Mofecon−GR (Mycophenolic Acid Gastro-Resistant Tablets)

VIMOFxx-12 (SIN)

DESCRIPTION

Mofecon−GR 180 (Mycophenolic Acid Gastro-Resistant Tablets 180 mg):
Lime green colored, enteric coated, round biconvex tablet, debossed with “C 1” on one side and plain on other side.

Mofecon−GR 360 (Mycophenolic Acid Gastro-Resistant Tablets 360 mg):
Pink to light pink colored, enteric coated, ovaloid biconvex tablet, debossed with “C 2” on one side and plain on other side.

COMPOSITION

Mofecon−GR 180 (Mycophenolic Acid Gastro-Resistant Tablets 180 mg):
Each enteric coated tablet contains: Mycophenolic acid 180 mg
Excipients: Microcrystalline cellulose, croscarmellose sodium, povidone, colloidal silicon dioxide, talc, magnesium stearate, methacrylic acid and ethyl acrylate copolymer, titanium dioxide, triethyl citrate, sodium bicarbonate, iron oxide yellow, indigo carmine aluminium lake, sodium lauryl sulfate.

Mofecon−GR 360 (Mycophenolic Acid Gastro-Resistant Tablets 360 mg):
Each enteric coated tablet contains: Mycophenolic acid 360 mg
Excipients: Microcrystalline cellulose, croscarmellose sodium, povidone, colloidal silicon dioxide, talc, magnesium stearate, methacrylic acid and ethyl acrylate copolymer, titanium dioxide, triethyl citrate, sodium bicarbonate, iron oxide yellow, iron oxide red, sodium lauryl sulfate.

PHARMACODYNAMICS

Mycophenolic acid (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 utilize salvage pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells.

PHARMACOKINETICS

Absorption
Following oral administration, mycophenolate sodium is extensively absorbed. Consistent with its enteric coated design, the time to maximal concentration (T_{max}) of MPA was approximately 1.5-2 hours.

Distribution
The volume of distribution at steady state for MPA is 50 litres. Both mycophenolic acid and mycophenolic acid glucuronide are highly protein bound. The free MPA concentration may increase under conditions of decreased protein binding sites (uraemia, hepatic failure, hypoalbuminaemia, concomitant use of drugs with high protein binding). This may put patients at increased risk of MPA-related adverse effects.

Biotransformation
MPA is metabolised principally by glucuronyl transferase to form the phenolic glucuronide of MPA, mycophenolic acid glucuronide (MPAG). MPAG is the predominant metabolite of MPA and does not manifest biological activity.

Elimination
The half life of MPA is approximately 12 hours and the clearance is 8.6 l/h. Although negligible amounts of MPA are present in the urine (<1.0%), the majority of MPA is eliminated in the urine as MPAG. MPAG secreted in the bile is available for deconjugation by gut flora. The MPA resulting from this deconjugation may then be reabsorbed. Approximately 6-8 hours after MPA dosing a second peak of MPA concentration can be measured, consistent with reabsorption of the deconjugated MPA.

CLINICAL STUDIES

Renal Transplant
Two multi-center randomized, double-blind pivotal trials were used for MPA approval in adults. Both studies were reference therapy-controlled clinical studies using commercially marketed Cellcept (MMF) as the comparator. Both studies demonstrated comparable efficacy and safety to MMF. The first study included 423 adult de novo renal transplants (ERLB301) and demonstrated that MPA was equivalent to MMF in efficacy and had a comparable safety profile. The second study was conducted in 322 maintenance kidney transplant recipients (ERLB302) and demonstrated that renal transplant patients receiving MMF maintenance immunosuppressive therapy could be safely converted to MPA without compromising efficacy.

De novo adult renal transplant patients (study ERL B301)
The double-blind, double-dummy randomized de novo study (ERLB301) was conducted in 423 renal transplant patients (MPA=213, MMF=210), aged 18-75 years, and was designed prospectively to test therapeutic equivalence of MPA to MMF as measured by the incidence of efficacy failure (i.e., biopsy proven acute rejection (BPAR), graft loss, death or loss to follow up) within the first 6 months of treatment (primary endpoint) and by the incidence of death, graft loss or loss to follow-up at 12 months (co-primary endpoint).

