FRONT

Mofecon™ 250 (Mycophenolate Mofetil 250 mg Capsules)

VIMOF05-var (MY SIN)

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

COMPOSITION
Each capsule contains : Mycophenolate mofetil 250 mg
Excipients: Microcrystalline cellulose, hydroxypropyl cellulose, povidone, croscarmellose sodium, talc, magnesium stearate.

PHARMACODYNAMICS
Mycophenolate mofetil is an immunosuppressive agent. 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
Absorption and Distribution
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 Mofecon is correlated with MPA concentration. Food had no effect on the extent of absorption of mycophenolate mofetil. There is a significant amount of enterohepatic recirculation for mycophenolate mofetil. MPA at clinically relevant concentrations is 97% bound to plasma albumin.

Biotransformation and Elimination
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).

Special Populations
Renal impairment
Patient with renal impairment have higher plasma concentration of MPA. Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied.
Delayed renal 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 Mofecon does not appear to be necessary.
Hepatic impairment
Hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.
Elderly
Pharmacokinetic behaviour of mycophenolate mofetil in the elderly (≥ 65 years) has not been formally evaluated.

INDICATIONS
Mofecon Capsules are indicated for the prophylaxis of acute organ rejection in patients receiving allogeneic renal transplants.
Mofecon Capsules are indicated for the prophylaxis of acute organ rejection in patients receiving allogeneic cardiac transplants.
Mofecon Capsules are indicated for the prophylaxis of acute organ rejection in patients receiving allogeneic hepatic transplants.
Mofecon should be used concomitantly with ciclosporin and corticosteroids.
Mofecon is indicated for induction and maintenance treatment of lupus nephritis. Mofecon should be used concomitantly with corticosteroids.

CONTRAINDICATIONS
- Mofecon is contraindicated during pregnancy due to its mutagenic and teratogenic potential (see Pregnancy and Lactation).
- Mofecon is contraindicated in women of childbearing potential not using highly effective contraceptive methods (see Pregnancy and Lactation).
- Mofecon is contraindicated in women who are breastfeeding (see Pregnancy and Lactation).

WARNING AND PRECAUTIONS
Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus associated nephropathy which has been observed in patients receiving immunosuppressants. These infections may lead to serious, including fatal outcomes.

Neoplasms
Patients receiving immunosuppressive regimens involving combinations of medicinal products, including Mofecon, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. 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 Mofecon, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis. Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation and infections caused by polyomaviruses (BK virus-associated nephropathy, JC virus-associated progressive multifocal leukoencephalopathy PML). Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. Mycophenolic acid has a cytostatic effect on B- and T-lymphocytes, therefore an increased severity of COVID-19 may occur. Dose reduction or discontinuation of Mofecon should be considered for patients in cases of clinically significant COVID-19.
Hypogammaglobulinaemia in association with recurrent infections may be observed in patients receiving Mofecon in combination with other immunosuppressants. Switching Mofecon to an alternative immunosuppressant may result in serum IgG levels returning to normal. Patients on Mofecon 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.
Bronchiectasis may be observed in adults and children who received Mofecon in combination with other immunosuppressants. Switching Mofecon to another immunosuppressant may result in improvement in respiratory symptoms. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect on the lung. Interstitial lung disease and pulmonary fibrosis are also reported, 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
Patients receiving Mofecon should be monitored for neutropenia, which may be related to Mofecon itself, concomitant medications, viral infections, or some combination of these causes. Patients taking Mofecon 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 Mofecon.
Pure red cell aplasia (PRCA) may be observed in patients treated with Mofecon in combination with other immunosuppressants. The mechanism for mycophenolate mofetil induced PRCA is unknown. PRCA may resolve with dose reduction or cessation of Mofecon therapy. Changes to Mofecon therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimise the risk of graft rejection.
Patients receiving Mofecon should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow failure.
Patients should be advised, that during treatment with Mofecon, 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
Mofecon has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, haemorrhage and perforation. Mofecon should be administered with caution in patients with active serious digestive system disease.
Mofecon is an IMPDH (inosine monophosphate dehydrogenase) inhibitor. Therefore, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Interactions
Caution should be exercised when switching combination therapy from regimens containing immunosuppressants, which interfere with MPA enterohepatic recirculation, e.g. ciclosporin, to others devoid of this effect, e.g. tacrolimus, sirolimus, belatacept, or vice versa, as this might result in changes of MPA exposure. Drugs which interfere with MPA's enterohepatic cycle (e.g. cholestyramine, antibiotics) should be used with caution due to their potential to reduce the plasma level and efficacy of Mofecon. Therapeutic drug monitoring of MPA may be appropriate when switching combination therapy (e.g. from ciclosporin to tacrolimus or vice versa) or to ensure adequate immunosuppression in patients with high immunological risk (e.g. risk of rejection, treatment with antibiotics, addition or removal of an interacting medication).
It is recommended that Mofecon should not be administered concomitantly with azathioprine because such concomitant administration has not been studied.
The risk/benefit ratio of mycophenolate mofetil in combination with sirolimus has not been established.

