). Your baby may be affected by one or more of these.

If you are a woman who could become pregnant, you must provide a negative pregnancy test before starting treatment and must follow the contraception advice given to you by your doctor. Your doctor may request more than one test to ensure you are not pregnant before starting treatment.

### **Breast-feeding**

Do not take Myclausen if you are breast-feeding. This is because small amounts of the medicine can pass into the mother's milk.

### **Driving and using machines**

Myclausen has a moderate influence on your ability to drive or use any tools or machines. If you feel drowsy, numb or confused, talk to your doctor or nurse and do not drive or use any tools or machines until you feel better.

### **Myclausen contains sodium**

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'

## **3. How to take Myclausen**

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

### **How much to take**

The amount you take depends on the type of transplant you have had. The usual doses are shown below. Treatment will continue for as long as you need to prevent rejection of your transplant organ.

### **Kidney transplant**

#### Adults

- The first dose is given within 3 days of the transplant operation.
- The daily dose is 4 tablets (2 g of the medicine) taken as 2 separate doses.
- Take 2 tablets in the morning and then 2 tablets in the evening.

#### Children aged 2 to 18 years

- The dose given will vary depending on the size of the child.
- Your doctor will decide the most appropriate dose based on your child's height and weight (body surface area – measured as square metres or 'm<sup>2</sup>'). The recommended dose is 600 mg per m<sup>2</sup> taken twice a day.

### **Heart transplant**

#### Adults

- The first dose is given within 5 days of the transplant operation.
- The daily dose is 6 tablets (3 g of the medicine) taken as 2 separate doses.
- Take 3 tablets in the morning and then 3 tablets in the evening.

#### Children

- There is no information for the use of Myclausen in children with a heart transplant.

### **Liver transplant**

#### Adults

- The first dose of oral Myclausen will be given to you at least 4 days after the transplant operation and when you are able to swallow oral medicines.
- The daily dose is 6 tablets (3 g of the medicine) taken as 2 separate doses.
- Take 3 tablets in the morning and then 3 tablets in the evening.

#### Children

- There is no information for the use of Myclausen in children with a liver transplant.

### **How to take Myclausen**

- Swallow your tablets whole with a glass of water.

- Do not break or crush them.

#### **If you take more Myclausen than you should**

If you take more Myclausen than you should, talk to a doctor or go to a hospital straight away. Also do this if someone else accidentally takes your medicine. Take the medicine pack with you.

#### **If you forget to take Myclausen**

If you forget to take your medicine at any time, take it as soon as you remember. Then continue to take it at the usual times. Do not take a double dose to make up for a missed dose.

#### **If you stop taking Myclausen**

Do not stop taking Myclausen unless your doctor tells you to. If you stop your treatment you may increase the chance of rejection of your transplanted organ.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

#### **Talk to a doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:**

- you have a sign of infection such as a fever or sore throat
- you have any unexpected bruising or bleeding
- you have a rash, swelling of your face, lips, tongue or throat, with difficulty breathing - you may be having a serious allergic reaction to the medicine (such as anaphylaxis, angioedema).

#### **Usual problems**

Some of the more usual problems are diarrhoea, fewer white cells or red cells in your blood, infection and vomiting. Your doctor will do regular blood tests to check for any changes in

- the number of your blood cells or signs of infections.

Children may be more likely than adults to have some side effects. These include diarrhoea, infections, fewer white cells and fewer red cells in the blood.

#### **Fighting infections**

Myclausen reduces your body's defences. This is to stop you rejecting your transplant. As a result, your body will not be as good as normal at fighting infections. This means you may catch more infections than usual. This includes infections of the brain, skin, mouth, stomach and gut, lungs and urinary system.

#### **Lymph and skin cancer**

As can happen in patients taking this type of medicine (immune-suppressants), a very small number of patients on Myclausen have developed cancer of the lymphoid tissues and skin.