Patients were administered either MPA 1.44 g/day or MMF 2 g/day within 48 hours posttransplant for 12 months in combination with cyclosporine, and corticosteroids. In the MPA and MMF groups, 39.4% and 42.9%, respectively, received antibody therapy as an induction treatment.

Based on the incidence of efficacy failure at 6 months (MPA 25.8% vs. MMF 26.2%; 95% CI: [-8.7, +8.0]) therapeutic equivalence was demonstrated. At 12 months, the incidence of BPAR, graft loss or death was 28.2% and 28.1%, and incidence of BPAR alone was 22.5% and 24.3% for MPA and MMF, respectively. Among those with BPAR, the incidence of severe acute rejection was 2.1% with MPA and 9.8% with MMF(p=ns).

Table 1 Analysis of primary efficacy endpoint and its components at 6 and 12 months (study ERLB301)

	MPA 1.44 g/day (n = 213)	**MMF 2 g/day (n = 210)**	**95% CI MPA-MMF**
6 months	n (%)	n (%)	
Biopsy-proven acute rejection episode,graft loss, death or lost to follow-up	55 (25.8)	55 (26.2)	(-8.7, 8.0)
Biopsy proven acute rejection episode	46 (21.6)	48 (22.9)	(-9.2, 6.7)
Graft loss or death	8 (3.8)	11 (5.2)	(-5.4, 2.5)
Graft loss	7 (3.3)	9 (4.3)	(-4.6, 2.6)
Death	1 (0.5)	2 (1.0)	
Lost to follow-up*	3 (1.4)	0	
12 months			
Biopsy-proven acute rejection episode, graft loss, death or lost to follow-up	60 (28.2)	59 (28.1)	(-8.5, 8.6)
Biopsy proven acute rejection episode	48 (22.5)	51 (24.3)	(-9.8, 6.3)
Graft loss or death	10 (4.7)	14 (6.7)	(-6.4, 2.4)
Graft loss	8 (3.8)	9 (4.3)	(-4.3, 3.2)
Death	2 (0.9)	5 (2.4)	
Lost to follow-up*	5 (2.3)	0	

* Lost to follow-up indicates patients that were lost to follow-up without prior biopsy-proven acute rejection, graft loss or death. The criteria for therapeutic equivalence were met: the 95% CI for the difference in incidence of the primary variable (BPAR, graft loss, death or lost to follow-up at Month 6) was entirely contained in the interval (-12%, 12%).

The overall safety and hematologic profiles were similar between the two treatment groups. Drug-suspected AEs were 53.1% and 60.5% in the MPA vs. MMF groups, respectively. No difference in overall incidence of infection was observed. The overall incidence of serious infections was 22.1% in the MPA group and 27.1% in the MMF group. The incidence of serious pneumonia was 0.5% and 4.3%, respectively, in MPA and MMF groups. No difference in the overall incidence of GI AEs was observed (79.8% vs 77.1%, p=ns, MPA vs. MMF, respectively).

Maintenance adult renal transplant patients (study ERL B302)
The maintenance study was conducted in 322 renal transplant patients (MPA=159, MMF=163), aged 18 to 75 years, who were at least 6 months post-transplant receiving 2 g/day MMF in combination with cyclosporine, with or without corticosteroids for at least four weeks prior to entry in the study. Patients were randomized 1:1 to MPA 1.44 g/day or MMF 2 g/day for 12 months. The efficacy endpoint was the incidence of efficacy failure (i.e., BPAR, graft loss, or death) at 6 and 12 months.

At 12 months, similar rates of efficacy failure (MPA 2.5%; MMF 6.1%; p=ns), biopsy-proven acute rejection (MPA 1.3%; MMF 3.1%; p=ns) and biopsy-proven chronic rejection (MPA 3.8%; MMF 4.9%; p=ns) were observed in both groups.