Special populations
Elderly
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.

Teratogenic effects
Mycophenolate is a powerful human teratogen. Spontaneous abortion (rate of 45% to 49%) and congenital malformations (estimated rate of 23% to 27%). Therefore, Mofecon is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejection. Female patients of childbearing potential should be made aware of the risks and follow the recommendations provided in (Use in Special Populations: Pregnancy and Use in Special Populations: Breast-feeding section) prior to, during, and after therapy with Mofecon. Physicians should ensure that women taking mycophenolate understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult their physician if there is a possibility of pregnancy.

Contraception
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 before starting Mofecon 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 Use in Special Populations: Pregnancy and Use in Special Populations: Breast-feeding section.

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.

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

PREGNANCY AND LACTATION
Pregnancy
Mofecon is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraceptive methods. (see Contraindications)
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.
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 25 mIU/mL; The second test should be performed 8-10 days after the first one and immediately before starting Mofecon. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should they become pregnant.
Due to the mutagenic and teratogenic potential of mycophenolate, women of child bearing potential should use two reliable forms of contraception simultaneously, including at least one highly effective method, before beginning mycophenolate 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 for both reproductively competent and vasectomised 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 are recommended to use highly effective during treatment and for total of 90 days after the last dose of Mofecon.
Congenital malformations, including multiple malformations have been reported post-marketing in children of patients exposed to mycophenolate 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/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).

In the medical literature, malformations in children from mycophenolate-exposed pregnancies have been reported in 23% to 27% of live births. For comparison, the risk of malformations is estimated at approximately 2% of live births in the overall population and at approximately 4% to 5% in solid organ transplant patients treated with immunosuppressants other than mycophenolate.
Cases of spontaneous abortions have also been reported in patients exposed to mycophenolate, mainly in the first trimester. In the medical literature, the risk has been reported at 45% to 49% following mycophenolate exposure, compared to a reported rate between 12 and 33% in solid organ transplant patients treated with other immunosuppressants.
Studies in animals have shown reproductive toxicity.

Breast-feeding
Mofecon is contraindicated during breastfeeding due to the potential for serious adverse reactions in nursing infants (see Contraindications). Studies in rats have shown mycophenolate to be excreted in milk. It is not known whether this medicine is excreted in human milk.

DRUG INTERACTIONS
Aciclovir
Higher aciclovir plasma concentrations were observed when mycophenolate mofetil was administered with aciclovir in comparison to the administration of aciclovir alone. 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.

Medicinal products that interfere with enterohepatic recirculation (e.g., cholestyramine, ciclosporin A, antibiotics)
Caution should be used with medicinal products that interfere with enterohepatic recirculation because of their potential to reduce the efficacy of Mofecon.

