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 adults, and children and adolescents aged 2 to 18 years 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 with Myclausen should be initiated and maintained by appropriately qualified transplant specialists.

Posology

Use in renal transplant

Adults
Oral Myclausen 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^2 administered orally twice daily (up to a maximum of 2 g daily). Myclausen film-coated tablets should only be prescribed to patients with a body surface area greater than 1.5 m^2, 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
Oral Myclausen 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 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^2), 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.

Method of administration

Myclausen is 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, Myclausen 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.

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 x 10^3/µl), 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 depression.

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. sirolimus, belatacept, or vice versa, as this might result in changes of MPA exposure. Medicinal products of other classes which interfere with MPA's enterohepatic cycle e.g. cholestyramine should be used with caution due to their potential to reduce the plasma levels and efficacy of Myclausen (see also section 4.5).

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 tacrolimus or 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.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. 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.

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.

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

Ciclosporin A
Ciclosporin A (CsA) pharmacokinetics are unaffected by mycophenolate mofetil. In contrast, if concomitant ciclosporin 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.

Telmisartan
Concomitant administration of telmisartan and mycophenolate mofetil esulted in an approximately 30 % decrease of MPA concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression, which in turn results in an enhanced UGT1A9 expression and activity. When comparing rates of transplant rejection, rates of graft loss or adverse event profiles between mycophenolate mofetil patients with and without concomitant telmisartan medication, no clinical consequences of the pharmacokinetic medicinal product-medicinal product 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 pharmacokinetics and pharmacodynamics of oral contraceptives were unaffected 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 (AUC0-12 h) 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 Cmax and AUC (0-12h) by 30 % and 25 %, respectively, were observed when mycophenolate mofetil was concomitantly administered with sevelamer without any clinical consequences (i.e. graft rejection). It is recommended, 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.

Trimethoprim/sulfamethoxazole
No effect on the bioavailability of MPA was observed.

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.

Ciprofloxacin and 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 predose 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.

Tacrolimus
In hepatic transplant patients initiated on mycophenolate mofetil and tacrolimus, the AUC and Cmax of MPA, the active metabolite of mycophenolate mofetil, were not significantly affected by coadministration 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).

Other 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.

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.

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 the embryo to mycophenolate. It is recommended that the second test should be performed 8 – 10 days after the first test. For transplants from deceased donors, if it is not possible to perform two test 8 – 10 days apart before treatment starts (because of the timing of transplant organ availability), a pregnancy test must be performed immediately before starting treatment and a further test performed 8 – 10 days later. Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported). Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.

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 artesia (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

Mycophenolate mofetil has been shown to be excreted in the milk of lactating rats. It is not known whether this substance is excreted in human milk. Because of the potential for serious adverse reactions to mycophenolate mofetil in breast-fed infants, Myclausen is contraindicated in nursing mothers (see section 4.3).

Men

Limited clinical evidence 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 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 the potential risk of fathering a child with a qualified health-care professional.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. The

pharmacodynamic profile and the reported adverse reactions indicate that an effect is unlikely.

4.8 Undesirable effects

The following undesirable effects cover adverse reactions from clinical trials
The principal adverse reactions associated with the administration of mycophenolate mofetil in combination with ciclosporin and corticosteroids include diarrhoea, leucopenia, sepsis and vomiting, and there is evidence of a higher frequency of certain types of infections (see section 4.4).

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). Lymphoproliferative disease or lymphoma developed in 0.6 % of patients receiving mycophenolate mofetil (2 g or 3 g daily) in combination with other immunosuppressants in controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients followed for at least 1 year. Non-melanoma skin carcinomas occurred in 3.6 % of patients; other types of malignancy occurred in 1.1 % of patients. 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.

Opportunistic infections
All transplant patients are at increased risk of opportunistic infections; the risk increased with total immunosuppressive load (see section 4.4). The most common opportunistic infections in patients receiving mycophenolate mofetil (2 g or 3 g daily) with other immunosuppressants in controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients followed for at least 1 year were candida mucocutaneous, CMV viraemia/syndrome and Herpes simplex. The proportion of patients with CMV viraemia/syndrome was 13.5 %.