Table 2 Secondary efficacy endpoints (study ERL B302)

	MPA 1.44 g/day (n = 159)	**MMF 2 g/day (n =163)**	**(95% CI) MPA-MMF**
6 months	n (%)	n (%)	
Biopsy-proven acute rejection episode, graft loss, death or lost to follow-up	6 (3.8)	10 (6.1)	(-7.1, 2.4)
Biopsy-proven acute rejection episode, biopsy-proven chronic rejection, graft loss, death or lost to follow-up	9 (5.7)	11 (6.7)	(-6.4, 4.2)
Acute rejection	2 (1.3)	3 (1.8)	(-10.9, 5.5)
Biopsy-proven acute rejection	2 (1.3)	2 (1.2)	
Biopsy-proven chronic rejection	4 (2.5)	4 (2.5)	
Lost to follow-up*	4 (2.5)	6 (3.7)	
Graft loss or death	0	2 (1.2)	
12 months	n (%) n = 110	n (%) n = 113	
Biopsy-proven acute rejection episode, graft loss, death or lost to follow-up	10 (9.1)	14 (12.4)	
Biopsy-proven acute rejection episode, biopsy-proven chronic rejection, graft loss, death or lost to follow-up	13 (11.8)	15 (13.3)	
Lost to follow-up*	7 (6.4)	8 (7.1)	
Graft loss or death	1 (0.9)	4 (3.5)	

* Lost to follow-up indicates patients that were lost to follow-up without prior BPRA, graft loss or death.

The maintenance study also demonstrated an overall similar safety profile, with the exception of the incidence of serious infections (8.8 vs 16%, p<0.05, MPRA vs. MMF). The incidence of overall infections was 59% in each group. Less pneumonia was observed in the MPA group (2.5%) than the MMF group (6.1%), but it was not statistically significant. A similar incidence of overall GI AEs within 12 months of randomization was observed (60.4 vs 61.3%, MPA vs MMF); the incidence of “any GI AE” was 26.4% vs 20.9% and 29.6% vs 24.5%, respectively, at the 3-month and 12-month visit windows.

INDICATIONS

Indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adult patients receiving allogeneic renal transplants.

CONTRAINDICATIONS

- Mofecon is contraindicated in patients with hypersensitivity to mycophenolate sodium, mycophenolic acid or mycophenolate mofetil or to any of the excipients.
- Mofecon is contraindicated in pregnant women.

WARNING AND PRECAUTIONS

Patients receiving immunosuppressive regimens involving combinations of drugs, including Mofecon, 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.

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

Patients treated with immunosuppressants, including Mofecon, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis. Among the opportunistic infections are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). 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 mycophenolic acid in combination with other immunosuppressants.

In some of these cases switching mycophenolic acid to an alternative immunosuppressant resulted 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.

There have been published reports of bronchiectasis in adults and children who received mycophenolic acid in combination with other immunosuppressants. In some of these cases switching mycophenolic acid 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.

Reactivation of hepatitis B (HBV) or hepatitis C (HCV) have been reported in patients treated with immunosuppressants, including the mycophenolic acid (MPA) derivatives and mycophenolate mofetil (MMF). Monitoring infected patients for clinical and laboratory signs of active HBV or HCV infection is recommended.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives (which include mycophenolate mofetil and mycophenolate sodium) in combination with other immunosuppressants. PRCA may resolve with dose reduction or cessation of therapy. Changes to mycophenolic acid 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 monitored for blood disorders (e.g. neutropenia or anemia), which may be related to MPA 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 blood disorders occur (e.g. neutropenia with absolute neutrophil count <1.5 x 10^3/µl or anemia) it may be appropriate to interrupt or discontinue Mofecon.

Patients should be advised that during treatment with MPA, vaccinations may be less effective and the use of live attenuated vaccines should be avoided.

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

It is recommended that mycophenolic acid not be administered concomitantly with azathioprine because concomitant administration of these drugs has not been evaluated.
Mycophenolic acid (as sodium salt) and mycophenolate mofetil should not be indiscriminately interchanged or substituted because of their different pharmacokinetic profiles.

Mycophenolic acid has been administered in combination with corticosteroids and ciclosporin.

There is limited experience with its concomitant use with induction therapies such as anti-T-lymphocyte globulin or basiliximab. The efficacy and safety of the use of mycophenolic acid with other immunosuppressive agents (for example, tacrolimus) have not been studied.

