PROFESSIONAL INFORMATION

WARNING: CARCINOGENICITY

Increased susceptibility to infection and the possible development of lymphoma and other malignancies, especially of the skin, may result from immuno-suppression. Only medical practitioners experienced in immuno-suppressive therapy and management of renal, cardiac or hepatic transplant patients should prescribe MYCOCEPT 250. Patients receiving the medicine should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The medical practitioner responsible for maintenance therapy should have complete information requisite for the follow up of the patient.

WARNING: TERATOGENICITY

Mycophenolate is powerfully teratogenic and mutagenic. Congenital malformations and spontaneous abortions have been reported with use of mycophenolate in pregnancy. Women of childbearing potential must have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL; the second test should be performed 8 to 10 days after the first one and immediately before starting treatment with MYCOCEPT 250. Repeat pregnancy tests should be performed during routine follow-up visits.

Women of childbearing potential should use two reliable forms of contraception simultaneously, including at least one highly effective method, before beginning MYCOCEPT 250 therapy, during therapy, and for six weeks following discontinuation of therapy; unless abstinence is the chosen method of contraception.

Sexually active men are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies both for

reproductively competent and vasectomised men; because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy.

Female partners of male patients are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of MYCOCEPT 250.

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

MYCOCEPT 250 (capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Mycocept 250 capsule contains 250 mg mycophenolate mofetil.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules (Blue opaque cap and orange opaque body containing white to off white coloured powder).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MYCOCEPT 250 is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac and hepatic transplants.

4.2 Posology and method of administration

Treatment with MYCOCEPT 250 should be initiated and maintained by appropriately qualified transplant specialists.

Posology:

Use in renal transplant:

Adults: Oral MYCOCEPT 250 should be initiated within 72 hours following transplantation. The recommended dose in renal transplant patients is 1 g orally twice daily (2 g daily dose).

Paediatric population aged 3 months to 18 years: The recommended dose of MYCOCEPT 250 is 600 mg/m^2 administered orally twice daily (up to a maximum of 2 g daily). Patients with a body surface area of 1,25 to 1,5 m^2 may be prescribed MYCOCEPT 250 at a dosage 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 MYCOCEPT 250 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 to adults, temporary dose reduction or interruption may be required; these will need to take into account relevant clinical factors including severity of reaction.

Use in cardiac transplant:

Adults: Oral MYCOCEPT 250 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 MYCOCEPT 250 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.

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).

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 MYCOCEPT 250. Renal transplant rejection does not lead to changes in MPA pharmacokinetics; dosage reduction or interruption of MYCOCEPT 250 is not required. There is no basis for MYCOCEPT 250 dose adjustment following cardiac transplant rejection. No pharmacokinetic data are available during hepatic transplant rejection.

Method of administration:

Oral administration:

MYCOCEPT 250 can be taken with or without food.

MYCOCEPT 250 capsules should not be emptied in order to retain the integrity of the medicine.

Precautions to be taken before handling or administering the medicine:

Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits, MYCOCEPT 250 capsules should not be opened or crushed to avoid inhalation or direct contact with skin or mucous membranes of the powder contained in MYCOCEPT 250 capsules. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.

4.3 Contraindications

MYCOCEPT 250 should not be given to patients with hypersensitivity to mycophenolate mofetil, or mycophenolic acid or to any of the excipients (see section 6.1). Hypersensitivity reactions to MYCOCEPT 250 have been observed (see section 4.8).

MYCOCEPT 250 should not be given to women of childbearing potential who are not using highly effective contraception (see section 4.6).

MYCOCEPT 250 treatment should not be initiated in women of childbearing potential without providing a pregnancy test result to rule out unintended use in pregnancy (see section 4.6).

MYCOCEPT 250 should not be given to women who are breastfeeding (see section 4.6).

Paediatric (see section 4.2) cardiac and hepatic transplant patients.