Paediatric population
The type and frequency of adverse reactions in a clinical study, which recruited 92 paediatric patients aged 2 to 18 years who were given 600 mg/m^2 mycophenolate mofetil orally twice daily, were generally similar to those observed in adult patients given 1 g mycophenolate mofetil twice daily. However, the following treatment-related adverse events were more frequent in the paediatric population, particularly in children under 6 years of age, when compared to adults: diarrhoea, sepsis, leucopenia, anaemia and infection.

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

Other adverse reactions
Adverse reactions, probably or possibly related to mycophenolate mofetil, reported in ≥ 1/10 and in ≥ 1/100 to < 1/10 of patients treated with mycophenolate mofetil in the controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients are listed in the following table.

Adverse reactions, reported in patients treated with mycophenolate mofetil in renal, cardiac and hepatic clinical trials when used in combination with ciclosporin and corticosteroids

Within the system organ classes, undesirable effects are listed under headings of frequency, using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class		**Adverse drug reactions**
Infections and infestations	Very common	Sepsis, gastrointestinal candidiasis, urinary tract infection, herpes simplex, herpes zoster
	Common	Pneumonia, influenza, respiratory tract infection, respiratory moniliasis, gastrointestinal infection, candidiasis, gastroenteritis, infection, bronchitis, pharyngitis, sinusitis, fungal skin infection, skin candida, vaginal candidiasis, rhinitis
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Very common	-
	Common	Skin cancer, benign neoplasm of skin
Blood and lymphatic system disorders	Very common	Leucopenia, thrombocytopenia, anaemia
	Common	Pancytopenia, leukocytosis
Metabolism and nutrition disorders	Very common	-
	Common	Acidosis, hyperkalaemia, hypokalaemia, hyperglycaemia, hypomagnesaemia, hypocalcaemia, hypercholesterolaemia, hyperlipidaemia, hypophosphataemia, hyperuricaemia, gout, anorexia
Psychiatric disorders	Very common	-
	Common	Agitation, confusional state, depression, anxiety, thinking abnormal, insomnia
Nervous system disorders	Very common	-
	Common	Convulsion, hypertonia, tremor, somnolence, myasthenic syndrome, dizziness, headache, paraesthesia, dysgeusia
Cardiac disorders	Very common	-
	Common	Tachycardia
Vascular disorders	Very common	-
	Common	Hypotension, hypertension, vasodilatation
Respiratory, thoracic and mediastinal disorders	Very common	-
	Common	Pleural effusion, dyspnoea, cough
Gastrointestinal disorders	Very common	Vomiting, abdominal pain, diarrhoea, nausea
	Common	Gastrointestinal haemorrhage, peritonitis, ileus, colitis, gastric ulcer, duodenal ulcer, gastritis, oesophagitis, stomatitis, constipation, dyspepsia, flatulence, eructation
Hepatobiliary disorders	Very common	-
	Common	Hepatitis, jaundice, hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Very common	-
	Common	Skin hypertrophy, rash, acne, alopecia

System organ class		Adverse drug reactions
Musculoskeletal and connective tissue disorders	Very common	-
	Common	Arthralgia
Renal and urinary disorders	Very common	-
	Common	Renal impairment
General disorders and administration site conditions	Very common	-
	Common	Oedema, pyrexia, chills, pain, malaise, asthenia
Investigations	Very common	-
	Common	Hepatic enzyme increased, blood creatinine increased, blood lactate dehydrogenase increased, blood urea increased, blood alkaline phosphatase increased, weight decreased

Note: 501 (2 g mycophenolate mofetil daily), 289 (3 g mycophenolate mofetil daily) and 277 (2 g intravenous / 3 g oral mycophenolate mofetil daily) patients were treated in Phase III studies for the prevention of rejection in renal, cardiac and hepatic transplantation, respectively.

The following undesirable effects cover adverse reactions from post-marketing experience
The types of adverse reactions reported during post-marketing with mycophenolate mofetil are similar to those seen in the controlled renal, cardiac and hepatic transplant studies. Additional adverse reactions reported during post-marketing are described below with the frequencies reported within brackets if known.

Gastrointestinal
Gingival hyperplasia (≥ 1/100 to < 1/10), colitis including cytomegalovirus colitis, (≥ 1/100 to < 1/10), pancreatitis (≥ 1/100 to < 1/10) and intestinal villous atrophy.