The concomitant administration of Mofecon and drugs which interfere with enterohepatic circulation, for example cholestyramine or activated charcoal, may result in sub-therapeutic systemic MPA exposure and reduced efficacy.

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.

Mycophenolic acid therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning mycophenolic acid therapy, during therapy and for six weeks following therapy discontinuation.

Teratogenic effects
- Mycophenolate is a powerful human teratogen, with an increased risk of spontaneous abortion and congenital malformations in case of exposure during pregnancy.
- Women with childbearing potential should use two reliable forms of contraception simultaneously before starting and during therapy, and for six weeks after stopping treatment; unless abstinence is the chosen method of contraception.
- Sexually active (including vasectomized) men are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Female partners of male patients treated with Mofecon are also recommended to use highly effective contraception for the same period.
- Before starting Mofecon treatment, women of child bearing potential should undergo pregnancy testing. 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. Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported).

Contraception
Due to 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 mycophenolic acid 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.

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 at least 90 days following discontinuation of mycophenolate.
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 mechanism of action and pharmacodynamic profile and the reported adverse reactions indicate that an effect is unlikely

PREGNANCY AND LACTATION
Pregnancy
Mofecon 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 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 Mofecon treatment, women of childbearing potential should have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL in order to exclude unintended exposure of the embryo to mycophenolate. It is recommended that the second test should be performed 8 – 10 days after the first test. For transplants from deceased donors, if it is not possible to perform two tests 8-10 days apart before treatment starts, a pregnancy test must be performed immediately before starting treatment and a further test performed 8-10 days later. Pregnancy tests should be repeated as clinically required. 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.

Breast-feeding
It is not known whether this substance is excreted in human breast milk. Because of the potential for serious adverse reactions to MPA in breast-fed infants, a decision should be made whether to abstain from breast-feeding during treatment and for 6 weeks after stopping the therapy or to abstain from using the product, taking into account the importance of the drug to the mother.

DRUG INTERACTIONS
The following interactions have been reported between MPA and other medicinal products:

Aciclovir and ganciclovir
The potential for myelosuppression in patients receiving both mycophenolic acid and aciclovir or ganciclovir has not been studied. Increased levels of mycophenolic acid glucuronide (MPAG) and aciclovir/ganciclovir may be expected when aciclovir/ganciclovir and mycophenolic acid are administered concomitantly, possibly as a result of competition for the tubular secretion pathway.

The changes in MPAG pharmacokinetics are unlikely to be of clinical significance in patients with adequate renal function. In the presence of renal impairment, the potential exists for increases in plasma MPAG and aciclovir/ganciclovir concentrations; dose recommendations for aciclovir/ganciclovir should be followed and patients carefully observed.

Gastroprotective agents
Magnesium and aluminium containing antacids:
Concomitant use of magnesium-aluminium containing antacids with Mofecon is not recommended due to the potential for decreased mycophenolic acid exposure and reduced efficacy.

Cholestyramine and drugs that bind bile acids:
Caution should be used when co-administering drugs or therapies that may bind bile acids, for example bile acid sequestrates or oral activated charcoal, because of the potential to decrease MPA exposure and thus reduce the efficacy of Mofecon.

Ciclosporin:
When co-administered with mycophenolate mofetil, ciclosporin is known to decrease the exposure of MPA. When co-administered with Mofecon, ciclosporin may decrease the concentration of MPA. In case of interruption or discontinuation of ciclosporin, Mofecon dosage should be re-evaluated depending on the immunosuppressive regimen.

Tacrolimus
When co-administered with tacrolimus, tacrolimus may increase concentration of Mycophenolic Acid. Clinicians should note this increase both in MPA AUC and variability, and adjustments to Mofecon dosing should be dictated by the clinical situation. Close clinical monitoring should be performed when a switch from one calcineurin inhibitor to another is planned.

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

Oral contraceptives
Concomitant use of Mofecon with oral contraceptives has not been studied. Oral contraceptives undergo oxidative metabolism while Mofecon is metabolized by glucuronidation. A clinically significant effect of oral contraceptives on Mofecon pharmacokinetics is not anticipated. However, as the long term effect of Mofecon dosing on the pharmacokinetics of oral contraceptives is not known, it is possible that the efficacy of oral contraceptives may be adversely affected.

