Summary of Product Characteristics

1. Name of the medicinal product

1.1 Invented name of the medicinal product
Mofecon-C 250 (Mycophenolate Mofetil Capsules, USP 250 mg)

1.2 Strength
250 mg

1.3 Pharmaceutical form
Hard Gelatin Capsule

2. Qualitative and quantitative composition
Each Hard Gelatin Capsule contains:

Mycophenolate Mofetil USP…250 mg.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Hard Gelatin Capsules.
"White to off white granular powder filled in size '1' hard gelatin capsule with opaque blue cap imprinted "C3 250" and opaque brown body."

4. Clinical particulars
4.1 Therapeutic indications
Mycophenolate mofetil Capsules, USP 250 mg are 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
Posology

Treatment with Mycophenolate mofetil Capsules, USP 250 mg should be initiated and maintained by appropriately qualified transplant specialists.

Use in renal transplant

Adults

Oral Mycophenolate mofetil Capsules, USP 250 mg should be initiated within 72 hours following transplantation. The recommended dose in renal transplant patients is 1g administered twice daily (2g daily dose).

Paediatric population aged 2 to 18 years

The recommended dose of mycophenolate mofetil is 600mg/m^2 administered

orally twice daily (up to a maximum of 2g daily).

Mycophenolate mofetil Capsules, USP 250 mg should only be prescribed to patients with a body surface area of at least 1.25m^2. Patients with a body surface area of 1.25 to 1.5m^2 may be prescribed Mycophenolate mofetil Capsules, USP 250 mg at a dose of 750mg twice daily (1.5g daily dose). Patients with a body surface area greater than 1.5 m^2 may be prescribed Mycophenolate mofetil Capsules, USP 250 mg at a dose of 1g twice daily (2g 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 Mycophenolate mofetil Capsules, USP 250 mg should be initiated within 5 days following transplantation. The recommended dose in cardiac transplant patients is 1.5g administered twice daily (3g daily dose).

Paediatric population

No data are available for paediatric cardiac transplant patients.

Use in hepatic transplant Adults

IV mycophenolate mofetil should be administered for the first 4 days following hepatic transplant, with oral Mycophenolate mofetil Capsules, USP 250 mg initiated as soon after this as it can be tolerated. The recommended oral dose in hepatic transplant patients is 1.5g administered twice daily (3g daily dose).

Paediatric population

No data are available for paediatric hepatic transplant patients.

Use in special populations Elderly

The recommended dose of 1g administered twice a day for renal transplant patients and 1.5g 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/minute per 1.73 m^2), outside the immediate post-

transplant period, doses greater than 1g 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 Mycophenolate mofetil Capsules, USP 250 mg is not required. There is no basis for Mycophenolate mofetil Capsules, USP 250 mg dose adjustment following cardiac transplant rejection. No pharmacokinetic data are available during hepatic transplant rejection.

Method of administration Oral administration

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

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

4.3 Contraindications

Mycophenolate mofetil Capsules, USP 250 mg 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).

Mycophenolate mofetil Capsules, USP 250 mg should not be given to women of childbearing potential who are not using highly effective contraception (see section 4.6).

Mycophenolate mofetil 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).

Mycophenolate mofetil should not be used in pregnancy unless there is no suitable alternative treatment to prevent transplant rejection (see section 4.6).

Mycophenolate mofetil Capsules, USP 250 mg should not be given in 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 Mycophenolate mofetil Capsules, USP 250 mg, 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 mycophenolate mofetil, 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 mycophenolate mofetil 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 Mycophenolate mofetil Capsules, USP 250 mg should be

monitored for neutropenia, which may be related to Mycophenolate mofetil Capsules, USP 250 mg itself, concomitant medications, viral infections, or some combination of these causes.

Patients taking Mycophenolate mofetil Capsules, USP 250 mg 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 Mycophenolate mofetil Capsules, USP 250 mg.

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 mycophenolate mofetil 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 Mycophenolate mofetil Capsules, USP 250 mg 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 Mycophenolate mofetil Capsules, USP 250 mg, 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, Mycophenolate mofetil Capsules, USP 250 mg should be administered with caution in patients with active serious digestive system disease.