Infections
Serious life-threatening infections including meningitis, endocarditis, tuberculosis and atypical mycobacterial infection. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leucoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including mycophenolate mofetil. Agranulocytosis (≥ 1/1000 to < 1/100) and neutropenia have been reported; therefore, regular monitoring of patients taking Myclausen is advised (see section 4.4). There have been reports of aplastic anaemia and bone marrow depression in patients treated with mycophenolate mofetil, some of which have been fatal.

Blood and lymphatic system disorder
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.

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

Pregnancy, puerperium and perinatal conditions
Cases of spontaneous abortions have been reported in patients exposed to mycophenolate mofetil, mainly in the first trimester, see section 4.6.

Congenital disorders
Congenital malformations have been observed post-marketing in children of patients exposed to mycophenolate mofetil in combination with other immunosuppressants, see section 4.6.

Respiratory, thoracic and mediastinal disorders
There have been isolated reports of interstitial lung disease and pulmonary fibrosis in patients treated with mycophenolate mofetil in combination with other immunosuppressants, some of which have been fatal. There have also been reports of bronchiectasis in children and adults (frequency not known).

Immune system disorders
Hypogammaglobulinaemia has been reported in patients receiving mycophenolate mofetil in combination with other immunosuppressants (frequency not known).

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 re-circulation of the drug (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressants, selective immunosuppressants, ATC code: L04AA06

Mechanism of action
Mycophenolate mofetil is the 2-morpholinoethyl ester of MPA. MPA is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase, 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.

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 Cmax was decreased by 40 % in the presence of food. Mycophenolate mofetil is not measurable systemically in plasma following oral administration.

Distribution

As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed at approximately 6-12 hours post-dose. A reduction in the AUC of MPA of approximately 40 % is associated with the co-administration of cholestyramine (4 g TID), indicating that there is a significant amount of enterohepatic recirculation.
MPA at clinically relevant concentrations is 97 % bound to plasma albumin.

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, leucopenia).

Elimination

A negligible amount of substance is excreted as MPA (< 1 % of 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 circulation of the medicinal product, bile acid sequestrants such as cholestyramine, reduce MPA AUC (see section 4.9).
MPA's disposition depends on several transporters. Organic anion-transporting polypeptides (OATPs) and multidrug resistance-associated protein 2 (MRP2) are involved in MPA's disposition; OATP isoforms, MRP2 and breast cancer resistance protein (BCRP) are transporters associated with the glucuronides' biliary excretion. Multidrug resistance protein 1 (MDR1) is also able to transport MPA, but its contribution seems to be confined to the absorption process. In the kidney MPA and its metabolites potently interact with renal organic anion transporters.

In the early post-transplant period (< 40 days post-transplant), renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30 % lower and Cmax approximately 40 % lower compared to the late post-transplant period (3-6 months post-transplant).

Special populations

Renal impairment
In a single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate < 25 mL/min/1.73 m^2) were 28-75 % higher relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. However, the mean single dose MPAG AUC was 3-6-fold higher in subjects with severe renal impairment than in subjects with mild renal impairment or normal healthy subjects, consistent with the known renal elimination of MPAG. Multiple dosing of mycophenolate mofetil in patients

with severe chronic renal impairment has not been studied. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Delayed renal graft function
In patients with delayed renal graft function post-transplant, mean MPA AUC (0–12 h) was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC (0-12 h) was 2-3-fold higher than in post-transplant patients without delayed graft function. There may be a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of 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 this process probably depend on the particular disease. However, 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^2 mycophenolate mofetil orally twice daily. This dose achieved MPA AUC values similar to those seen in adult renal transplant patients receiving mycophenolate mofetil at a dose of 1 g bid in the early and late posttransplant period. MPA AUC values across age groups were similar in the early and late posttransplant period.

Elderly
Pharmacokinetic behaviour of mycophenolate mofetil in the elderly (≥ 65 years) has not been formally evaluated.

Patients taking oral contraceptives
The pharmacokinetics of oral contraceptives were unaffected by coadministration of mycophenolate mofetil (see also section 4.5). 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 0.15 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) conducted in 18 non-transplant women (not taking other immunosupressants) 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.

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 Cmax) observed in renal transplant patients at the recommended clinical dose of 2 g/day and 1.3-2 times the systemic exposure (AUC or C_{max}) 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.

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.

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

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Germany
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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 with Myclausen should be initiated and maintained by appropriately qualified transplant specialists.