4.4 Special warnings and precautions for use

Neoplasms:

Patients receiving immunosuppressive regimens involving combinations of medicines, including MYCOCEPT 250, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.8). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific medicine. 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 MYCOCEPT 250, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis (see section 4.8). Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation and infections caused by polyomaviruses (BK virus associated nephropathy, JC virus associated progressive multifocal leukoencephalopathy PML). Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that doctors should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. Mycophenolic acid has a cytostatic effect on B- and T-lymphocytes, therefore an increased severity of COVID-19 may occur, and appropriate clinical action should be considered.

There have been reports of hypogammaglobinaemia 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 MYCOCEPT 250 who develop recurrent infections should have their serum immunoglobulins measured. In cases of sustained, clinically relevant hypogammaglobinaemia, 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 hypogammaglobinaemia 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 be investigated.

Blood and immune system:

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

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 mycophenolate mofetil therapy. Changes to MYCOCEPT 250 therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimise the risk of graft rejection (see section 4.8).

Patients receiving MYCOCEPT 250 should be instructed to immediately report any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

Patients should be advised that during treatment with MYCOCEPT 250, 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.

Gastrointestinal:

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

MYCOCEPT 250 is an IMPDH (inosine monophosphate dehydrogenase) inhibitor. On theoretical grounds, 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 mycophenolic acid (MPA) enterohepatic recirculation, e.g. ciclosporin, to others devoid of this effect, e.g. tacrolimus, sirolimus, belatacept, or *vice versa*, as this might result in changes of MPA exposure. Medicines which interfere with MPA's enterohepatic cycle (e.g. cholestyramine, antibiotics) should be used with caution due to their potential to reduce the plasma levels and efficacy of MYCOCEPT 250 (see section 4.5).

Therapeutic medicinal monitoring of MPA may be appropriate when switching combination therapy (e.g. from ciclosporin to tacrolimus or *vice versa*) or to ensure adequate immunosuppression in patients with high immunological risk (e.g. risk of rejection, treatment with antibiotics, additional or removal of interacting medication).

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

MYCOCEPT 250 has been administered in combination with the following medicines in clinical trials: antithymocyte globulin, basiliximab, ciclosporin and corticosteroids.

The efficacy and safety of the use of MYCOCEPT 250 with other immunosuppressive medicines have not been established, including the risk/benefit ratio of MYCOCEPT 250 in combination with sirolimus.

Caution should be used when co-administering antacids containing magnesium and aluminium hydroxide with MYCOCEPT 250 (see 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 mycophenolate mofetil exposure during pregnancy. Therefore, MYCOCEPT 250 is contraindicated in pregnancy (see sections 4.3 and 4.6). 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 MYCOCEPT 250. Doctors should ensure that women taking MYCOCEPT 250 understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult their doctor if there is a possibility of pregnancy. It is recommended that MYCOCEPT 250 therapy should not be initiated until a negative pregnancy test has been obtained (see section 4.6).

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 MYCOCEPT 250 therapy, during therapy, and for six weeks after stopping the therapy; unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred to minimise the potential for contraceptive failure and unintended pregnancy.

For contraception advice for men, see section 4.6.

Hepatic insufficiency:

Safety and efficacy in patients with hepatic insufficiency have not been established.

Educational materials:

In order to assist patients in avoiding foetal exposure to MYCOCEPT 250 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 MYCOCEPT 250, provide advice on contraception before therapy is started and give guidance on the need for pregnancy testing. Full patient information about the teratogenic risk and the pregnancy prevention measures should be given by the doctor 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 MYCOCEPT 250. Men should not donate semen during therapy or for 90 days following discontinuation of MYCOCEPT 250.

4.5 Interaction with other medicines and other forms of interaction

Aciclovir:

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

tubular secretion, resulting in a further increase in the concentration of both MPAG and aciclovir. In this situation, patients should be carefully followed up.

