ICOFATE™-M Tablets

(Mycophenolate Mofetil)

WARNING: EMBRYOFETAL TOXICITY, MALIGNANCIES AND SERIOUS INFECTIONS

Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Avoid if safer treatment options are available. Females of reproductive potential must be counseled regarding pregnancy prevention and planning .Increased risk of development of lymphoma and other malignancies, particularly of the skin increased susceptibility to infections, including opportunistic infections and severe infections with fatal outcome

QUALITATIVE & QUANTITATIVE COMPOSITION

ICOFATE™-M Tablets 500mg
Each film coated tablet contains:
Mycophenolate Mofetil USP.....500mg

PHARMACEUTICAL FORM

Tablets

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS:
ICOFATE™-M is an antimetabolite immunosuppressant indicated for the prophylaxis of organ rejection in recipients of allogeneic kidney, heart or liver transplants, and should be used in combination with other immune suppressants.
ICOFATE™-M tablets are indicated in combination with cyclosporine and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

POSOLOGY AND METHOD OF ADMINISTRATION:
Treatment with ICOFATE™-M tablets 500mg should be initiated and maintained by appropriately qualified transplant specialists.

POSOLOGY:
Use in renal transplant
Adults
Oral ICOFATE™-M tablets 500mg should be initiated within 72 hours following transplantation. The recommended dose in renal transplant patients is 1g administered twice daily (2g daily dose).
Paediatric population aged 2 to 18 years
The recommended dose of mycophenolate mofetil is 600mg/m² administered orally twice daily (up to a maximum of 2g daily). Mycophenolate mofetil 500mg Tablets should only be prescribed to patients with a body surface area greater than 1.5 m², at a dose of 1g twice daily (2g daily dose). As some adverse reactions occur with greater frequency in this age group compared with adults, temporary dose reduction or interruption may be required; these will need to take into account relevant clinical factors including severity of reaction.
Paediatric population < 2 years
There are limited safety and efficacy data in children below the age of 2 years.
These are insufficient to make dosage recommendations and therefore use in this age group is not recommended.

Use in cardiac transplant
Adults
Oral ICOFATE™-M tablets 500mg should be initiated within 5 days following transplantation. The recommended dose in cardiac transplant patients is 1.5g administered twice daily (3g daily dose).
Paediatric population
No data are available for paediatric cardiac transplant patients.

Use in hepatic transplant
Adults
IV mycophenolate mofetil should be administered for the first 4 days following hepatic transplant, with oral ICOFATE™-M tablets 500mg initiated as soon after this as it can be tolerated. The recommended oral dose in hepatic transplant patients is 1.5g administered twice daily (3g daily dose).
Paediatric population
No data are available for paediatric hepatic transplant patients.

Renal Impairment: In renal transplant patients with severe chronic renal impairment (glomerular filtration rate < 25 mL/min-1/1.73 m²), outside the immediate post-transplant period, doses greater than 1g administered twice a day should be avoided. These patients should also be carefully observed.
No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.
Hepatic Impairment: No dose adjustments are needed for renal transplant patients with severe hepatic parenchymal disease. No data are available for cardiac transplant patients with severe hepatic parenchymal disease.
Elderly patients:The recommended dose of 1g administered twice a day for renal transplant patients and 1.5g twice a day for cardiac or hepatic transplant patients is appropriate for the elderly.
Treatment during rejection episodes: Mycophenolic acid (MPA) is the active metabolite of mycophenolate mofetil. Renal transplant rejection does not lead to changes in MPA pharmacokinetics; dosage reduction or interruption of ICOFATE™-M tablets 500mg is not required. There is no basis for ICOFATE™-M tablets 500mg dose adjustment following cardiac transplant rejection. No pharmacokinetic data are available during hepatic transplant rejection.
Method of Administration: Oral administration.
Precautions to be taken before handling or administering the medicinal product: Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits, Mycophenolate mofetil 500mg tablets should not be crushed.