Posology

Use in renal transplant

Adults
Oral Myclausen 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^2 administered orally twice daily (up to a maximum of 2 g daily). Myclausen capsules should only be prescribed to patients with a body surface area of at least 1.25 m^2. Patients with a body surface area of 1.25 to 1.5 m^2 may be prescribed Myclausen 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^2 may be prescribed Myclausen 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
Oral Myclausen 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 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^2), 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.

Method of administration

Myclausen is 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, Myclausen capsules should not be opened or crushed to avoid inhalation or direct contact with skin or mucous membranes of the powder contained in Myclausen 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 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.

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 < $1.3 \times 10^3/\mu l$), 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 depression.

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. sirolimus, belatacept, or vice versa, as this might result in changes of MPA exposure. Medicinal products of other classes which interfere with MPA's enterohepatic cycle e.g. cholestyramine should be used with caution due to their potential to reduce the plasma levels and efficacy of Myclausen (see also section 4.5).

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 tacrolimus or 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.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. 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.

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.

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

Ciclosporin A
Ciclosporin A (CsA) pharmacokinetics are unaffected by mycophenolate mofetil. In contrast, if concomitant ciclosporin 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.

Telmisartan
Concomitant administration of telmisartan and mycophenolate mofetil esulted in an approximately 30 % decrease of MPA concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression, which in turn results in an enhanced UGT1A9 expression and activity. When comparing rates of transplant rejection, rates of graft loss or adverse event profiles between mycophenolate mofetil patients with and without concomitant telmisartan medication, no clinical consequences of the pharmacokinetic medicinal product-medicinal product 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 pharmacokinetics and pharmacodynamics of oral contraceptives were unaffected 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 (AUC0-12 h) 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 Cmax and AUC (0-12h) by 30 % and 25 %, respectively, were observed when mycophenolate mofetil was concomitantly administered with sevelamer without any clinical consequences (i.e. graft rejection). It is recommended, 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.

Trimethoprim/sulfamethoxazole
No effect on the bioavailability of MPA was observed.

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.

Ciprofloxacin and 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 predose 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.

Tacrolimus
In hepatic transplant patients initiated on mycophenolate mofetil and tacrolimus, the AUC and Cmax of MPA, the active metabolite of mycophenolate mofetil, were not significantly affected by coadministration 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).

Other 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.

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.

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 counseled 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 the embryo to mycophenolate. It is recommended that the second test should be performed 8 – 10 days after the first test. For transplants from deceased donors, if it is not possible to perform two test 8 – 10 days apart before treatment starts (because of the timing of transplant organ availability), a pregnancy test must be performed immediately before starting treatment and a further test performed 8 – 10 days later. Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported). Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.

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 artesia (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

Mycophenolate mofetil has been shown to be excreted in the milk of lactating rats. It is not known whether this substance is excreted in human milk. Because of the potential for serious adverse reactions to mycophenolate mofetil in breast-fed infants, Myclausen is contraindicated in nursing mothers (see section 4.3).

Men

Limited clinical evidence 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 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 the potential risk of fathering a child with a qualified health-care professional.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. The pharmacodynamic profile and the reported adverse reactions indicate that an effect is unlikely.

4.8 Undesirable effects

The following undesirable effects cover adverse reactions from clinical trials
The principal adverse reactions associated with the administration of mycophenolate mofetil in combination with ciclosporin and corticosteroids include diarrhoea, leucopenia, sepsis and vomiting, and there is evidence of a higher frequency of certain types of infections (see section 4.4).

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). Lymphoproliferative disease or lymphoma developed in 0.6 % of patients receiving mycophenolate mofetil (2 g or 3 g daily) in combination with other immunosuppressants in controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients followed for at least 1 year. Non-melanoma skin carcinomas occurred in 3.6 % of patients; other types of malignancy occurred in 1.1 % of patients. 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.

Opportunistic infections
All transplant patients are at increased risk of opportunistic infections; the risk increased with total immunosuppressive load (see section 4.4). The most common opportunistic infections in patients receiving mycophenolate mofetil (2 g or 3 g daily) with other immunosuppressants in controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients followed for at least 1 year were candida mucocutaneous, CMV viraemia/syndrome and Herpes simplex. The proportion of patients with CMV viraemia/syndrome was 13.5 %.