Mycophenolate mofetil Capsules, USP 250 mg 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. Drugs 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 Mycophenolate mofetil Capsules, USP 250 mg (see also section 4.5).

It is recommended that Mycophenolate mofetil Capsules, USP 250 mg 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 45-49%) and congenital malformations (estimated rate of 23-27%) have been reported following MMF exposure during pregnancy. Therefore mycophenolate mofetil is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejection. Female and male patients of reproductive 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 mycophenolate mofetil. Physicians should ensure that women and men 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 the genotoxic and teratogenic potential of mycophenolate mofetil, women with childbearing potential should use two reliable forms of contraception simultaneously before starting mycophenolate mofetil therapy, during therapy, and for six weeks after stopping the therapy; unless abstinence is the chosen method of contraception (see section 4.5).

Sexually active men are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomized men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. In addition, female partners of male patients treated with mycophenolate mofetil are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of mycophenolate mofetil.

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.

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 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.

Colestyramine

Following single dose administration of 1.5g of mycophenolate mofetil to normal healthy subjects pre-treated with 4g TID of colestyramine 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 Mycophenolate mofetil Capsules, USP 250 mg.

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 Mycophenolate mofetil Capsules, USP 250 mg.

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 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 drug-drug interaction were seen.

Ganciclovir

Based on the results of a single dose administration study of recommended doses of oral mycophenolate and IV ganciclovir and the known effects of renal impairment on the pharmacokinetics of mycophenolate mofetil (see section 4.2) and ganciclovir, it is anticipated that co-administration of these agents (which compete for mechanisms of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics is anticipated and mycophenolate mofetil dose adjustment is not required. In patients with renal impairment in whom mycophenolate mofetil 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 co-administration 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 (AUC0-12h) of 18% to 70%. It is recommended to monitor MPA exposure levels and to adjust mycophenolate mofetil 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 mycophenolate mofetil 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 mycophenolate mofetil 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 co-administration with tacrolimus. In contrast, there was an increase of approximately 20 % in tacrolimus AUC when multiple doses of mycophenolate mofetil (1.5g 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 Pregnancy and lactation

Contraception in males and females

Mycophenolate mofetil Capsules, USP 250 mg is contraindicated in women of childbearing potential who are not using highly effective contraception.

Because of the genotoxic and teratogenic potential of Mycophenolate mofetil Capsules, USP 250 mg, women with childbearing potential should use two reliable forms of contraception simultaneously before starting Mycophenolate mofetil Capsules, USP 250 mg therapy, during therapy, and for six weeks after stopping the therapy; unless abstinence is the chosen method of contraception (see section 4.5).

Sexually active men are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomized men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. In addition, female partners of male patients treated with mycophenolate mofetil are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of Mycophenolate mofetil Capsules, USP 250 mg.

Pregnancy

Mycophenolate mofetil Capsules, USP 250 mg is contraindicated during pregnancy unless there is no suitable alternative treatment to prevent transplant rejection. Treatment should not be initiated without providing a negative pregnancy test result to rule out unintended use in pregnancy.

Female and male 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 Mycophenolate mofetil Capsules, USP 250 mg treatment, women of child bearing potential should have a pregnancy test in order to exclude unintended exposure of the embryo to mycophenolate. Two serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL are recommended; the second test should be performed 8 – 10 days after the first one and immediately before starting mycophenolate mofetil. 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 Mycophenolate mofetil Capsules, USP 250 mg 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/middle ear), external auditory canal atresia;

- Congenital heart disease such as atrial and ventricular septal defects;

- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;

- Abnormalities of the eye (e.g. coloboma);

- 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

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, Mycophenolate mofetil Capsules, USP 250 mg is contraindicated in nursing mothers (see section 4.3).

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 (2g or 3g daily) in combination with other immunosuppressants in controlled clinical trials of renal (2g 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 (2g or 3g daily) with other immunosuppressants in controlled clinical trials of renal (2g 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 1g 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 (2g data), cardiac and hepatic transplant patients are listed in the following table.