Antacids and proton pump inhibitors (PPIs):

Decreased mycophenolic acid (MPA) exposure has been observed when antacids, such as magnesium and aluminium hydroxides, and PPIs, including lansoprazole and pantoprazole, were administered with mycophenolate mofetil.

The absorption of MYCOCEPT 250 decreases by 37 % (systemic exposure) and 25 % maximal concentration when administered with antacids.

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

Azathioprine:

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

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

Caution should be used with medicines that interfere with enterohepatic circulation because of their potential to reduce the efficacy of MYCOCEPT 250.

Cholestyramine:

Due to its capacity to block the enteric circulation of medicines, cholestyramine may decrease the systemic exposure of MYCOCEPT 250. 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 when co-administering cholestyramine because of the potential to reduce the efficacy of MYCOCEPT 250.

Ciclosporin A:

Ciclosporin A (CsA) pharmacokinetics are unaffected by steady state dosing of MYCOCEPT 250 in stable renal transplant patients. 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 to 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 section 4.4).

Conversely, changes of MPA exposure should be expected when switching patients from CsA to one of the immunosuppressants, which does not interfere with MPA's enterohepatic cycle.

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

Information concerning the following antibiotics is available:

Ciprofloxacin or amoxicillin plus clavulanic acid:

Reductions in pre-dose (trough) MPA concentrations of about 50 % have been reported in renal transplant recipients in the days immediately following commencement of oral

ciprofloxacin or amoxicillin plus clavulanic acid. This effect tended to diminish with continued antibiotic use and to cease within a few days of antibiotic discontinuation. The change in pre-dose level may not accurately represent changes in overall MPA exposure.
Therefore, a change in the dose of MYCOCEPT 250 should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

Norfloxacin and metronidazole:

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

Trimethoprim/sulfamethoxazole:

No effect on the bioavailability of MPA was observed.

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

Concomitant administration of medicines inhibiting glucuronidation of MPA may increase MPA exposure. Caution is therefore recommended when administering these medicines concomitantly with MYCOCEPT 250.

Isavuconazole:

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

Telmisartan:

Concomitant administration of telmisartan and mycophenolate mofetil resulted in an approximately 30 % decrease of MPA concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression, which in turn results in an enhanced 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 medicine-medicine interaction were seen.

Ganciclovir:

Based on the results of a single dose administration study of recommended doses of oral mycophenolate mofetil 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 medicines (which compete for mechanisms of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. MYCOCEPT 250 and MPAG pharmacokinetics are unaffected by the addition of ganciclovir and dose adjustment is not required. The clearance of ganciclovir is unchanged in the setting of therapeutic MYCOCEPT 250 exposure. However, in patients with renal impairment in which MYCOCEPT 250 and ganciclovir or its prodrugs, e.g. valganciclovir, are co-administered, the dose recommendations for ganciclovir should be observed and patients monitored carefully.

Oral contraceptives:

Oral contraceptives undergo oxidative metabolism while MYCOCEPT 250 is metabolized by glucuronidation. A clinically significant effect of oral contraceptives on MYCOCEPT 250 pharmacokinetics is not anticipated. However, given that the long-term effect of MYCOCEPT 250 dosing on the pharmacokinetics of oral contraceptives is not known, it is possible that the efficacy of oral contraceptives may be adversely affected.

Rifampicin:

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

Sevelamer:

Decrease in MPA C_{max} and AUC_{0-12h} by 30 % and 25 %, respectively, were observed when mycophenolate mofetil was concomitantly administered with sevelamer without any clinical consequences (i.e. graft rejection). It is recommended, however, to administer MYCOCEPT 250 at least one hour before or three hours after sevelamer intake to minimise the impact on the absorption of MPA. There are no data on mycophenolate mofetil with phosphate binders other than sevelamer.