Paediatric population
The type and frequency of adverse reactions in a clinical study, which recruited 92 paediatric patients aged 2 to 18 years who were given 600 mg/m^2 mycophenolate mofetil orally twice daily, were generally similar to those observed in adult patients given 1 g mycophenolate mofetil twice daily. However, the following treatment-related adverse events were more frequent in the paediatric population, particularly in children under 6 years of age, when compared to adults: diarrhoea, sepsis, leucopenia, anaemia and infection.

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

Other adverse reactions
Adverse reactions, probably or possibly related to mycophenolate mofetil, reported in ≥ 1/10 and in ≥ 1/100 to < 1/10 of patients treated with mycophenolate mofetil in the controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients are listed in the following table.

Adverse reactions, reported in patients treated with mycophenolate mofetil in renal, cardiac and hepatic clinical trials when used in combination with ciclosporin and corticosteroids

Within the system organ classes, undesirable effects are listed under headings of frequency, using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of

decreasing seriousness.

System organ class		**Adverse drug reactions**
Infections and infestations	Very common	Sepsis, gastrointestinal candidiasis, urinary tract infection, herpes simplex, herpes zoster
	Common	Pneumonia, influenza, respiratory tract infection, respiratory moniliasis, gastrointestinal infection, candidiasis, gastroenteritis, infection, bronchitis, pharyngitis, sinusitis, fungal skin infection, skin candida, vaginal candidiasis, rhinitis
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Very common	-
	Common	Skin cancer, benign neoplasm of skin
Blood and lymphatic system disorders	Very common	Leucopenia, thrombocytopenia, anaemia
	Common	Pancytopenia, leukocytosis
Metabolism and nutrition disorders	Very common	-
	Common	Acidosis, hyperkalaemia, hypokalaemia, hyperglycaemia, hypomagnesaemia, hypocalcaemia, hypercholesterolaemia, hyperlipidaemia, hypophosphataemia, hyperuricaemia, gout, anorexia
Psychiatric disorders	Very common	-
	Common	Agitation, confusional state, depression, anxiety, thinking abnormal, insomnia
Nervous system disorders	Very common	-
	Common	Convulsion, hypertonia, tremor, somnolence, myasthenic syndrome, dizziness, headache, paraesthesia, dysgeusia
Cardiac disorders	Very common	-
	Common	Tachycardia
Vascular disorders	Very common	-
	Common	Hypotension, hypertension, vasodilatation
Respiratory, thoracic and mediastinal disorders	Very common	-
	Common	Pleural effusion, dyspnoea, cough
Gastrointestinal disorders	Very common	Vomiting, abdominal pain, diarrhoea, nausea
	Common	Gastrointestinal haemorrhage, peritonitis, ileus, colitis, gastric ulcer, duodenal ulcer, gastritis, oesophagitis, stomatitis, constipation, dyspepsia, flatulence, eructation
Hepatobiliary disorders	Very common	-
	Common	Hepatitis, jaundice, hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Very common	-

System organ class		Adverse drug reactions
	Common	Skin hypertrophy, rash, acne, alopecia
Musculoskeletal and connective tissue disorders	Very common	-
	Common	Arthralgia
Renal and urinary disorders	Very common	-
	Common	Renal impairment
General disorders and administration site conditions	Very common	-
	Common	Oedema, pyrexia, chills, pain, malaise, asthenia
Investigations	Very common	-
	Common	Hepatic enzyme increased, blood creatinine increased, blood lactate dehydrogenase increased, blood urea increased, blood alkaline phosphatase increased, weight decreased

Note: 501 (2 g mycophenolate mofetil daily), 289 (3 g mycophenolate mofetil daily) and 277 (2 g intravenous / 3 g oral mycophenolate mofetil daily) patients were treated in Phase III studies for the prevention of rejection in renal, cardiac and hepatic transplantation, respectively.

The following undesirable effects cover adverse reactions from post-marketing experience
The types of adverse reactions reported during post-marketing with mycophenolate mofetil are similar to those seen in the controlled renal, cardiac and hepatic transplant studies. Additional adverse reactions reported during post-marketing are described below with the frequencies reported within brackets if known.

Gastrointestinal
Gingival hyperplasia (≥ 1/100 to < 1/10), colitis including cytomegalovirus colitis, (≥ 1/100 to < 1/10), pancreatitis, (≥ 1/100 to < 1/10) and intestinal villous atrophy.

