FRONT

Mofecon™

VIMOF01-var (SIN)

DESCRIPTION

Mofecon™ 250: White to off white granular powder filled in size '1' hard gelatin capsule with opaque blue cap imprinted 'C3 250' and opaque brown body.

Mofecon™ 500: Lavender-colored, caplet-shaped, film-coated tablet, debossed with "C4" on one side and plain on the other side.

COMPOSITION

Mofecon™ 250: each capsule contains mycophenolate mofetil 250 mg.
Excipients: Microcrystalline cellulose, hydroxypropyl cellulose, povidone, croscarmellose sodium, talc, magnesium stearate.

Mofecon™ 500: Each tablet contains mycophenolate mofetil 500 mg.
Excipients: Microcrystalline cellulose, croscarmellose sodium, povidone, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol, iron oxide red, indigo carmine aluminium lake, black iron oxide.

Capsule shell (FD & C Blue 2, titanium dioxide, iron oxide red, iron oxide yellow, gelatin, water, SLS (sodium lauryl sulphate)).

PHARMACODYNAMICS

Mycophenolate mofetil is an immunosuppressive agents. 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.

PHARMACOKINETICS

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

In general, the pharmacokinetic profile of MPA is similar in renal and in cardiac transplant patients. In the early transplant period, hepatic transplant patients receiving a 1.5g oral MMF dose or 1g i.v. MMF dose have similar MPA levels compared to renal transplant patients receiving 1g oral or i.v. MMF.

Absorption
Following oral and intravenous administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete pre-systemic metabolism to the active metabolite, MPA. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94% relative to i.v. mycophenolate mofetil. Mycophenolate mofetil, can be measured systemically during intravenous infusion; however, after oral administration it is below the limit of quantification (0.4 mg/mL). Immediately post-transplant period (<40 days), renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30% lower and C_{max} approximately 40% lower compared to the late transplant period (3-6 months post-transplant). MPA AUC values obtained following administration of 1g twice daily intravenous mycophenolate mofetil at the recommended infusion rate to renal transplant patients in the immediate post-transplant phase are comparable to those observed following oral dosing. In hepatic transplant patients, administration of 1g twice daily intravenous mycophenolate mofetil followed by 1.5g twice daily. Oral mycophenolate mofetil resulted in MPA AUC values similar to those found in renal transplant patients administered 1g mycophenolate mofetil twice daily. Food had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil administered at doses of 1.5 g twice daily to renal transplant patients. However, MPA C_{max} was decreased by 40% in the presence of food.

Distribution
Secondary increases in plasma MPA concentrations are usually observed at approximately 6-12 hours post-dose, consistent with enterohepatic recirculation. A reduction of approximately 40% in the AUC of MPA is associated with co-administration of cholestyramine (4 g three times daily), consistent with interruption of enterohepatic recirculation. At clinically relevant concentrations, MPA is 97% bound to plasma albumin.

Metabolism
MPA is metabolized principally by glucuronyl transferase (isoform UGT1A9) to form the inactive phenolic glucoronide 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
Oral administration of radio-labelled mycophenolate mofetil resulted in complete recovery of the administered dose, with 93% of the administered dose recovered in the urine and 6% recovered in the feces. Most (about 87%) of the administered dose is excreted in the urine as MPAG. A negligible amount of drug (<1% of dose) is excreted as MPA in the urine. At clinically encountered concentrations, MPA and MPAG are not removed by hemodialysis. However, at high MPAG concentrations (>100µg/mL), small amounts of MPAG are removed. By interfering with enterohepatic circulation of the drug, bile acid sequestrants, such as cholestyramine, reduce MPA AUC. 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.

Pharmacokinetics in special populations
Patients with severe renal impairment
In a single-dose study (6 subjects per group), mean plasma MPA AUCs observed after oral dosing in subjects with severe chronic renal impairment (glomerular filtration rate <25 mL/min/1.73m2) were 28- 75% higher than those observed in normal healthy subjects or subjects with lesser degrees of renal impairment. However, the mean single-dose MPAG AUC was 3- to 6-fold higher in subjects with severe renal impairment than in subjects with mild renal impairment 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.

Patients with delayed renal graft function post-transplant
In patients with delayed graft function post-transplant, mean MPA AUC0-12 was comparable to that seen 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. Mean plasma MPAG. AUC0-12 was 2- to 3 fold higher than in post-transplant patients without delayed graft function. In patients with primary non-functioning graft following renal transplantation, plasma concentrations of MPAG accumulated; accumulation of MPA, if any, was much smaller.