#### **General unwanted effects**

You may get general side effects affecting your body as a whole. These include serious allergic reactions (such as anaphylaxis, angioedema), fever, feeling very tired, difficulty sleeping, pains (such as stomach, chest, joint or muscle), headache, flu symptoms and swelling.

#### **Other unwanted effects may include:**

##### **Skin problems** such as:

- acne, cold sores, shingles, skin growth, hair loss, rash, itching.

##### **Urinary problems** such as:



- blood in the urine.

**Digestive system and mouth problems** such as:

- swelling of the gums and mouth ulcers
- inflammation of the pancreas, colon or stomach
- gastrointestinal disorders including bleeding
- liver disorders
- diarrhoea, constipation, feeling sick (nausea), indigestion, loss of appetite, flatulence.

**Nervous system problems** such as:

- feeling dizzy, drowsy or numb
- tremor, muscle spasms, convulsions
- feeling anxious or depressed, changes in your mood or thoughts.

**Heart and blood vessel problems** such as:

- change in blood pressure, accelerated heartbeat, widening of blood vessels.

**Lung problems** such as:

- pneumonia, bronchitis
- shortness of breath, cough, which can be due to bronchiectasis (a condition in which the lung airways are abnormally dilated) or pulmonary fibrosis (scarring of the lung). Talk to your doctor if you develop a persistent cough or breathlessness
- fluid on the lungs or inside the chest
- sinus problems.

**Other problems** such as:

- weight loss, gout, high blood sugar, bleeding, bruising.

**Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Myclausen

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Myclausen contains

The active substance is mycophenolate mofetil.  
Each tablet contains 500 mg mycophenolate mofetil

The other ingredients are:

Tablet core:

Microcrystalline cellulose, povidone (K-30), croscarmellose sodium, magnesium stearate

Tablet coat:

Polyvinyl alcohol (partially hydrolysed), titanium dioxide (E 171) macrogol 3000,talc

### **What Myclausen looks like and contents of the pack**

White round film-coated tablets.

Myclausen 500 mg film-coated tablets are available in PVC-aluminium blisters containing 10 tablets.

Each carton contains either 50 or 150 tablets.

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder**

Passauer Pharma GmbH

Eiderstedter Weg 3

14129 Berlin

Germany

### **Manufacturer**

Passauer Pharma GmbH

Eiderstedter Weg 3

14129 Berlin

Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

#### **België/Belgique/Belgien**

Passauer Pharma GmbH,

Duitsland/Allemagne/Deutschland

Tél/Tel: +49(0)3074460-11

#### **Lietuva**

Passauer Pharma GmbH,

Vokietija

Tel: +49(0)3074460-11

#### **България**

Passauer Pharma GmbH,

Германия

Тел: +49(0)3074460-11

#### **Luxembourg/Luxemburg**

Passauer Pharma GmbH,

Allemagne/Deutschland

Tél/Tel: +49(0)3074460-11

#### **Česká republika**

Pharmagen CZ, s.r.o.

Česká republika

Tel: +420 721 137 749

#### **Magyarország**

Passauer Pharma GmbH,

Németország

Tel: +49(0)3074460-11

#### **Danmark**

Passauer Pharma GmbH,

Tyskland

Tlf: +49(0)3074460-11

#### **Malta**

Passauer Pharma GmbH,

Il-Ġermanja

Tel: +49(0)3074460-11

#### **Deutschland**

Aristo Pharma GmbH,

Deutschland

Tel: +49 3071094-4200

#### **Nederland**

Passauer Pharma GmbH,

Duitsland

Tel: +49(0)3074460-11

**Eesti**

Passauer Pharma GmbH,  
Saksamaa  
Tel: +49(0)3074460-11

**Ελλάδα**

YAS Pharma L.P.  
Λεωφ. Κηφισίας 120 & Φλοίας 10  
151 25 Μαρούσι,  
Αθήνα - Ελλάδα  
Τηλ: + 30 210-6194190