Infections
Serious life-threatening infections including meningitis, endocarditis, tuberculosis and atypical mycobacterial infection. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leucoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including mycophenolate mofetil. Agranulocytosis (≥ 1/1000 to < 1/100) and neutropenia have been reported; therefore, regular monitoring of patients taking Myclausen is advised (see section 4.4). There have been reports of aplastic anaemia and bone marrow depression in patients treated with mycophenolate mofetil, some of which have been fatal.

Blood and lymphatic system disorder
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.

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

Pregnancy, puerperium and perinatal conditions

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

Congenital disorders
Congenital malformations have been observed post-marketing in children of patients exposed to mycophenolate mofetil in combination with other immunosuppressants, see section 4.6.

Respiratory, thoracic and mediastinal disorders
There have been isolated reports of interstitial lung disease and pulmonary fibrosis in patients treated with mycophenolate mofetil in combination with other immunosuppressants, some of which have been fatal. There have also been reports of bronchiectasis in children and adults (frequency not known).

Immune system disorders
Hypogammaglobulinaemia has been reported in patients receiving mycophenolate mofetil in combination with other immunosuppressants (frequency not known).

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 re-circulation of the drug (see section 5.2)..

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressants, selective immunosuppressants, ATC code L04AA06

Mechanism of action
Mycophenolate mofetil is the 2-morpholinoethyl ester of MPA. MPA is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase, 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.

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 Cmax was decreased by 40 % in the presence of food. Mycophenolate mofetil is not measurable systemically in plasma following oral administration.

Distribution

As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed at approximately 6-12 hours post-dose. A reduction in the AUC of MPA of approximately 40 % is associated with the co-administration of cholestyramine (4 g TID), indicating that there is a significant amount of enterohepatic recirculation.
MPA at clinically relevant concentrations is 97 % bound to plasma albumin.

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, leucopenia).

Elimination

A negligible amount of substance is excreted as MPA (< 1 % of 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 circulation of the medicinal product, bile acid sequestrants such as cholestyramine, reduce MPA AUC (see section 4.9).
MPA's disposition depends on several transporters. Organic anion-transporting polypeptides (OATPs) and multidrug resistance-associated protein 2 (MRP2) are involved in MPA's disposition; OATP isoforms, MRP2 and breast cancer resistance protein (BCRP) are transporters associated with the glucuronides' biliary excretion. Multidrug resistance protein 1 (MDR1) is also able to transport MPA, but its contribution seems to be confined to the absorption process. In the kidney MPA and its metabolites potently interact with renal organic anion transporters.

In the early post-transplant period (< 40 days post-transplant), renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30 % lower and Cmax approximately 40 % lower compared to the late post-transplant period (3-6 months post-transplant).

Special populations

Renal impairment
In a single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate < 25 mL•min^{-1}•1.73 m^{-2}) were 28-75 % higher relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. However, the mean single dose MPAG AUC was 3-6-fold higher in subjects with severe

renal impairment than in subjects with mild renal impairment or normal healthy subjects, consistent with the known renal elimination of MPAG. Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Delayed renal graft function
In patients with delayed renal graft function post-transplant, mean MPA AUC (0–12 h) was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC (0-12 h) was 2-3-fold higher than in post-transplant patients without delayed graft function. There may be a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of 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 this process probably depend on the particular disease. However, 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^2 mycophenolate mofetil orally twice daily. This dose achieved MPA AUC values similar to those seen in adult renal transplant patients receiving mycophenolate mofetil at a dose of 1 g bid in the early and late posttransplant period. MPA AUC values across age groups were similar in the early and late posttransplant period.

Elderly
Pharmacokinetic behaviour of mycophenolate mofetil in the elderly (≥ 65 years) has not been formally evaluated.

Patients taking oral contraceptives
The pharmacokinetics of oral contraceptives were unaffected by coadministration of mycophenolate mofetil (see also section 4.5). 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 0.15 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) conducted in 18 non-transplant women (not taking other immunosupressants) 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.

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 Cmax) observed in renal transplant patients at the recommended clinical dose of 2 g/day and 1.3-2 times the systemic exposure (AUC or C_{max}) 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.

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.

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

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

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

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 user

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

The full name of your medicine is Myclausen 500 mg film-coated tablets.
In this leaflet the shorter name Myclausen is used.

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 (hypersensitive) to mycophenolate mofetil, mycophenolic acid or any of the other ingredients in 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 taking Myclausen
- 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 taking Myclausen.