Patients with hepatic impairment
Overall, the pharmacokinetics of MPA and MPAG were relatively unaffected by hepatic parenchymal disease in volunteers with alcoholic cirrhosis dosed with oral or intravenous MMF. Effects of hepatic disease on these processes probably depend on the particular disease. Hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.

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

INDICATIONS

Mofecon is indicated for:
- prophylaxis of acute organ rejection and treatment of refractory organ rejection in patients receiving allogeneic renal transplants.
- prophylaxis of acute organ rejection and increased graft and patient survival in patients receiving allogeneic cardiac transplants.
- prophylaxis of acute organ rejection in patients receiving allogeneic hepatic transplants.

Mofecon should be used concomitantly with cyclosporin and corticosteroids.

CONTRAINDICATIONS

Mofecon should not be given to:
- Patients with hypersensitivity to mycophenolate mofetil, mycophenolic acid or to any of the excipients shown above.
- Women of childbearing potential who are not using highly effective contraception.
- Women of child bearing potential without providing a pregnancy test result to rule out unintended use in pregnancy.
- During pregnancy due to its mutagenic and teratogenic potential.
- Women who are breastfeeding.

WARNING AND PRECAUTIONS

Neoplasms
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. 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.

Infection
Oversuppression of the immune system can also increase susceptibility to infection including opportunistic infections, fatal infections and sepsis. Such infections include latent viral reactivation, such as by heptatitis B or hepatitis C reactivation, or infections caused by polyomaviruses. Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. Cases of Progressive Multifocal Leukoencephalopathy (PML) associated with the JC virus, sometimes fatal, have been reported in mycophenolate mofetil treated patients. The reported cases generally had risk factors for PML, including immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a Neurologist should be considered as clinically indicated. BK virus-associated nephropathy has been observed during the use of mycophenolate mofetil in patients post renal transplant. This infection can be associated with serious outcomes, sometimes leading to renal graft loss. Patient monitoring may help detect patients at risk for BK virus-associated nephropathy. Reduction in immunosuppression should be considered for patients who develop evidence of BK virus-associated nephropathy. 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 infectionsshould 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. It is recommended that patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, are investigated.

Blood and immune system
Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil in combination with other immunosuppressive agents. The mechanism for mycophenolate mofetil induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppression regimen are also unknown. In some cases PRCA was found to be reversible with dose reduction or cessation of mycophenolate mofetil therapy. In transplant patients however reduced immunosuppression may place the graft at risk. Patients receiving mycophenolate mofetil should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression. Patients on mycophenolate mofetil should have complete blood counts weekly during the first month of treatment, twice monthly for the second and third months, then monthly through the first year. In particular, patients receiving mycophenolate mofetil should be monitored for neutropenia. The development of neutropenia may be related to mycophenolate mofetil, concomitant medications, viral infection or some combination of these causes. If neutropenia develops (absolute neutrophil count <1.3 x 103/mL), dosing with mycophenolate mofetil should be interrupted or the dose should be reduced and the patient carefully observed. Patients should not donate blood during therapy and for at least 6 weeks following discontinuation of mycophenolate mofetil. Patients should be advised that during treatment with mycophenolate mofetil vaccinations may be less effective and the use of live attenuated vaccines should be avoided. 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 should be administered with caution in patients with active serious digestive system disease.

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

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

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.

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. Mycophenolate mofetil is contraindicated in pregnancy and during breastfeeding. Men should not donate semen during therapy and for 90 days following discontinuation of mycophenolate mofetil administration of doses greater than 1 g twice daily. To renal transplant patients with severe chronic renal impairment should be avoided. No dose adjustment is recommended for post-transplant patients with delayed renal graft function, but patients should be carefully monitored. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Effects on ability to drive and use machines
Mycophenolate mofetil may have a moderate influence on the ability to drive and use machines.

Patients should be advised to use caution when driving or using machines if they experience adverse drug reactions such as somnolence, confusion, dizziness, tremor or hypotension during treatment with mycophenolate mofetil.

PREGNANCY AND LACTATION

Fertility
Mofecon is contraindicated in women of childbearing potential not using highly effective contraceptive methods. Malformations (including anophthalmia, agnathia, and hydrocephaly) occurred in the first generation offspring of female rats treated with oral doses of mycophenolate mofetil in the absence of maternal toxicity. No effect was seen on the fertility of male rats treated with mycophenolate mofetil.