Tacrolimus:

In hepatic transplant patients initiated on mycophenolate mofetil and tacrolimus, the AUC and C_{max} of MPA, the active metabolite of mycophenolate mofetil, were not significantly affected by co-administration with tacrolimus. In contrast, there was an increase of approximately 20 % in tacrolimus AUC when multiple doses of mycophenolate mofetil (1,5 g BID) were administered to hepatic transplant patients taking tacrolimus.

However, in renal transplant patients, tacrolimus concentration did not appear to be altered by mycophenolate mofetil (see also section 4.4).

Live vaccines:

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

Paediatric population:

Interaction studies have only been performed in adults.

Potential interaction:

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential:

Pregnancy whilst taking MYCOCEPT 250 must be avoided. Therefore, women of childbearing potential must use at least one form of reliable contraception before starting MYCOCEPT 250 therapy, during therapy, and for six weeks following discontinuation of therapy (see section 4.3), unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred.

Men:

Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to MYCOCEPT 250. 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. MYCOCEPT 250 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 MYCOCEPT 250.

Male patients of reproductive potential should be made aware of and discuss the potential risks of fathering a child with a qualified healthcare professional.

Pregnancy:

Safety and efficacy in pregnant women has not been established. MYCOCEPT 250 is contraindicated during pregnancy (see section 4.3).

MYCOCEPT 250 therapy should not be initiated until a negative pregnancy test has been obtained.

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 MYCOCEPT 250 treatment, women of childbearing 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 MYCOCEPT 250. It is recommended that the second test should be performed 8 to 10 days after the first test. For transplants from deceased donors, if it is not possible to perform two tests 8 to 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 to 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 doctor immediately should pregnancy occur.

MYCOCEPT 250 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 mycophenolate mofetil in combination with other immunosuppressants during pregnancy.

The following malformations were most frequently reported:

- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits.
- Abnormalities of the ear (e.g. abnormally formed or absent external ear), external auditory canal atresia (middle ear).
- Abnormalities of the eye (e.g. coloboma, microphthalmos).
- Malformations of the fingers (e.g. polydactyly, syndactyly, brachydactyly).
- 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).

Breastfeeding:

Limited data show that mycophenolic acid is excreted in human milk. Because of the potential for serious adverse reactions to mycophenolic acid in breast-fed infants, MYCOCEPT 250 is contraindicated in nursing mothers (see section 4.3).

4.7 Effects on ability to drive and use machines

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

MYCOCEPT 250 may cause somnolence, confusion, dizziness, tremor or hypotension, and therefore patients are advised to use caution when driving or using machines.

4.8 Undesirable effects

The following undesirable effects cover adverse reactions from clinical trials:

The principal adverse reactions associated with the administration of MYCOCEPT 250 in combination with ciclosporin and corticosteroids include leukopenia, sepsis, vomiting and diarrhoea, 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 medicines, including MYCOCEPT 250, 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 in renal (2 g data), cardiac and hepatic transplant patients followed for

at least 1 year were candida mucocutaneous, CMV viremia/syndrome and Herpes simplex. The proportion of patients with CMV viremia/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/m2 mycophenolate mofetil orally twice daily, were generally similar to those observed in adult patients given 1 g mycophenolate mofetil twice daily.

However, the following treatment-related adverse events were more frequent in the paediatric population, particularly in children under 6 years of age, when compared to adults: diarrhoea, sepsis, leukopenia, anaemia and infection.

Elderly patients:

Elderly patients (≥ 65 years) may generally be at increased risk of adverse reactions due to immunosuppression. Elderly patients receiving MYCOCEPT 250 as part of a combination immunosuppressive regimen did not show an increased risk of adverse reaction compared to younger individuals in the MYCOCEPT 250 clinical trial, however elderly patients may be at increased risk of certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema.

Other Adverse Reactions:

The table below contains reported adverse medicine reactions.