MAIN SIDE/ ADVERSE EFFECTS
Table 3 below contains adverse drug reactions possibly or probably related to mycophenolic acid reported in the controlled clinical trials in renal transplant patients, in which mycophenolic acid was administered together with ciclosporin microemulsion and corticosteroids at a dose of 1,440 mg/day for 12 months. It is compiled according to MedDRA system organ class.

Adverse reactions are listed according to 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)

Table 3

Infections and infestations	
Very common:	Viral, bacterial and fungal infections
Common:	Upper respiratory tract infections, pneumonia
Uncommon:	Wound infection, sepsis*, osteomyelitis*
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon:	Skin papilloma*, basal cell carcinoma*, Kaposi´s sarcoma*, lymphoproliferative disorder, squamous cell carcinoma*
Blood and lymphatic system disorders	
Very common:	Leukopenia
Common:	Anaemia, thrombocytopenia
Uncommon:	Lymphopenia*, neutropenia*, lymphadenopathy*
Metabolism and nutrition disorders	
Very common:	Hypocalcemia, hypokalemia, hyperuricemia
Common:	Hyperkalemia, hypomagnesemia
Uncommon:	Anorexia, hyperlipidaemia, diabetes mellitus*, hypercholesterolaemia*, hypophosphataemia
Psychiatric disorders	
Very common:	Anxiety
Uncommon:	Abnormal dreams*, delusional perception*, insomnia*
Nervous system disorders	
Very common:	Dizziness, headache
Uncommon:	Tremor
Eye disorders	
Uncommon:	Conjunctivitis*, vision blurred*
Cardiac disorders	
Uncommon:	Tachycardia, ventricular extrasystoles
Vascular disorders	
Very common:	Hypertension
Common:	Hypotension
Uncommon:	Lymphocele*
Respiratory, thoracic and mediastinal disorders	
Common:	Cough, dyspnoea
Uncommon:	Interstitial lung disease, pulmonary congestion*, wheezing*, pulmonary oedema*
Gastrointestinal disorders	
Very Common:	Diarrhoea
Common:	Abdominal distension, abdominal pain, constipation, dyspepsia, flatulence, gastritis, nausea, vomiting
Uncommon:	Abdominal tenderness, gastrointestinal haemorrhage, eructation, halitosis*, ileus*, lip ulceration*, oesophagitis*, subileus*, tongue discolouration*, dry mouth*, gastro-oesophageal reflux disease*, gingival hyperplasia*, pancreatitis, parotid duct obstruction*, peptic ulcer*, peritonitis*
Hepato-biliary disorders	
Common:	Liver function tests abnormal
Reproductive system and breast disorders	
Uncommon:	Impotence*
General disorders and administration site conditions	
Common:	Asthenia, Fatigue, oedema peripheral, pyrexia
Uncommon:	Influenza like illness, oedema lower limb*, pain, rigors*, thirst*, weakness*
Injury, poisoning and procedural complications	
Uncommon:	Contusion*
Skin and subcutaneous tissue disorders	
Common:	Acne, pruritus
Uncommon:	Alopecia
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia
Common:	Myalgia
Uncommon:	Arthritis*, back pain*, muscle cramps
Renal and urinary disorders	
Common:	Blood creatinine increased
Uncommon:	Haematuria*, renal tubular necrosis*, urethral stricture

* event reported in a single patient (out of 372) only.

Note: renal transplant patients were treated with 1,440 mg mycophenolic acid daily up to one year. A similar profile was seen in the *de novo* and maintenance transplant population although the incidence tended to be lower in the maintenance patients.

Listing of adverse drug reactions from post-marketing experience
The following adverse drug reactions have been derived from post-marketing experience with MPA via spontaneous case reports and literature cases. As these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to MedDRA system organ class. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Skin and subcutaneous tissue disorders: Rash has been identified as an adverse drug reaction from post-approval clinical trials, post marketing surveillance and spontaneous reports.