Pregnancy Testing
Prior to starting therapy with Mofecon, female patients of childbearing potential must have two negative serum or urine pregnancy tests with a sensitivity of at least 25mIU/mL. A second test should be performed 8-10 days later. If it is not possible to perform two tests 8-10 days apart before treatment starts (because of the timing of transplant organ availability), a pregnancy test must be performed immediately before starting treatment and a second test performed 8-10 days later.

Contraception
Females
Mofecon is contraindicated in women of childbearing potential not using highly effective contraceptive methods. Before the start of treatment, female and male patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention, and planning.

Women of child bearing potential should use two reliable forms of contraception simultaneously, including at least one of which must be highly effective before beginning Mofecon therapy, during therapy and for six weeks following discontinuation of therapy, unless abstinence is the chosen method of contraception.

Males
Limited clinical evidence is currently available on paternal exposure to Mofecon. This evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to mycophenolate. Thus, the risk of genotoxic effects on sperm cells cannot completely be excluded. In absence of sufficient data to exclude a risk of harm to the fetus conceived during or directly after the treatment of the father, the following precautionary measure is recommended: sexually active male patients and/or their female partners are recommended to use effective contraception during treatment of the male patient and for at least 90 days after cessation of treatment.

Pregnancy
Mofecon is contraindicated during pregnancy due to its mutagenic and teratogenic potential. Mofecon is a human teratogen, with an increased risk of spontaneous abortions (mainly in the first trimester) and congenital malformations in case of maternal exposure during. The following malformations were most frequently reported post-marketing, in children of patients exposed to mycophenolate mofetil in combination with other immunosuppressants during pregnancy:
- 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/middle ear) and eye (e.g. coloboma, microphthalmos);
- Malformations of the fingers (e.g. polydactyly, syndactyly, brachydactyly);
- Cardiac abnormalities such as atrial and ventricular septal defects;
- Oesophageal malformations (e.g. oesophageal atresia);
- Nervous system malformations (such as spina bifida).

Labor and delivery: The safe use of Mofecon during labor and delivery has not been established.

Lactation
It is not known whether the drug is excreted in human milk. Due to the potential for serious adverse reactions in nursing infants, Mofecon is contraindicated during. Although the relevance to humans is unknown, studies in rats have shown mycophenolate mofetil to be excreted in milk.

Geriatric Use
The recommended oral doses of 1 g twice daily for renal transplant patients, 1.5 g twice daily. for cardiac or hepatic transplant patients is appropriate for elderly patients.

DRUG INTERACTIONS

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

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 Mofecon.

Cholestyramine
Caution should be used during concomitant administration of drugs that interfere with enterohepatic circulation.

Cyclosporin A
Cyclosporin A (CsA) pharmacokinetics were unaffected by mycophenolate mofetil. However CsA interferes with MPA enterohepatic recycling, resulting in reduced MPA exposures by 30-50% in renal transplant patients treated with Mofecon and CsA compared with patients receiving sirolimus or belatacept and similar doses of Mofecon. Conversely, changes of MPA exposure should be expected when switching patients from CsA to one of the immunosuppressants which do not interfere with MPA's enterohepatic cycle.

Drugs affecting glucuronidation
Concomitant administration of drugs inhibiting glucuronidation of MPA may increase MPA exposure. Caution is therefore recommended when administering these drugs concomitantly with Mofecon.

Telmisartan
Concomitant administration of telmisartan and Mofecon resulted in an approximately 30% decrease of mycophenolic acid (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 Mofecon patients with and without concomitant telmisartan medication, no clinical consequences of the pharmacokinetic DDI were seen. However, caution should be exercised when Mofecon is co-administered with telmisartan and monitoring of Mofecon levels may be considered.

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 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 which mycophenolate mofetil and ganciclovir or its prodrugs, e.g. valganciclovir are coadministered, patients should be monitored carefully.

Oral contraceptives
The pharmacokinetics of oral contraceptives were not affected to a clinically relevant degree by coadministration of Mofecon.

BACK

Rifampicin
After correction for dose a 70% decrease in MPA exposure (AUC0-12h) has been observed with concomitant rifampicin administration in a single heart-lung transplant patient. It is therefore recommended to monitor MPA exposure levels and to adjust Mofecon doses accordingly to maintain clinical efficacy when the drugs are administered concomitantly.