Body system	***Incidence***	***Adverse reaction***

Infections and infestations	*Frequent*	Sepsis, gastrointestinal candidiasis, viral, bacterial and fungal infections, including urinary tract infection, herpes simplex, herpes zoster, wound infection, osteomyelitis, pneumonia, influenza, respiratory tract infection, respiratory moniliasis, gastrointestinal infection, candidiasis, gastroenteritis, infection, bronchitis, pharyngitis, sinusitis, fungal skin infection, skin candida, vaginal candidiasis, rhinitis, abscess, cellulitis, bacterial infections, fungal infections, viral infections.
	Less frequent	Protozoal Infections.
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	*Frequent*	Skin cancer, including skin papilloma, basal cell carcinoma, Kaposi's sarcoma, squamous cell carcinoma, benign neoplasm of skin, cysts (including lymphocele and hydrocele).
	Less frequent	Lymphoma, lymphoproliferative disorder.
Blood and lymphatic system disorders	*Frequent*	Leukopenia, anaemia, thrombocytopenia, lymphocele, lymphopenia, neutropenia, lymphadenopathy, pancytopenia, leucocytosis, ecchymosis, haemorrhage, petechial, increased prothrombin time, increased thromboplastin time.

	Less Frequent	Aplasia pure red cell, bones marrow failure, pseudolymphoma.
Endocrine disorders	*Frequent*	Diabetes mellitus, parathyroid disorder (elevated PTH level), Cushing's syndrome, hypothyroidism.
Metabolism and nutrition disorders	*Frequent*	Anorexia, hyperlipidaemia, diabetes mellitus, hypercholesterolemia, hyperphosphatemia, acidosis, hyperkalaemia, hypokalaemia, hyperglycaemia, hypomagnesaemia, hypocalcaemia, hyperuricemia, gout, weight decreased, hypercholesterolaemia, hyperlipidaemia, weight decreased, elevated blood urea, elevated creatinine, elevated enzyme levels (lactic dehydrogenase, AST and ALT), hypervolaemia, hyponatraemia, hypoproteinaemia, dehydration, alkalosis, hypochloraemia, hypoxia, respiratory acidosis, thirst.
Psychiatric disorders	*Frequent*	Agitation, confusional state, depression, anxiety, thinking abnormal, insomnia, emotional lability, hallucinations, delirium, psychosis.
Nervous system disorders	*Frequent*	Headache, tremor, convulsion, hypertonia, somnolence, myasthenic syndrome, dizziness,

		paraesthesia, dysgeusia, hypertonia, neuropathy, vertigo, hyperaesthesia.
Eye disorders	*Frequent*	Conjunctivitis, blurred vision, amblyopia, cataract, conjunctivitis, abnormal vision, eye haemorrhage.
Ear and labyrinth disorders	*Frequent*	Ear pain, deafness, tinnitus.
Cardiac disorders	*Frequent*	Tachycardia, pulmonary oedema, ventricular extrasystoles, dysrhythmia, bradycardia, cardiac failure, pericardial effusion, angina pectoris, atrial fibrillation, cardiac arrest, pulmonary hypertension.
Vascular disorders	*Frequent*	Hypotension, hypertension, vasodilatation, venous thrombosis, postural hypotension, syncope, vasospasm, increased venous pressure.
	Less Frequent	Lymphocele
Respiratory, thoracic and mediastinal disorders	*Frequent*	Cough, wheezing, pulmonary congestion, pleural effusion, dyspnoea, asthma, atelectasis, pulmonary oedema.
	Less Frequent	Bronchiectasis, Interstitial lung disease Pulmonary fibrosis