**España**

Passauer Pharma GmbH,  
Alemania  
Tel: +49(0)3074460-1112

**France**

Passauer Pharma GmbH,  
Allemagne  
Tél: +49(0)3074460-11

**Hrvatska**

Passauer Pharma GmbH,  
Njemačka  
Tel: +49(0)3074460-11

**Ireland**

Passauer Pharma GmbH,  
Germany  
Tel: +49(0)3074460-11

**Ísland**

Passauer Pharma GmbH,  
Þýskaland  
Sími: +49(0)3074460-11

**Italia**

Passauer Pharma GmbH,  
Germania  
Tel: +49(0)3074460-11

**Κύπρος**

ISANGEN PHARMA CYPRUS LTD  
Guricon House, Ηνωμένων Εθνών 48, 2ος &  
3ος όροφος  
6042, Λάρνακα, Κύπρος  
Τηλ.: +357-24-638833

**Latvija**

Passauer Pharma GmbH,  
Vācija  
Tel: +49(0)3074460-11

**Norge**

Passauer Pharma GmbH,  
Tyskland  
Tlf: +49(0)3074460-11

**Österreich**

Passauer Pharma GmbH,  
Deutschland  
Tel: +49(0)3074460-11

**Polska**

Passauer Pharma GmbH,  
Niemcy  
Tel: +49(0)3074460-11

**Portugal**

Passauer Pharma GmbH,  
Alemanha  
Tel: +49(0)3074460-11

**România**

Passauer Pharma GmbH,  
Germania  
Tel: +49(0)3074460-11

**Slovenija**

Passauer Pharma GmbH,  
Nemčija  
Tel: +49(0)3074460-11

**Slovenská republika**

Passauer Pharma GmbH,  
Nemecko  
Tel: +49(0)3074460-11

**Suomi/Finland**

Passauer Pharma GmbH,  
Saksa  
Puh/Tel: +49(0)3074460-11

**Sverige**

Passauer Pharma GmbH,  
Tyskland  
Tel: +49(0)3074460-11

**United Kingdom (Northern Ireland)**

Passauer Pharma GmbH,  
Germany  
Tel: +49(0)3074460-11

**This leaflet was last revised in {MM/YYYY}**

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

## Package leaflet: Information for the patient

### Myclausen 250 mg hard capsules Mycophenolate mofetil

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### What is in this leaflet

- 1 What Myclausen is and what it is used for
- 2 What you need to know before you take Myclausen
- 3 How to take Myclausen
- 4 Possible side effects
- 5 How to store Myclausen
- 6 Content of the pack and other information

#### 1. What Myclausen is and what it is used for

Myclausen contains mycophenolate mofetil.

- This belongs to a group of medicines called “immunosuppressants”.

Myclausen is used to prevent your body rejecting a transplanted organ.

- A kidney, heart or liver.

Myclausen should be used together with other medicines:

- Ciclosporin and corticosteroids.

#### 2. What you need to know before you take Myclausen

##### WARNING

Mycophenolate causes birth defects and miscarriage. If you are a woman who could become pregnant, you must provide a negative pregnancy test before starting treatment and must follow the contraception advice given to you by your doctor.

Your doctor will speak to you and give you written information, particularly on the effects of mycophenolate on unborn babies. Read the information carefully and follow the instructions. If you do not fully understand these instructions, please ask your doctor to explain them again before you take mycophenolate. See also further information in this section under “Warnings and precautions” and “Pregnancy and breast-feeding”.

##### Do not take Myclausen

- If you are allergic to mycophenolate mofetil, mycophenolic acid or any of the other ingredients of this medicine (listed in section 6).
- If you are a woman who could be pregnant and you have not provided a negative pregnancy test before your first prescription, as mycophenolate causes birth defects and miscarriage.
- If you are pregnant or planning to become pregnant or think you may be pregnant
- If you are not using effective contraception (see Pregnancy, contraception and breast-feeding).
- If you are breast-feeding.