Tacrolimus
Exposure to tacrolimus concomitantly administered with Mofecon had no effect on the AUC or Cmax of MPA in liver transplant recipients. A similar finding was observed in a recent study in kidney transplant recipients. In renal transplant patients it was shown that the tacrolimus concentration did not appear to be altered by Mofecon. However, in hepatic transplant patients, there was an increase of approximately 20% in tacrolimus AUC when multiple doses of Mofecon (1.5 g twice daily.) were administered to patients taking tacrolimus.

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 54% have been reported in renal transplant recipients in the days immediately following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. Effects tended to diminish with continued antibiotic use and cease after discontinuation. The change in predose level may not accurately represent changes in overall MPA exposure, therefore clinical relevance of these observations is unclear.

Norfloxacin and metronidazole
Norfloxacin in combination with metronidazole reduced the MPA AUC0- 48 by 30% following a single dose of Mofecon. No such effect on the systemic exposure of MPA with either of these antibiotics occurred when they were administered separately.

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

Concomitant administration of sevelamer and Mofecon in adults and pediatric patients decreased the MPA Cmax and AUC0-12 by 30% and 25 %, respectively. This data suggest that sevelamer and other calcium free phosphate binders preferentially should be given 2 hours after Mofecon intake to minimize the impact on the absorption of MPA.

Live vaccines
Live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished.

UNDESIREABLE EFFECTS

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

Clinical trials
An estimated total of 1557 patients received mycophenolate mofetil during pivotal clinical trials in the prevention of acute organ rejection. Of these, 991 were included in the pooled renal studies ICM1866, MYC022, MYC023, 277 were included in the hepatic study MYC2646, and 289 were included in the cardiac study MYC1864. Patients in all study arms also received ciclosporin and corticosteroids. Diarrhea, leukopenia, sepsis, and vomiting were among the most common and/or serious adverse drug reactions associated with the administration of mycophenolate mofetil in the pivotal trials.

There was also evidence of a higher frequency of certain types of infection, e.g. opportunistic infections. In the three pivotal trials for prevention of renal transplant rejection, patients receiving 2 g per day of mycophenolate mofetil demonstrated an overall better safety profile than patients receiving 3 g mycophenolate mofetil. The safety profile of mycophenolate mofetil in patients treated for refractory renal transplant rejection was similar to that observed in the pivotal trials for prevention of renal rejection at doses of 3 g per day. Diarrhea and leukopenia, followed by anemia, nausea, abdominal pain, sepsis, nausea and vomiting, and dyspepsia were the predominant adverse events reported more frequently in patients receiving mycophenolate mofetil in comparison to patients receiving i.v. corticosteroids.

Tabulated summary of adverse drug reactions from clinical trials
Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class along with their incidence. The corresponding frequency category for each adverse drug reaction is based on the following convention: 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). Due to the large differences observed in the frequency of certain ADRs across the different transplant indications, the frequency is presented separately for renal, hepatic and cardiac transplant patients.

Table 1 Summary of adverse drug reactions occurring in patients treated with mycophenolate mofetil in pivotal clinical trials and post-marketing surveilance