Gastrointestinal disorders	*Frequent*	Diarrhoea, abdominal pain, nausea, vomiting, abdominal distension, abdominal tenderness, constipation, dyspepsia, flatulence, gastritis, loose stools, ileus, colitis, oesophagitis, peptic ulcer, duodenal ulcer, gastrointestinal haemorrhage, gastro-oesophageal reflux disease, gingival hyperplasia, peritonitis, stomatitis, eructation, decreased appetite, gastritis, gastrointestinal ulcer, pancreatitis, mouth ulceration, enlarged abdomen, hernia, oral moniliasis, cholangitis, gingivitis, gum hyperplasia, melaena, dysphagia, rectal disorder.
	Less frequent	Pancreatitis, halitosis, subileus, tongue discolouration, dry mouth, eructation.
Immune system disorders	*Frequent*	Hypersensitivity.
	Less Frequent	Hypogammaglobulinaemia
Hepato-biliary disorders	*Frequent*	Hepatitis, jaundice, hyperbilirubinemia, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, hepatic enzyme increased, ascites.
Skin and subcutaneous tissue disorders	*Frequent*	Alopecia, skin hypertrophy, rash, acne.
	Less frequent	Contusion, skin hypertrophy (including actinic keratosis), rash, acne, alopecia, pruritus, sweating, hirsutism, skin ulcer, facial oedema.

Musculoskeletal and connective tissue disorders	*Frequent*	Arthralgia, muscle weakness, pelvic pain, neck pain, leg cramps, myalgia, osteoporosis.
Renal and urinary disorders	*Frequent*	Renal tubular necrosis, urethral stricture, renal impairment, blood creatinine increased, blood urea increased, renal impairment, haematuria, abnormal kidney function (decrease in renal function, elevated serum creatinine), oliguria, albuminuria, dysuria, hydronephrosis, pyelonephritis, urinary frequency, nocturia, renal failure, urinary incontinence, urinary retention, scrotal oedema.
General disorders and administration site conditions	*Frequent*	Fatigue, pyrexia, influenza-like illness, oedema, pain, asthenia, chills, pallor, hernia and malaise.
	Less frequent	De novo purine synthesis inhibitors associated acute inflammatory syndrome
Reproductive system and breast disorders	*Frequent*	Impotence.
Investigations	*Frequent*	Hepatic function tests abnormal, 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 IV/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 disorders:

Gingival hyperplasia (frequent), colitis including cytomegalovirus (CMV) colitis (frequent), pancreatitis (frequent), intestinal villous atrophy and intestinal perforation.

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 Leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including mycophenolate mofetil.

Agranulocytosis (less frequent) and neutropenia have been reported; therefore, regular monitoring of patients taking MYCOCEPT 250 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 MYCOCEPT 250.

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:

The following side effects have been reported but frequencies are unknown:

Serious, sometimes life-threatening infections, including meningitis, infectious endocarditis, tuberculosis, and atypical mycobacterial infection. Hypogammaglobulinaemia has been reported in patients receiving mycophenolate mofetil in combination with other immunosuppressants.

General disorders and administration site conditions:

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

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

Reporting of suspected adverse reactions

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

Suspected adverse reactions may also be reported directed to the Holder of Certificate of Registration (HCR) via the link: https://pvi1j.solutions.iqvia.com or the e-mail address, adverse.event.sac@sandoz.com.

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 medicine.

It is expected that an overdose of MYCOCEPT 250 could possibly result in over suppression of the immune system and increase susceptibility to infections and bone marrow suppression (see section 4.4). If neutropenia develops, dosing with MYCOCEPT 250 should be interrupted or the dose reduced (see section 4.4).

Although dialysis may be used to remove the inactive metabolite MPAG, it would not be expected to remove clinically significant amounts of the active moiety of MYCOCEPT 250.

By interfering with enterohepatic circulation of MYCOCEPT 250, bile acid sequestrants, such as cholestyramine, may reduce the systemic MYCOCEPT 250 exposure.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 34 Other (Immuno-suppressants)

5.1 Pharmacodynamic properties

Mycophenolate mofetil is a prodrug that is rapidly hydrolysed to the active chemical entity, mycophenolic acid (MPA). MPA is a potent, selective, non-competitive, and reversible inhibitor of inosine monophosphate dehydrogenase, and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA. Mycophenolic acid (MPA) prohibits the proliferation of T- and B- lymphocytes.