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

The following adverse reactions are attributed to MPA derivatives as a class effect
Infections and infestations: Serious, sometimes life-threatening infections, including meningitis, infectious endocarditis, tuberculosis, and atypical mycobacterial infection. Polyomavirus associated nephropathy (PVAN), especially due to BK virus infection. Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported (see section WARNINGS AND PRECAUTIONS).

Blood and lymphatic system disorders: Agranulocytosis, neutropenia, pancytopenia. Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives in combination with other immunosuppressants (see section WARNINGS AND PRECAUTIONS).

Immune system disorders: Hypogammaglobulinaemia has been reported in patients receiving MPA in combination with other immunosuppressants.

Respiratory, thoracic and mediastinal disorders: There have been isolated reports of interstitial lung disease in patients treated with MPA in combination with other immunosuppressants. There have also been reports of bronchiectasis in combination with other immunosuppressants.

Gastrointestinal disorders: Colitis, oesophagitis (including CMV-colitis and -oesophagitis), CMV gastritis, pancreatitis, intestinal perforation, gastrointestinal haemorrhage, gastric ulcers, duodenal ulcers, ileus.

OVERDOSE
There have been reports of intentional or accidental overdoses with mycophenolic acid, whereas not all patients experienced related adverse events.
In those overdose cases in which adverse events were reported, the events fall within the known safety profile of the class, mainly blood dyscrasias and sepsis.

Although dialysis may be used to remove the inactive metabolite MPAG, it would not be expected to remove clinically significant amounts of the active moiety MPA. This is in large part due to the very high plasma protein binding of MPA, 97%. By interfering with enterohepatic circulation of MPA, bile acid sequestrants, such as cholestyramine, may reduce the systemic MPA exposure.

DOSAGE AND ADMINISTRATION
Oral. Mofecon can be taken with or without food. Patients may select either option but must adhere to their selected option.

In order to retain the integrity of the enteric coating, Mofecon tablets should not be crushed. If for any reason the Mofecon tablet is crushed, avoid inhalation of the powder or direct contact of the powder with skin or mucous membrane. If such contact occurs, wash throughly with soap and water; rinse eyes with plain water. This is due to the teratogenic effects of mycophenolate.

Dosage
The recommended dose is 720 mg (four 180 mg or two 360 mg Mofecon gastro-resistant tablets) twice daily (1440 mg daily dose). Mofecon gastro-resistant tablets and mycophenolate mofetil tablets and capsules should not be used interchangeably without physician supervision because the rate of absorption following the administration of these two products is not equivalent.

General target population
Treatment with Mofecon should be initiated and maintained by appropriately qualified transplant specialist.

Mofecon should be initiated in de-novo patients within 48 hours following transplantation.

Mofecon can be taken with or without food.

Special population
Renal impairment
No dose adjustments are needed in patients experiencing delayed post-operative renal graft function. Patients with severe chronic renal impairment (glomerular filtration rate <25 ml . min^{-1} . 1.73 m^{-2}) should be carefully monitored.

Hepatic impairment
No dose adjustments are needed for renal transplant patients with severe hepatic impairment.

Paediatric patients (below 18 years)
Safety and efficacy in paediatric patients have not been established. Limited pharmacokinetic data are available for paediatric renal transplant patients.

Geriatic patients (65 years of age or above)
Geriatric patients may generally be at increased risk of adverse drug reactions due to immunosuppression. Geriatric patients receiving MPA as part of a combination immunosuppressive regimen, did not show an increased risk of adverse reactions, compared to younger individuals in the MPA clinical trials. No dose adjustment is required in this patient population.

Treatment during rejection episodes
Renal transplant rejection does not affect mycophenolic acid pharmacokinetics; dosage reduction or interruption of Mofecon is not required.

Method of administration
Mofecon tablets should not be crushed in order to maintain the integrity of the enteric coating.

Note: The information given here is limited. For further information, consult your doctor or pharmacist.

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

Presentation/ Packing:
Aluminium-aluminium blister pack of 6 x 10's.

Product Registration Holder (Malaysia) / Product Owner /
Manufactured for: **HOVID Bhd.**
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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