Do not take this medicine if any of the above applies to you. If you are not sure, talk to your doctor or

pharmacist before taking Myclausen.

### **Warnings and precautions**

Talk to your doctor straight away before starting treatment with Myclausen:

- If you are older than 65 years as you may have an increased risk of developing adverse events such as certain viral infections, gastrointestinal bleeding and pulmonary oedema when compared to younger patients
- If you have a sign of infection such as a fever or sore throat
- If you have any unexpected bruising or bleeding
- If you have ever had a problem with your digestive system such as a stomach ulcer
- If you are planning to become pregnant or if you get pregnant while you or your partner are taking Myclausen.
- If you have a hereditary enzyme deficiency such as Lesch-Nyhan and Kelley-Seegmiller syndrome

If any of the above apply to you (or you are not sure), talk to your doctor straight away before starting treatment with Myclausen.

### **The effect of sunlight**

Myclausen reduces your body's defences. As a result, there is an increased risk of skin cancer. Limit the amount of sunlight and UV light you get. Do this by:

- wearing protective clothing that also covers your head, neck, arms and legs
- using a sunscreen with a high protection factor.

### **Children**

Do not give this medicine to children younger than 2 years because based on the limited safety and efficacy data for this age group no dose recommendations can be made.

### **Other medicines and Myclausen**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, including herbal medicines. This is because Myclausen can affect the way some other medicines work. Also other medicines can affect the way Myclausen works.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines before you start Myclausen:

- azathioprine or other medicines that suppress your immune system (given after a transplant operation)
- cholestyramine (used to treat high cholesterol)
- rifampicin (an antibiotic used to prevent and treat infections such as tuberculosis (TB))
- antacids or proton pump inhibitors (used for acid problems in your stomach such as indigestion)
- phosphate binders (used by people with chronic kidney failure to reduce how much phosphate gets absorbed into their blood).
- antibiotics (used to treat bacterial infections)
- isavuconazole (used to treat fungal infections)
- telmisartan (used to treat high blood pressure)

### **Vaccines**

If you need to have a vaccination (a live vaccine) while taking Myclausen, talk to your doctor or pharmacist first. Your doctor will have to advise you on what vaccines you can have.

You must not donate blood during treatment with Myclausen and for at least 6 weeks after stopping treatment. Men must not donate semen during treatment with Myclausen and for at least 90 days after stopping treatment.

### **Myclausen with food and drink**

Taking food and drink has no effect on your treatment with Myclausen.

### **Contraception in women taking Myclausen**

If you are a woman who could become pregnant you must use an effective method of contraception with Myclausen. This includes:

- Before you start taking Myclausen
- During your entire treatment with Myclausen
- For 6 weeks after you stop taking Myclausen.

Talk to your doctor about the most suitable contraception for you. This will depend on your individual situation. Two forms of contraception are preferable as this will reduce the risk of unintended pregnancy. **Contact your doctor as soon as possible, if you think your contraception may not have been effective or if you have forgotten to take your contraceptive pill.**

You cannot become pregnant if any of the following conditions applies to you:

- You are post-menopausal, i.e. at least 50 years old and your last period was more than a year ago (if your periods have stopped because you have had treatment for cancer, then there is still a chance you could become pregnant)
- Your fallopian tubes and both ovaries have been removed by surgery (bilateral salpingo-oophorectomy)
- Your womb (uterus) has been removed by surgery (hysterectomy)
- Your ovaries no longer work (premature ovarian failure, which has been confirmed by a specialist gynaecologist)
- You were born with one of the following rare conditions that make pregnancy impossible: the XY genotype, Turner's syndrome or uterine agenesis
- You are a child or teenager who has not started having periods.

### **Contraception in men taking Myclausen**

The available evidence does not indicate an increased risk of malformations or miscarriage if the father takes mycophenolate. However, a risk cannot be completely excluded. As a precaution you or your female partner are recommended to use reliable contraception during treatment and for 90 days after you stop taking Myclausen.