CONTRAINDICATIONS:
Mycophenolate mofetil should not be given to patients with hypersensitivity to mycophenolate mofetil, mycophenolic acid or to any of the excipients listed. Hypersensitivity reactions to Mycophenolate mofetil have been observed.
Mycophenolate mofetil should not be given to women of childbearing potential who are not using highly effective contraception.
Mycophenolate mofetil treatment should not be initiated in women of child bearing potential without providing a pregnancy test result to rule out unintended use in pregnancy.
Mycophenolate mofetil should not be used during pregnancy unless there is no suitable alternative treatment to prevent transplant rejection.
Mycophenolate mofetil should not be given to women who are breastfeeding.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
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. 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 minimize 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 immune suppressants, including mycophenolate mofetil, 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 and JC virus associated progressive multifocal leukoencephalopathy, PML). Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. There have been reports of hypogammaglobulinaemia in association with recurrent infections in patients receiving mycophenolate mofetil in combination with other immunosuppressants. In some of these cases switching mycophenolate mofetil to an alternative immunosuppressant resulted in serum IgG levels returning to normal. Patients on mycophenolate mofetil who develop recurrent infections should have their serum immunoglobulins measured. In cases of sustained, clinically relevant hypogammaglobulinaemia, appropriate clinical action should be considered taking into account the potent cytostatic effects that mycophenolic acid has on T- and B-lymphocytes.
There have been published reports of bronchiectasis in adults and children who received mycophenolate mofetil in combination with other immune suppressants. 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 dyspnea, are investigated.
Blood and immune system: Patients receiving mycophenolate mofetil should be monitored for neutropenia, which may be related to mycophenolate mofetil itself, concomitant medications, viral infections, or some combination of these causes. Patients taking mycophenolate mofetil 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 <1.3x10³/µl) it may be