If any of the above apply to you (or you are not sure), talk to your doctor straight away before taking 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 which also covers your head, neck, arms and legs
- using a sunscreen with a high protection factor.

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 which 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)
- 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).

Vaccines
If you need to have a vaccine (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.

Pregnancy, contraception and breast-feeding

Contraception in women taking Myclausen
If you are a woman who could become pregnant you must use an effective methods 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 are a woman who is not capable of becoming pregnant if any of the following 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 precautionyou 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.

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 an effective method 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 is not likely to affect you being able to drive or use any tools or machines.

Myclausen contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'

3. How to take Myclausen

Always take Myclausen exactly as your doctor has told you. You should 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 you from rejecting your transplant organ.

Kidney transplant
Adults
- The first dose will be given within 3 days after 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 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^2'). The recommended dose is 600 mg per m^2 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 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 medications.
- 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 forgotten 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
- the amount in your blood of things like sugar, fat or cholesterol.

Children may be more likely than adults to have some side effects. This includes 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 Myclausen patients have developed cancer of the lymphoid tissues and skin.

General unwanted effects
You may get general side effects affecting your body as a whole. This include serious allergic reactions (such as anaphylaxis, angioedema), fever, feeling very tired, difficulty in sleeping, pains (such as stomach, chest, joint or muscle, pain on passing urine), 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:
- kidney problems or the urgent need to pass water (urine).

Digestive system and mouth problems such as:
- swelling of the gums and mouth ulcers
- inflammation of the pancreas, colon or stomach
- gut problems including bleeding, liver problems
- 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, unusual 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:

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Passauer Pharma GmbH,
Duitsland/Allemagne/Deutschland
Tél/Tel: +49(0)3074460-12

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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 user

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 Contents of the pack and other information

1. What Myclausen is and what it is used for

The full name of your medicine is Myclausen 250 mg hard capsules.
In this leaflet the shorter name Myclausen is used.

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 (hypersensitive) to mycophenolate mofetil, mycophenolic acid or any of the other ingredients in 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 taking Myclausen:
- 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 taking Myclausen.

If any of the above apply to you (or you are not sure), talk to your doctor straight away before taking 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 which also covers your head, neck, arms and legs
- using a sunscreen with a high protection factor.

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 which 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)
- 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).

Vaccines
If you need to have a vaccine (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.

Pregnancy, contraception and breast-feeding

Contraception in women taking Myclausen
If you are a woman who could become pregnant you must use an effective methods 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 are a woman who is not capable of becoming pregnant if any of the following 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.

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 an effective method 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 is not likely to affect you being able to drive or use any tools or machines.

Myclausen contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially

'sodium-free'

3. How to take Myclausen

Always take Myclausen exactly as your doctor has told you. You should 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 you from rejecting your transplant organ.

Kidney transplant
Adults
- The first dose will be given within 3 days after 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 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^2'). The recommended dose is 600 mg per m^2 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 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 medications.
- 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 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 forgotten 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
- the amount in your blood of things like sugar, fat or cholesterol.

Children may be more likely than adults to have some side effects. This includes 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 Myclausen patients have developed cancer of the lymphoid tissues and skin.

General unwanted effects
You may get general side effects affecting your body as a whole. This include serious allergic reactions (such as anaphylaxis, angioedema), fever, feeling very tired, difficulty in sleeping, pains (such as stomach, chest, joint or muscle, pain on passing urine), 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:
- kidney problems or the urgent need to pass water (urine).

Digestive system and mouth problems such as:
- swelling of the gums and mouth ulcers

- inflammation of the pancreas, colon or stomach
- gut problems including bleeding, liver problems
- 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, unusual 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.
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.

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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 CHMP are as follows:
Following a review of all available information regarding pregnancies following paternal exposure to mycophenolate mofetil or mycophenolic acid, including a review of all non-clinical data and information on transmission of mycophenolic acid via the semen, the PRAC concluded that the data does not highlight any patterns or an increase in congenital malformations or spontaneous abortions. The PRAC therefore recommended to amend the product information, to update information on teratogenic effects and pregnancy as well as the contraception recommendations for male patients. Additional amendments have been made regarding use of contraception in women and pregnancy testing, to clarify the requirements.

The CHMP agrees with the scientific conclusions made by the PRAC.

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.