If you are planning to have a child, talk to your doctor about the potential risks and alternative therapies.

### **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will talk to you about the risks in case of pregnancy and the alternatives you can take to prevent rejection of your transplant organ if:

- You plan to become pregnant.
- You miss or think you have missed a period, or you have unusual menstrual bleeding, or suspect you are pregnant.
- You have sex without using effective methods of contraception.

If you do become pregnant during the treatment with mycophenolate, you must inform your doctor immediately. However, keep taking Myclausen until you see him or her.

### **Pregnancy**

Mycophenolate causes a very high frequency of miscarriage (50%) and of severe birth defects (23 - 27%) in the unborn baby. Birth defects that have been reported include anomalies of ears, of eyes, of face (cleft lip/palate), of development of fingers, of heart, oesophagus (tube that connects the throat with the stomach), kidneys and nervous system (for example spina bifida (where the bones of the spine are not properly developed)). Your baby may be affected by one or more of these.

If you are a woman who could become pregnant, you must provide a negative pregnancy test before starting treatment and must follow the contraception advice given to you by your doctor. Your doctor may request more than one test to ensure you are not pregnant before starting treatment.

### **Breast-feeding**

Do not take Myclausen if you are breast-feeding. This is because small amounts of the medicine can pass into the mother's milk.

### **Driving and using machines**

Myclausen has a moderate influence on your ability to drive or use any tools or machines. If you feel drowsy, numb or confused, talk to your doctor or nurse and do not drive or use any tools or machines until you feel better.

### **Myclausen contains sodium**

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'

## **3. How to take Myclausen**

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

### **How much to take**

The amount you take depends on the type of transplant you have had. The usual doses are shown below. Treatment will continue for as long as you need to prevent rejection of your transplant organ.

### **Kidney transplant**

#### Adults

- The first dose is given within 3 days of the transplant operation.
- The daily dose is 8 capsules (2 g of the medicine) taken as 2 separate doses.
- Take 4 capsules in the morning and then 4 capsules in the evening.

#### Children aged 2 to 18 years

- The dose given will vary depending on the size of the child.
- Your doctor will decide the most appropriate dose based on your child's height and weight (body surface area - measured as square metres or 'm<sup>2</sup>'). The recommended dose is 600 mg per m<sup>2</sup> taken twice a day.

### **Heart transplant**

#### Adults

- The first dose is given within 5 days of the transplant operation.
- The daily dose is 12 capsules (3 g of the medicine) taken as 2 separate doses.
- Take 6 capsules in the morning and then 6 capsules in the evening.

#### Children

- There is no information for the use of Myclausen in children with a heart transplant.

### **Liver transplant**

#### Adults

- The first dose of oral Myclausen will be given to you at least 4 days after the transplant operation and when you are able to swallow oral medicines.
- The daily dose is 12 capsules (3 g of the medicine) taken as 2 separate doses.
- Take 6 capsules in the morning and then 6 capsules in the evening.

#### Children

- There is no information for the use of Myclausen in children with a liver transplant.

### **How to take Myclausen**

- Swallow your capsules whole with a glass of water.
- Do not open or crush them.



- Do not take any capsules that have broken open or split.

Take care not to let any powder from inside a broken capsule get into your eyes or mouth.

- If this happens, rinse with plenty of plain water.

Take care not to let any powder from inside a broken capsule get onto your skin.

- If this happens, wash the area thoroughly with soap and water.

### **If you take more Myclausen than you should**

If you take more Myclausen than you should, talk to a doctor or go to a hospital straight away. Also do this if someone else accidentally takes your medicine. Take the medicine pack with you.

### **If you forget to take Myclausen**

If you forget to take your medicine at any time, take it as soon as you remember. Then continue to take it at the usual times. Do not take a double dose to make up for a missed dose.