appropriate to interrupt or discontinue Mycophenolate mofetil.
Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil in combination with other immunosuppressant's. The mechanism for mycophenolate mofetil induced PRCA is unknown. PRCA may resolve with dose reduction or cessation of mycophenolate mofetil therapy. Changes to mycophenolate mofetil therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimise the risk of graft rejection.
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 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. cyclosporine to others devoid of this effect e.g. sirolimus, belatacept, or vice versa, as this might result in changes of MPA exposure. Drugs of other classes which interfere with MPA's enterohepatic cycle e.g. cholestyramine should be used with caution due to their potential to reduce the plasma levels and efficacy of Mycophenolate mofetil.
It is recommended that Mycophenolate mofetil should not be administered concomitantly with azathioprine because such concomitant administration has not been studied. The risk/benefit ratio of mycophenolate mofetil in combination with tacrolimus or sirolimus has not been established.
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 hemorrhage and pulmonary edema, 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%) have been reported following exposure during pregnancy. Therefore Mycophenolate mofetil 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 (e.g. contraceptive methods, pregnancy testing) prior to, during, and after therapy with Mycophenolate mofetil. 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 Mycophenolate mofetil 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 90 days following discontinuation of mycophenolate.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:
Acyclovir: Higher acyclovir plasma concentrations were observed when mycophenolate mofetil was administered with acyclovir in comparison to the administration of acyclovir alone. The changes in MPAG (the phenolic glucuronide of MPA) pharmacokinetics (MPAG increased by 8 %) were minimal and are not considered clinically significant. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for mycophenolate mofetil and acyclovir, 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 aluminum hydroxides, and PPIs, including lansoprazole and pantoprazole, were administered with mycophenolate mofetil. The data support extrapolation of this finding to all antacids because the reduction in exposure when mycophenolate mofetil was co- administered with magnesium and aluminum hydroxides is considerably less than when mycophenolate mofetil was co-administered with PPIs.
Cholestyramine: Following single dose administration of 1.5g of mycophenolate mofetil to normal healthy subjects pre-treated with 4g TID of cholestyramine for 4 days, there was a 40 % reduction in the AUC of MPA. Caution should be used during concomitant administration because of the potential to reduce efficacy of mycophenolate mofetil.
Medicinal products that interfere with enterohepatic circulation
Caution should be used with medicinal products that interfere with enterohepatic circulation because of their potential to reduce the efficacy of mycophenolate mofetil.
Cyclosporine A: Cyclosporine A (CsA) pharmacokinetics are unaffected by mycophenolate mofetil. In contrast, if concomitant cyclosporine treatment is stopped, an increase in MPA AUC of around 30% should be expected. CsA interferes with MPA enterohepatic recycling, resulting in reduced MPA exposures by 30-50% in renal transplant patients treated with mycophenolate mofetil and CsA compared with patients receiving sirolimus or belatacept and similar doses of mycophenolate mofetil. Conversely, changes of MPA exposure should be expected when switching patients from CsA to one of the immunosuppressant's which does not interfere with MPA´s enterohepatic cycle.
Telmisartan: Concomitant administration of telmisartan and mycophenolate mofetil resulted in an approximately 30% decrease of MPA concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression, which in turn results in an enhanced UGT1A9 expression and activity. When comparing rates of transplant rejection, rates of graft loss or adverse event profiles between mycophenolate mofetil patients with and without concomitant telmisartan medication, no clinical consequences of the pharmacokinetic drug-drug interaction were seen.
Ganciclovir: In patients with renal impairment in whom mycophenolate mofetil and ganciclovir or its prodrugs, e.g. valganciclovir, are co-administered, the dose recommendations for ganciclovir should be observed and patients should be monitored carefully.
Oral contraceptives: The pharmacokinetics and pharmacodynamics of oral contraceptives were unaffected by co administration of mycophenolate mofetil
Rifampicin: In patients not also taking cyclosporine, concomitant administration of mycophenolate mofetil and rifampicin resulted in a decrease in MPA exposure (AUC0-12h) of 18% to 70%. It is recommended to monitor MPA exposure levels and to adjust mycophenolate mofetil doses accordingly to maintain clinical efficacy when rifampicin is administered concomitantly.
Sevelamer: Decrease in MPA C_{max} and AUC (0-12h) by 30% and 25%, respectively, were observed when mycophenolate mofetil was concomitantly administered with sevelamer without any clinical consequences (i.e. graft rejection). It is recommended, however, to administer mycophenolate mofetil at least one hour before or three hours after sevelamer intake to minimise the impact on the absorption of MPA. There are no data on mycophenolate mofetil with phosphate binders other than sevelamer.
Trimethoprim/sulfamethoxazole: No effect on the bioavailability of MPA was observed.
Norfloxacin and metronidazole: In healthy volunteers, no significant interaction was observed when mycophenolate mofetil was concomitantly administered with norfloxacin or metronidazole separately. However, norfloxacin and metronidazole combined reduced the MPA exposure by approximately 30 % following a single dose of mycophenolate mofetil.
Ciprofloxacin and amoxicillin plus clavulanic acid: Reductions in pre-dose (trough) MPA concentrations of about 50% have been reported in renal transplant recipients in the days immediately following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. This effect tended to diminish with continued antibiotic use and to cease within a few days of antibiotic discontinuation. The change in pre dose level may not accurately represent changes in overall MPA exposure. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.
Tacrolimus: In hepatic transplant patients initiated on mycophenolate mofetil and tacrolimus, the AUC and C_{max} of MPA, the active metabolite of mycophenolate mofetil, were not significantly affected by coadministration with tacrolimus. In contrast, there was an increase of approximately 20 % in tacrolimus AUC when multiple doses of mycophenolate mofetil (1.5 g BID) were administered to hepatic transplant patients taking tacrolimus. However, in renal transplant patients, tacrolimus concentration did not appear to be altered by mycophenolate mofetil
Other interactions: Co-administration of probenecid with mycophenolate mofetil in monkeys raises plasma AUC of MPAG by 3-fold. Thus, other substances known to undergo renal tubular secretion may compete with MPAG, and thereby raise plasma concentrations of MPAG or the other substance undergoing tubular secretion.
Live vaccines: Live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished
Paediatric population: Interaction studies have only been performed in adults.

FERTILITY, PREGNANCY AND LACTATION:
Women of childbearing potential: Pregnancy whilst taking mycophenolate must be avoided. Therefore women of childbearing potential must use at least one form of reliable contraception before starting Mycophenolate mofetil 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.
Pregnancy: Mycophenolate mofetil 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 Mycophenolate mofetil treatment, women of child bearing potential should have two negative serum or urine pregnancy tests with a sensitivity of at least 25mIU/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.
Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported). Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.
Mycophenolate mofetil is a powerful human teratogen, with an increased risk of spontaneous abortions and congenital malformations in case of exposure during pregnancy. Spontaneous abortions have been reported in 45 to 49% of pregnant women exposed to mycophenolate mofetil, compared to a reported rate of between 12 and 33% in solid organ transplant patients treated with immunosuppressants other than mycophenolate mofetil.
Based on literature reports, malformations occurred in 23 to 27% of live births in women exposed to mycophenolate mofetil during pregnancy (compared to 2 to 3 % of live births in the overall population and approximately 4 to 5% of live births in solid organ transplant recipients treated with immunosuppressant's other than mycophenolate mofetil).
- Abnormalities of the ear (e.g. abnormally formed or absent external ear), external auditory canal atresia (middle ear)
- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits
- Abnormalities of the eye (e.g. coloboma);