Since T- and B- lymphocytes are highly dependent on this *de novo* synthesis of purines pathway for cell proliferation, while other cell types can use salvage pathways, MPA therefore selectively inhibits lymphocyte proliferation and functions, including antibody formation, cellular adhesion, and migration. MPA has more potent cytostatic effects on lymphocytes than on other cells. The mode of action is complementary to calcineurin inhibitors, which interfere with cytokine transcription and resting T-lymphocytes.

5.2 Pharmacokinetic properties

Absorption:

Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete pre-systemic 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 gastrointestinal absorption of MPA in stable renal transplant patients on ciclosporin based immunosuppression is 93 % and the absolute bioavailability, 72 %. Food had no effect on the

extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1,5 g BID to renal transplant patients. However, MPA C_{max} was decreased by 40 % in the presence of food. Mycophenolate mofetil 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 to 12 hours post-dose. The apparent volume of distribution at steady state for MPA is 50 litres. Both mycophenolic acid and mycophenolic acid glucuronide are highly protein bound, 97 % and 82 %, respectively. 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. The free MPA concentration may increase under conditions of decreased protein binding sites (uraemia, hepatic failure, hypoalbuminemia, concomitant use of medicines with high protein binding). This may put patients at increased risk of MPA related adverse effects.

Biotransformation:

The half-life of MPA is about 11,7 hours and the clearance is 8,6 l/h. MPA is metabolised principally by glucuronyl transferase (isoform UGT1A9) to form the inactive phenolic glucuronide of MPA, mycophenolic acid glucuronide (MPAG). MPAG is the predominant metabolite of MPA and does not manifest biologic activity. *In vivo*, MPAG is converted back to free MPA via enterohepatic recirculation. In stable renal transplant patients on ciclosporin-based immunosuppression, approximately 28 % of the oral MPA dose is converted to MPAG by pre-systemic metabolism. The half-life of MPAG is longer than that of MPA, approximately 15,7 hours and its clearance is 0,45 l/h.

A minor acyl glucuronide (AcMPAG) is also formed. AcMPAG is pharmacologically active and is suspected to be responsible for some of mycophenolate mofetil's side effects (diarrhoea, leukopenia).

Elimination:

A negligible amount of substance is excreted as MPA (< 1 % of 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.

MPAG secreted in the bile is deconjugated by the gut flora to MPA. The MPA resulting from this deconjugation may then be reabsorbed. Approximately 6 to 8 hours after MPA dosing a second peak of MPA concentration can be measured, consistent with reabsorption of the deconjugated MPA.

By interfering with enterohepatic circulation of the active substance, 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 C_{max} approximately 40 % lower compared to the late post-transplant period (3 to 6 months post-transplant).

Pharmacokinetics in renal transplant patients on ciclosporin based immunosuppression:

The table below shows the mean pharmacokinetic parameters for MPA following the administration of this medicine. Single dose pharmacokinetics predicts multiple dose and chronic dosing pharmacokinetics. In the early post-transplant period, mean MPA AUC and MPA C_{max} was approximately one-half of the measured six months post-transplant.

Mean (SD) pharmacokinetic parameters for MPA following oral administration to renal transplant patients on ciclosporin for microemulsion based immunosuppression:

Adult ***Single dose*** ***n = 24***	***Dose*** ***(oral)***	***T_{max}*** ***(h)***	***C_{max}*** ***(µg/ml)***	***AUC $_{0-\infty}$*** ***(µg*h/ml)***
	720 mg	2	26,1 (12,0)	66,5 (22,6)
Adult ***Multiple dose x 6 days*** ***BID*** ***n = 12***	***Dose*** ***(oral)***	***T_{max}*** ***(h)***	***C_{max}*** ***(µg/mL)***	***AUC $_{0-12}$*** ***(µg*h/mL)***
	720 mg	2	37,0 (13,3)	67,9 (20,3)
Adult **chronic, multiple dosing** **BID**	***Dose*** ***(oral)***	***T_{max}*** ***(h)***	***C_{max}*** ***(µg/mL)***	***AUC $_{0-12}$*** ***(µg*h/mL)***

n = 48				
14 days post-transplant	720 mg	2	13,9 (8,6)	29,1 (10,4)
3 months post-transplant	720 mg	2	24,6 (13,2)	50,7 (17,3)
6 months post-transplant	720 mg	2	23,0 (10,1)	55,7 (14,6)