Adverse drug Reaction (MedDRA) System Organ Class	Renal transplant n = 991	Hepatic transplant n = 277	Cardiac transplant n = 289
Infections and infestations			
Bacterial infections	V.Common	V.Common	V.Common
Fungal infections	Common	V.Common	V.Common
Viral infections	V.Common	V.Common	V.Common
Protozoal infections	Uncommon[2]		
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Benign neoplasm of skin	Common	Common	Common
Neoplasm	Common	Common	Common
Skin cancer	Common	Uncommon	Common
Lymphoma	Uncommon[2]		
Lymphoproliferative disorder	Uncommon[2]		
Blood and lymphatic system disorders			
Anemia	V.Common	V.Common	V.Common
Ecchymosis	Common	Common	V.Common
Leukocytosis	Common	V.Common	V.Common
Leukopenia	V.Common	V.Common	V.Common
Pancytopenia	Common	Common	Uncommon
Pseudolymphoma	Uncommon	Uncommon	Common
Thrombocytopenia	Common	V.Common	V.Common
Aplasia pure red cell	Uncommon[2]		
Bone marrow failure	Uncommon[2]		
Metabolism and nutrition disorders			
Acidosis	Common	Common	V.Common
Hypercholes-terolemia	V. Common	Common	V.Common
Hyperglycemia	Common	V.Common	V.Common
Hyperkalemia	Common	V.Common	V.Common
Ileus	Common	Common	V.Common
Hypocalcemia	Common	V.Common	Common
Hypokalemia	Common	V.Common	V.Common
Hypomagnesemia	Common	V.Common	V.Common
Hypophosphatemia	V.Common	V.Common	Common
Weight decreased	Common	Common	Common
Psychiatric disorders			
Confusional state	Common	V.Common	V.Common
Depression	Common	V.Common	V.Common
Insomnia	Common	V.Common	V.Common
Nervous system disorders			
Dizziness	Common	V.Common	V.Common
Headache	V.Common	V.Common	V.Common
Hypertonia	Common	Common	V.Common
Paresthenia	Common	V.Common	V.Common
Somnolence	Common	Common	V.Common
Tremor	Common	V.Common	V.Common
Cardiac disorders			
Tachycardia	Common	V.Common	V.Common
Vascular disorders			
Hypertension	V.Common	V.Common	V.Common
Hypotension	Common	V.Common	V.Common
Venous thrombosis*	Common	Common	Common
Lymphocele	Uncommon[2]		
Respiratory, thoracic and mediastinal disorders			
Cough	V.Common	V.Common	V.Common
Dyspnea	V.Common	V.Common	V.Common
Pleural effusion	Common	V.Common	V.Common
Bronchiectasis	Uncommon[2]		
Interstitial lung disease	Uncommon		
Pulmonary fibrosis	Uncommon[2]		
Gastrointestinal disorders			
Abdominal pain	V.Common	V.Common	V.Common
Colitis	V.Common	Common	Common
Constipation	V.Common	V.Common	V.Common
Decreased appetite	V.Common	V.Common	V.Common
Diarrhea	V.Common	V.Common	V.Common
Dyspepsia	V.Common	V.Common	V.Common
Esophagitis	Common	V.Common	V.Common
Flatulence	Common	Common	Common
Gastritis	Common	V.Common	Common
Gastrointestinal hemorrhage	Common	Common	Common
Gastrointestinal ulcer	Common	Common	Common
Ileus	Common	Common	Common
Nausea	V.Common	V.Common	V.Common
Stomatitis	Common	Common	Common
Vomiting	V.Common	V.Common	V.Common
Pancreatitis	Common		
Hepatobiliary disorders			
Blood alkaline phosphatase increased	Common	Common	Common
Blood lactate dehydrogenase increased	Common	Uncommon	Very common
Hepatic enzyme increased	Common	V.Common	V.Common
Hepatitis	Common	V.Common	Uncommon
Skin and subcutaneous tissues disorders			
Alopecia	Common	Common	Common
Rash/Pruritus	Common	V.Common	V.Common
Musculoskeletal and connective tissue disorders			
Arthralgia	Common	Common	V.Common
Muscular weakness	Common	Common	V.Common
Renal and urinary disorders			
Blood creatinine increased	Common	Very common	Very common
Blood urea increased	Uncommon	Very common	Very common
Hematuria	V.Common	Common	Common
General disorders and administration site conditions			
Asthenia	V.Common	V.Common	V.Common
Chills	Common	V.Common	V.Common
Edema	V.Common	V.Common	V.Common
Hernia	Common	V.Common	V.Common
Malaise	Common	V.Common	Common
Pain	Common	V.Common	V.Common
Pyrexia	V.Common	V.Common	V.Common
Immune system disorders			
Hypersensitivity	Common		
Hypogamma-globulinemia	Uncommon		

** Reported following intravenous administration.*
[1] Highest incidence observed during the pivotal clinical trials
[2] The frequency category for ADRs observed only in the postmarketing setting is defined as the upper limit of the 95% confidence interval calculated on the basis of the total number of patients exposed to mycophenolate mofetil in pivotal trials

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

Progressive Multifocal Leukoencephalopathy (PML) and BK virus associated nephropathy, have been reported in mycophenolate mofetil treated patients.

Congenital disorders and Pregnancy, puerperium, and perinatal conditions: See section pregnancy for further information.