Cholestyramine
Caution should be used during concomitant administration because of the potential to reduce efficacy of Mofecon.

Ciclosporin A
Ciclosporin A (CsA) pharmacokinetics are unaffected by mycophenolate mofetil. In contrast, if concomitant CsA treatment is stopped, an increase in MPA AUC should be expected. 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 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 Mofecon 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
No significant interaction was observed when mycophenolate mofetil was concomitantly administered with norfloxacin or metronidazole separately. However, norfloxacin and metronidazole combined have shown to reduce the MPA exposure following a single dose of mycophenolate mofetil.

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

Medicinal products that affect glucuronidation (e.g., isavuconazole, telmisartan)
Concomitant administration of drugs affecting glucuronidation of MPA may change MPA exposure. Caution is therefore recommended when administering these drugs concomitantly with Mofecon.

Isavuconazole
An increase of MPA $AUC_{0-\infty}$ was observed in studies with concomitant administration of isavuconazole.

Telmisartan
Concomitant administration of telmisartan and mycophenolate mofetil have shown to result in a 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 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 Mofecon dose adjustment is not required. In patients with renal impairment in whom Mofecon 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.

Rifampicin
In patients not also taking ciclosporin, concomitant administration of mycophenolate mofetil and rifampicin have shown to result in a decrease in MPA exposure. It is recommended to monitor MPA exposure levels and to adjust Mofecon doses accordingly to maintain clinical efficacy when rifampicin is administered concomitantly.

Sevelamer
Decrease in MPA C_{max} and AUC_{0-12h} were observed when mycophenolate mofetil was concomitantly administered with sevelamer without any clinical consequences (i.e., graft rejection). It is recommended, however, to administer Mofecon 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
Studies have shown that 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 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.

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

Paediatric population
Interaction studies have only been performed in adults.

Potential interaction
Co-administration of probenecid with mycophenolate mofetil may raise 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.

BACK

Mofecon™ 250 (Mycophenolate Mofetil 250 mg Capsules)

MAIN SIDE/ ADVERSE EFFECTS

The adverse drug reactions (ADRs) are listed in the table below, by MedDRA system organ class (SOC) along with their frequencies.