Special populations:

Renal impairment:

MPA pharmacokinetics appeared to be unchanged over the range of normal to absent renal function. 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 to 75 % higher relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. MPAG exposure increased with decreased renal function; MPAG exposure being approximately 8-fold higher in the setting of anuria. Clearance of either MPA or MPAG was unaffected by haemodialysis. Free MPA may also significantly increase in the setting of renal failure. This may be due to decreased plasma protein binding of MPA in the presence of high blood urea concentration.

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 to 12h) was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC (0 to 12h) was 2 to 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 mycophenolate mofetil does not appear to be necessary.

Hepatic impairment:

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 post-transplant period. MPA AUC values across age groups were similar in the early and late post-transplant period.

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 post-transplant period. MPA AUC values across age groups were similar in the early and late post-transplant period.

Gender:

There are no clinically significant gender differences in pharmacokinetics.

Elderly:

Exposure does not appear to vary to a clinically significant degree by age. 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 co-administration 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 immunosuppressants) over 3 consecutive menstrual cycles; showed no clinically relevant influence of mycophenolate mofetil on the ovulation suppressing action of the oral contraceptives. Serum levels of LH, FSH and progesterone were not significantly affected.

5.3 Pre-clinical safety data

In experimental models, mycophenolate mofetil was not tumourigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2 to 3 times the systemic exposure (AUC or C_{max}) observed in renal transplant patients at the recommended clinical dose of 2 g/day and 1,3 to 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 to 3 times the clinical exposure at the recommended clinical dose of 2 g/day in renal transplant patients and 1,3 to 2 times the clinical exposure at the recommended clinical dose of 3 g/day in cardiac transplant patients. In a female fertility and reproduction study conducted in rats, oral doses of 4,5 mg/kg/day caused malformations (including anophthalmia, agnathia, and hydrocephaly) in the first-generation offspring in the absence of maternal toxicity. The systemic exposure at this dose was approximately 0,5 times the clinical exposure at the recommended clinical dose of 2 g/day for

renal transplant patients and approximately 0,3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

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

Croscarmellose sodium

Povidone (K-90F)

Starch, pregelatinised

Magnesium stearate

Capsule shell:

Body composition:

Gelatine

Red iron oxide (E172)

Titanium dioxide (E172)

Yellow iron oxide (E172)

Cap Composition:

FD & C Blue #2 (E132)

Gelatine

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C. Store in the original container. Protect from light and moisture.

6.5 Nature and contents of container

100 capsules packed in a white opaque PVC/PE/PVdC/Al blister in a cardboard carton or in a HDPE container with polypropylene caps.

6.6 Special precautions for disposal and other handling

Any unused MYCOCEPT 250 should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Waterfall 5-lr

Magwa Crescent West

Waterfall City

Jukskei View

2090

Sandoz SA Customer Call Centre 0861 726 225 (SANCAL)

8. REGISTRATION NUMBER

41/34/0815

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 March 2009

10. DATE OF REVISION OF THE TEXT

14 May 2025

Additional countries registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Namibia	Mycocept 250	NS2	10/34/0146

Name and address of manufacturer:

Sandoz Private Limited

MIDC Plot no. 8-A/2 and 8-B;

TTC Industrial Area, Kalwe Block,

Village-Dighe 400708,

Navi Mumbai, India

[1]Company Reg. No.: 1990/001979/07