Description of selected adverse drug reactions
Infections
All patients treated with immunosuppressants are at increased risk of bacterial, viral, and fungal infections (some of which may lead to a fatal outcome), including those caused by opportunistic agents and latent viral reactivation. The risk increases with total immunosuppressive load. The most serious infections were sepsis and peritonitis. The most common opportunistic infections in patients receiving mycophenolate mofetil with other immunosuppressants were mucocutaneous candida, CMV viremia/syndrome, and herpes simplex. The proportion of patients with CMV viremia/syndrome was 13.5%.

Malignancies
Patients receiving mycophenolate mofetil as part of an immunosuppressive regime are at increased risk of developing lymphomas and other malignancies, particularly of the skin. Three-year safety data in renal and cardiac transplant patients did not reveal any unexpected changes in the incidence of malignancy compared to the 1-year data. Hepatic transplant patients were followed for at least 1 year, but less than 3 years. In supportive clinical trials of treatment of refractory renal rejection, the lymphoma rate was 3.9% at an average follow up of 42 months.

Blood and lymphatic disorders
Cytopenias, including leukopenia, anemia, thrombocytopenia and pancytopenia, are a known risk associated with mycophenolate and may lead or contribute to the occurrence of infections and hemorrhages.

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

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.

Special Populations
Children (aged 3 months to 18 years)
The type and frequency of adverse drug reactions in a clinical study of 100 pediatric patients aged 3 months to 18 years 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 occurred with a frequency of ≥ 10 % in children and were more frequent in the pediatric population, particularly in children under 6 years of age, when the frequency of treatment-related adverse events were compared to adults: diarrhea, leukopenia, sepsis, infection, and anemia. The safety and efficacy of mycophenolate mofetil in children below the age of 18 years have not been established.

Elderly patients (≥ 65 years)
Elderly patients, particularly those who are receiving mycophenolate mofetil as part of a combination immunosuppressive regimen, may be at greater increased risk of certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal hemorrhage and pulmonary edema, compared to younger individuals.

OVERDOSE

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 over suppression of the immune system and increase susceptibility to infections and bone marrow suppression. If neutropenia develops, dosing with Mofecon should be interrupted or the dose reduced.

Haemodialysis would not be expected to remove clinically significant amounts of MPA or MPAG. Bile acid sequestrants, such as cholestyramine, can remove MPA by decreasing the enterohepatic re-circulation of the drug.

DOSAGE AND ADMINISTRATION

Please refer to full prescribing information for corticosteroids and either ciclosporin or tacrolimus, which are used in combination with Mofecon.

Standard Dosage for prophylaxis of renal rejection
A dose of 1 g administered orally or intravenously (over NO LESS THAN 2 HOURS) twice a day (daily dose of 2 g) is recommended for use in renal transplant patients.

Although a dose of 1.5 g administered twice daily (daily dose of 3 g) was used in clinical trials and was shown to be safe and effective, no efficacy advantage could be established for renal transplant patients. Patients receiving 2 g per day of Mofecon demonstrated an overall better safety profile compared to patients receiving 3 f per day of Mofecon.

Standard Dosage for prophylaxis of cardiac rejection
A dose of 1.5g administered orally or intravenously (over NO LESS THAN 2 HOURS) twice a day (daily dose of 3g) is recommended for use in cardiac transplant patients.

Standard Dosage for prophylaxis of hepatic rejection
A dose of 1.0g administred intravenously (over NO LESS THAN 2 HOURS) twice a day (daily dose of 2g) or 1.5g orally twice a day (daily dose of 3g) is recommended for use in hepatic transplant patients.

Standard dosage for treatment of refractory renal rejection
A dose of 1.5 g administered twice a day (daily dose of 3g) is recommended for management of refractory rejection.
The initial dose of Mofecon should be given as soon as possible following renal, cardiac or hepatic transplantation.

Special dosage instructions
Patients with neutropenia: If neutropenia develops (absolute neutrophil count <1.3 x 103/ml), dosing with Mofecon should be interrupted or the dose should be reduced and the patient carefully observed.

For dosage instructions in special population, please refer to sections Special Populations.

Storage: Store below 30°C. Protect from light and moisture.

Presentation/ Packing: Alu-alu blister pack of 6x10's.

Manufactured for / Product Registration Holder (Malaysia) / Product Owner: **HOVID Berhad**
121, Jalan Tunku Abdul Rahman (Jalan Kuala Kangsar), 30010 Ipoh, Perak, Malaysia.
Manufactured by: Concord Biotech Limited
297-298/2p, Siyawada, Valthera, Ahmedabad, Gujarat 382225, India.

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