Adverse drug reaction (MedDRA) System Organ Class	Renal transplant	Hepatic transplant	Cardiac transplant
	Frequency	Frequency	Frequency
Infections and infestations			
Bacterial infections	Very Common	Very Common	Very Common
Fungal infections	Common	Very Common	Very Common
Protozoal infections	Uncommon	Uncommon	Uncommon
Viral infections	Very Common	Very Common	Very Common
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Benign neoplasm of skin	Common	Common	Common
Lymphoma	Uncommon	Uncommon	Uncommon
Lymphoproliferative disorder	Uncommon	Uncommon	Uncommon
Neoplasm	Common	Common	Common
Skin cancer	Common	Uncommon	Common
Blood and lymphatic system disorders			
Anemia	Very Common	Very Common	Very Common
Aplasia pure red cell	Uncommon	Uncommon	Uncommon
Bone marrow failure	Uncommon	Uncommon	Uncommon
Ecchymosis	Common	Common	Very Common
Leukocytosis	Common	Very Common	Very Common
Leucopenia	Very Common	Very Common	Very Common
Pancytopenia	Common	Common	Uncommon
Pseudolymphoma	Uncommon	Uncommon	Common
Thrombocytopenia	Common	Very Common	Very Common
Metabolism and nutrition disorders			
Acidosis	Common	Common	Very Common
Hypercholesterolemia	Very Common	Common	Very Common
Hyperglycemia	Common	Very Common	Very Common
Hyperkalemia	Common	Very Common	Very Common
Hyperlipidemia	Common	Common	Very Common
Hypocalcemia	Common	Very Common	Common
Hypokalemia	Common	Very Common	Very Common
Hypomagnesemia	Common	Very Common	Very Common
Hypophosphatemia	Very Common	Very Common	Common
Hyperuricaemia	Common	Common	Very Common
Gout	Common	Common	Very Common
Weight decreased	Common	Common	Common
Psychiatric disorders			
Confusional state	Common	Very Common	Very Common
Depression	Common	Very Common	Very Common
Insomnia	Common	Very Common	Very Common
Agitation	Uncommon	Common	Very Common
Anxiety	Common	Very Common	Very Common
Thinking abnormal	Uncommon	Common	Common
Nervous system disorders			
Dizziness	Common	Very Common	Very Common
Headache	Very Common	Very Common	Very Common
Hypertonia	Common	Common	Very Common
Paresthesia	Common	Very Common	Very Common
Somnolence	Common	Common	Very Common
Tremor	Common	Very Common	Very Common
Convulsion	Common	Common	Common
Dysgeusia	Uncommon	Uncommon	Common
Cardiac disorders			
Tachycardia	Common	Very Common	Very Common
Vascular disorders			
Hypertension	Very Common	Very Common	Very Common
Hypotension	Common	Very Common	Very Common
Lymphocele	Uncommon	Uncommon	Uncommon
Venous thrombosis	Common	Common	Common
Vasodilatation	Common	Common	Very Common
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis	Uncommon	Uncommon	Uncommon
Cough	Very Common	Very Common	Very Common
Dyspnea	Very Common	Very Common	Very Common
Interstitial lung disease	Uncommon	Very Rare	Very Rare
Pleural effusion	Common	Very Common	Very Common
Pulmonary fibrosis	Very Rare	Uncommon	Uncommon
Gastrointestinal disorders			
Abdominal distension	Common	Very Common	Common
Abdominal pain	Very Common	Very Common	Very Common
Colitis	Common	Common	Common
Constipation	Very Common	Very Common	Very Common
Decreased appetite	Common	Very Common	Very Common
Diarrhoea	Very Common	Very Common	Very Common
Dyspepsia	Very Common	Very Common	Very Common
Esophagitis	Common	Common	Common
Eructation	Uncommon	Uncommon	Common
Flatulence	Common	Very Common	Very Common
Gastritis	Common	Common	Common
Gastrointestinal hemorrhage	Common	Common	Common
Gastrointestinal ulcer	Common	Common	Common
Ileus	Common	Common	Common
Mouth ulceration	Common	Common	Common
Nausea	Very Common	Very Common	Very Common
Pancreatitis	Uncommon	Common	Uncommon
Stomatitis	Common	Common	Common
Vomiting	Very Common	Very Common	Very Common
Immune system disorders			
Hypersensitivity	Uncommon	Common	Common
Hypogammaglobulinemia	Uncommon	Very Rare	Very Rare
Hepatobiliary disorders			
Blood alkaline phosphatase increased	Common	Common	Common
Blood lactate dehydrogenase increased	Common	Uncommon	Very Common
Hepatic enzyme increased	Common	Very Common	Very Common
Hepatitis	Common	Very Common	Uncommon
Hyperbilirubinaemia	Common	Very Common	Very Common
Jaundice	Uncommon	Common	Common
Skin and subcutaneous tissues disorders			
Acne	Common	Common	Very Common
Alopecia	Common	Common	Common
Rash	Common	Very Common	Very Common
Skin hypertrophy	Common	Common	Very Common
Musculoskeletal and connective tissue disorders			
Arthralgia	Common	Common	Very Common
Muscular weakness	Common	Common	Very Common
Renal and urinary disorders			
Blood creatinine increased	Common	Very Common	Very Common
Blood urea increased	Uncommon	Very Common	Very Common
Hematuria	Very Common	Common	Common
Renal impairment	Common	Very Common	Very Common
General disorders and administration site conditions			
Asthenia	Very Common	Very Common	Very Common
Chills	Common	Very Common	Very Common
Edema	Very Common	Very Common	Very Common
Hernia	Common	Very Common	Very Common
Malaise	Common	Common	Common
Pain	Common	Very Common	Very Common
Pyrexia	Very Common	Very Common	Very Common
De novo purine synthesis inhibitors associated acute inflammatory syndrome	Uncommon	Uncommon	Uncommon

Description of selected adverse reactions

Malignancies

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including mycophenolate mofetil, are at increased risk of developing lymphomas and other malignancies, particularly of the skin.