### **If you stop taking Myclausen**

Do not stop taking Myclausen unless your doctor tells you to. If you stop your treatment you may increase the chance of rejection of your transplant organ.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

### **Talk to a doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:**

- you have a sign of infection such as a fever or sore throat
- you have any unexpected bruising or bleeding
- you have a rash, swelling of your face, lips, tongue or throat, with difficulty breathing - you may be having a serious allergic reaction to the medicine (such as anaphylaxis, angioedema).

### **Usual problems**

Some of the more usual problems are diarrhoea, fewer white cells or red cells in your blood, infection and vomiting. Your doctor will do regular blood tests to check for any changes in

- the number of your blood cells or signs of infections

Children may be more likely than adults to have some side effects. These include diarrhoea, infections, fewer white cells and fewer red cells in the blood.

### **Fighting infections**

Myclausen reduces your body's defences. This is to stop you rejecting your transplant. As a result, your body will not be as good as normal at fighting infections. This means you may catch more infections than usual. This includes infections of the brain, skin, mouth, stomach and gut, lungs and urinary system.

### **Lymph and skin cancer**

As can happen in patients taking this type of medicine (immune-suppressants), a very small number of patients on Myclausen have developed cancer of the lymphoid tissues and skin.

### **General unwanted effects**

You may get general side effects affecting your body as a whole. These include serious allergic reactions (such as anaphylaxis, angioedema), fever, feeling very tired, difficulty sleeping, pains (such as stomach, chest, joint or muscle), headache, flu symptoms and swelling.

Other unwanted effects may include:

**Skin problems** such as

- acne, cold sores, shingles, skin growth, hair loss, rash, itching.

**Urinary problems** such as:

- blood in the urine.

**Digestive system and mouth problems** such as:

- swelling of the gums and mouth ulcers
- inflammation of the pancreas, colon or stomach
- gastrointestinal disorders including bleeding,
- liver disorder
- diarrhoea, constipation, feeling sick (nausea), indigestion, loss of appetite, flatulence.

**Nervous system problems** such as:

- feeling dizzy, drowsy or numb
- tremor, muscle spasms, convulsions
- feeling anxious or depressed, changes in your mood or thoughts.

**Heart and blood vessel problems** such as:

- change in blood pressure, accelerated heartbeat, widening of blood vessels.

**Lung problems** such as:

- pneumonia, bronchitis
- shortness of breath, cough, which can be due to bronchiectasis (a condition in which the lung airways are abnormally dilated) or pulmonary fibrosis (scarring of the lung). Talk to your doctor if you develop a persistent cough or breathlessness
- fluid on the lungs or inside the chest
- sinus problems.

**Other problems** such as:

- weight loss, gout, high blood sugar, bleeding, bruising.

### **Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store Myclausen**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.

Store below 30 °C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Myclausen contains**

The active substance is mycophenolate mofetil. Each capsule contains 250 mg mycophenolate mofetil.

The other ingredients are:

Capsule content:

pre-gelatinised starch (maize), croscarmellose sodium, povidone (K-30), magnesium stearate

Capsule shells:

gelatine, titanium dioxide (E 171)

### **What Myclausen looks like and contents of the pack**

White oblong capsules.

Myclausen 250 mg capsules is available PVC-aluminium blister containing 10 capsules. Each carton contains either 100 or 300 capsules.

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder**

Passauer Pharma GmbH

Eiderstedter Weg 3

14129 Berlin

Germany

### **Manufacturer**

Passauer Pharma GmbH

Eiderstedter Weg 3

14129 Berlin

Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

#### **België/Belgique/Belgien**

Passauer Pharma GmbH,

Duitsland/Allemagne/Deutschland

Tél/Tel: +49(0)3074460-11

#### **Lietuva**

Passauer Pharma GmbH,

Vokietija

Tel: +49(0)3074460-11

#### **България**

Passauer Pharma GmbH,

Германия

Тел: +49(0)3074460-11

#### **Luxembourg/Luxemburg**

Passauer Pharma GmbH,

Allemagne/Deutschland

Tél/Tel: +49(0)3074460-11

#### **Česká republika**

Pharmagen CZ, s.r.o.