Adverse reactions, probably or possibly related to mycophenolate mofetil, 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 (including cysts and polyps)	Very common	-
	Common	Skin cancer, benign neoplasm of skin
Blood and lymphatic system disorders	Very common	Leucopenia, thrombocytopenia, anaemia
	Common	Pancytopenia, leucocytosis
Metabolis and nutritio m n 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, tremor, somnolence, hypertonia, 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,
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 (2g mycophenolate mofetil daily), 289 (3g mycophenolate mofetil daily) and 277 (2g IV / 3g oral mycophenolate mofetil daily) patients were treated in Phase III studies for the prevention of rejection in renal, cardiac and hepatic transplantation, respectively.

<u>The following undesirable effects cover adverse reactions from post-marketing experience:</u>

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 leukoencephalopathy (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 mycophenolate mofetil 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 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 Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org/

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 Mycophenolate mofetil Capsules, USP 250 mg 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 colestyramine, can remove MPA by decreasing the enterohepatic recirculation of the drug (see section 5.2).

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressive

agents. ATC code L04AA06

Mechanism of action

Mycophenolate mofetil is the 2-morpholinoethyl ester of MPA. MPA is a 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 1.5g 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 – 12 hours post-dose. A reduction in the AUC of MPA of approximately 40 % is associated with the co-administration of colestyramine (4g 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 MMF´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 drug, bile acid sequestrants such as cholestyramine, reduce MPA AUC (see section 4.9). MPA's disposition depends on several transporters. Organic anion-transporting polypeptides (OATPs) and multidrug resistance-associated protein 2 (MRP2) are involved in MPA's disposition; OATP isoforms, MRP2 and breast cancer resistance protein (BCRP) are transporters associated with the glucuronides' biliary excretion.

Multidrug resistance protein 1 (MDR1) is also able to transport MPA, but its contribution seems to be confined to the absorption process. In the kidney MPA and its metabolites potently interact with renal organic anion transporters.

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

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 (0–12h) was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC (0-12h) was 2 – 3-fold higher than in post-transplant patients without delayed graft function. There may be a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of mycophenolate mofetil does not appear to be necessary.

Hepatic impairment

In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease. Effects of hepatic disease on 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 1g BID in the early and late post-transplant period. MPA AUC values across age groups were similar in the early and late post transplant period.

Elderly

Pharmacokinetic behavior 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 (1g BID) and combined oral contraceptives containing ethinylestradiol (0.02mg to 0.04mg) and levonorgestrel (0.05mg to 0.15mg), desogestrel (0.15mg) or gestodene (0.05mg to 0.10mg) 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 Preclinical safety data

In experimental models, mycophenolate mofetil was not tumourigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2 – 3 times the systemic exposure (AUC or C_{max}) observed in renal transplant patients at the recommended clinical dose of 2g/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^{-1}/day^{-1}. The systemic exposure at this dose represents 2 – 3 times the clinical exposure at the recommended clinical dose of 2g/day in renal transplant patients and 1.3 – 2 times the clinical exposure at the recommended clinical dose of 3g/day in cardiac transplant patients. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg^{-1}/day^{-1} 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 2g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3g/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^{-1}/day^{-1}(including anophthalmia, agnathia, and hydrocephaly) and in rabbits at 90 mg/kg^{1}/day^{-1} (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 2g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3g/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 2g/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

Mycophenolate Mofetil Capsules, USP 250mg Microcrystalline Cellulose (Microcel MC 101) Hydroxypropyl Cellulose (Klucel LXF Pharm)

Povidone (Kollidon 90F)

Purified Water

Microcrystalline Cellulose (Microcel MC 102) Croscarmellose Sodium (SOLUTAB Type A) Talc (Luzenac Pharma)

Magnesium Stearate NF (LIGAMED MF-2-V)

Empty hard gelatin capsule size "1" opaque blue cap imprinted with "C3 250" and opaque brown body.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from moisture

6.5 Nature and contents of container

Mycophenolate Mofetil Capsules, USP 250 mg: 1 carton contains 60 Capsules (in blister packs of 10).

6.6 Special precautions for disposal and other handling

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

7. Market Authorization Holder

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