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, peritonitis, 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.

Blood and lymphatic disorders

Cytopenias, including leucopenia, anemia, thrombocytopenia and pancytopenia, are known risks associated with mycophenolate mofetil and may lead or contribute to the occurrence of infections and hemorrhages.

Gastrointestinal disorders

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

Hypersensitivity

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

Respiratory, thoracic and mediastinal disorders

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

Immune system disorders

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

General disorders and administration site conditions

General disorders and administration site conditions: (uncommon) de novo purine synthesis inhibitors-associated acute inflammatory syndrome.

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

Special populations

Elderly patients (≥ 65 years) may generally be at increased risk of adverse reactions due to immunosuppression. Elderly patients receiving Mofecon 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.

Post-marketing experience

Congenital Disorders

Congenital malformations have been reported post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy (see Use in Pregnancy).

Pregnancy, Puerperium and Perinatal Conditions

Cases of spontaneous abortions mainly in the first trimester in patients exposed to mycophenolate have been reported (see Use in Pregnancy).

OVERDOSE

Overdoses with mycophenolate mofetil could occur but generally with no adverse events. If adverse events were present, 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

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

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

Transplant patients

Standard dosage for prophylaxis of renal rejection

A dose of 1 g administered 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 studies 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 mycophenolate mofetil demonstrated an overall better safety profile compared to patients receiving 3 g per day of mycophenolate mofetil.

Standard dosage for prophylaxis of cardiac rejection

A dose of 1.5 g administered orally twice a day (daily dose of 3 g) is recommended for use in cardiac transplant patients.

Standard dosage for prophylaxis of hepatic rejection

A dose of 1.5 g administered orally twice daily (daily dose of 3 g) is recommended for use in hepatic transplant patients.

Oral administration

The initial dose of Mofecon should be given as soon as possible following renal, cardiac and hepatic transplantation.

Lupus nephritis patients

Induction and maintenance treatment of lupus nephritis

The recommended dose is 1 g administered twice a day (daily dose of 2 g). Mofecon should be used in combination with corticosteroids. Doses should be introduced gradually and adjusted according to clinical response. Therapeutic drug monitoring could help prevent sub-therapeutic exposure (C_{min} ≥3.0 mg/L or inter-dose AUC ≥35 h*mg/L).

Special Dosage Instructions

Paediatric use

See Dosage and Administration and Pharmacokinetics in Special Populations.

Elderly use

For transplant patients, no oral dosage adjustment is recommended.
For lupus nephritis patients, no recommendation is available.

Renal impairment

For renal transplant patients with severe chronic renal impairment (glomerular filtration rate <25 mL/min/1.73 m^2) outside of the immediate post-transplant period or after treatment of acute or refractory rejection, administration of doses greater than 1 g twice daily should be avoided.

For post-transplant patients with delayed renal graft function, no dose adjustment is recommended but patients should be carefully monitored.

For cardiac or hepatic transplant patients with severe renal impairment, no data are available.
For lupus nephritis patients with GFR <30 mL/min, therapeutic drug monitoring is advised.

Hepatic impairment

For renal transplant patients with severe hepatic parenchymal disease, no dose adjustments are recommended.
For cardiac transplant and lupus nephritis patients with severe hepatic parenchymal disease, no data are available.

Patients with neutropenia

For patients that develop neutropenia (absolute neutrophil count <1.3 x 10^3/µL), dosing with Mofecon should be interrupted or the dose should be reduced.

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

Presentation/ Packing: 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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