Česká republika

Tel: +420 721 137 749

#### **Magyarország**

Passauer Pharma GmbH,

Németország

Tel: +49(0)3074460-11

#### **Danmark**

Passauer Pharma GmbH,

Tyskland

Tlf: +49(0)3074460-11

#### **Malta**

Passauer Pharma GmbH,

Il-Ġermanja

Tel: +49(0)3074460-11

#### **Deutschland**

Aristo Pharma GmbH,

Deutschland

Tel: +49 3071094-4200

#### **Nederland**

Passauer Pharma GmbH,

Duitsland

Tel: +49(0)3074460-11

**Eesti**

Passauer Pharma GmbH,  
Saksamaa  
Tel: +49(0)3074460-11

**Ελλάδα**

YAS Pharma L.P.  
Λεωφ. Κηφισίας 120 & Φλοίας 10  
151 25 Μαρούσι,  
Αθήνα - Ελλάδα  
Τηλ: + 30 210-6194190

**España**

Passauer Pharma GmbH,  
Alemania  
Tel: +49(0)3074460-11

**France**

Passauer Pharma GmbH,  
Allemagne  
Tél: +49(0)3074460-11

**Hrvatska**

Passauer Pharma GmbH,  
Njemačka  
Tel: +49(0)3074460-11

**Ireland**

Passauer Pharma GmbH,  
Germany  
Tel: +49(0)3074460-11

**Ísland**

Passauer Pharma GmbH,  
Þýskaland  
Sími: +49(0)3074460-11

**Italia**

Passauer Pharma GmbH,  
Germania  
Tel: +49(0)3074460-11

**Κύπρος**

ISANGEN PHARMA CYPRUS LTD  
Guricon House, Ηνωμένων Εθνών 48, 2ος &  
3ος όροφος  
6042, Λάρνακα, Κύπρος  
Τηλ.: +357-24-638833

**Latvija**

Passauer Pharma GmbH,  
Vācija  
Tel: +49(0)3074460-11

**Norge**

Passauer Pharma GmbH,  
Tyskland  
Tlf: +49(0)3074460-11

**Österreich**

Passauer Pharma GmbH,  
Deutschland  
Tel: +49(0)3074460-11

**Polska**

Passauer Pharma GmbH,  
Niemcy  
Tel: +49(0)3074460-11

**Portugal**

Passauer Pharma GmbH,  
Alemanha  
Tel: +49(0)3074460-11

**România**

Passauer Pharma GmbH,  
Germania  
Tel: +49(0)3074460-11

**Slovenija**

Passauer Pharma GmbH,  
Nemčija  
Tel: +49(0)3074460-11

**Slovenská republika**

Passauer Pharma GmbH,  
Nemecko  
Tel: +49(0)3074460-11

**Suomi/Finland**

Passauer Pharma GmbH,  
Saksa  
Puh/Tel: +49(0)3074460-11

**Sverige**

Passauer Pharma GmbH,  
Tyskland  
Tel: +49(0)3074460-11

**United Kingdom (Northern Ireland)**

Passauer Pharma GmbH,  
Germany  
Tel: +49(0)3074460-11

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Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

**ANNEX IV**

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS  
OF THE MARKETING AUTHORISATION(S)**

### **Scientific conclusions**

Taking into account the PRAC Assessment Report on the PSUR(s) for mycophenolate mofetil, mycophenolic acid, the scientific conclusions of PRAC are as follows:

In view of available data regarding excretion of mycophenolic acid in human milk from the literature, the PRAC considers that excretion of mycophenolic acid in human milk is at least a reasonable possibility. The PRAC concluded that the product information of products containing mycophenolate mofetil, mycophenolic acid should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

### **Grounds for the variation to the terms of the marketing authorisation(s)**

On the basis of the scientific conclusions for mycophenolate mofetil, mycophenolic acid the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing mycophenolate mofetil, mycophenolic acid is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.