- Congenital heart disease such as atrial and ventricular septal defects;
- Malformations of the fingers (e.g. polydactyly, syndactyly);
- Tracheo-esophageal malformations (e.g. esophageal atresia);
- Nervous system malformations such as spina bifida;
- Renal abnormalities.

In addition there have been isolated reports of the following malformations:
Microphthalmia, congenital choroid plexus cyst, septum pellucidum agenesis, olfactory nerve agenesis.
Studies in animals have shown reproductive toxicity
Breast-feeding
It is not known whether this substance is excreted in human milk. Because of the potential for serious adverse reactions to mycophenolate mofetil in breast-fed infants, Mycophenolate mofetil are contraindicated in nursing mothers.
Men: Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to mycophenolate mofetil. MPA is a powerful teratogen. It is not known if MPA is present in semen. Mycophenolate has been shown to be genotoxic in animal studies at concentrations exceeding the human therapeutic exposures by small margins, such that the risk of genotoxic effects on sperm cells cannot completely be excluded.
Therefore, the following precautionary measures are recommended: sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 90 days after cessation of mycophenolate mofetil. Male patients of reproductive potential should be made aware of and discuss the potential risks of fathering a child with a qualified health-care professional.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
No studies on the effects on the ability to drive and use machines have been performed. The pharmacodynamic profile and the reported adverse reactions indicate that an effect is unlikely.

UNDESIRABLE EFFECTS:
The following undesirable effects cover adverse reactions from clinical trials:
The principal adverse reactions associated with the administration of mycophenolate mofetil in combination with cyclosporine and corticosteroids include diarrhoea, leucopenia, sepsis and vomiting, and there is evidence of a higher frequency of certain types of infections

System Organ Class		Adverse drug reaction
Infections and infestations	Very common	Sepsis, gastrointestinal candidiasis, urinary tract infection, herpes simplex, herpes zoster
	Common	Pneumonia, influenza, respiratory tract infection, respiratory moniliasis, gastrointestinal infection, candidiasis, gastroenteritis, infection, bronchitis, pharyngitis, sinusitis, fungal skin infection, skin candida, vaginal candidiasis, rhinitis
Neoplasms benign,	Very common	-
malignant and unspecified (including cysts and polyps)	Common	Skin cancer, benign neoplasm of skin
Blood and lymphatic system disorders	Very common	Leucopenia, thrombocytopenia, anaemia
	Common	Pancytopenia, leucocytosis
Metabolism and nutrition disorders	Very common	-
	Common	Acidosis, hyperkalaemia, hypokalaemia, hyperglycaemia, hypomagnesaemia, hypocalcaemia, hypercholesterolaemia, hyperlipidaemia, hypophosphataemia, hyperuricaemia, gout, anorexia
Psychiatric disorders	Very common	-
	Common	Agitation, confusional state, depression, anxiety, thinking abnormal, insomnia
Nervous system disorders	Very common	-
	Common	Convulsion, hypertonia, tremor, somnolence, myasthenic syndrome, dizziness, headache, paraesthesia, dysgeusia
Cardiac disorders	Very common	-
	Common	Tachycardia
Vascular disorders	Very common	-
	Common	Hypotension, hypertension, vasodilatation
Respiratory, thoracic and mediastinal disorders	Very common	-
	Common	Pleural effusion, dyspnoea, cough
Gastrointestinal disorders	Very common	Vomiting, abdominal pain, diarrhoea, nausea
	Common	Gastrointestinal haemorrhage, peritonitis, ileus, colitis, gastric ulcer, duodenal ulcer, gastritis, esophagitis, stomatitis, constipation, dyspepsia, flatulence, eructation
Hepatobiliary disorders	Very common	-
	Common	Hepatitis, jaundice, hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Very common	-
	Common	Skin hypertrophy, rash, acne, alopecia,
Musculoskeletal and connective tissue disorders	Very common	-
	Common	Arthralgia
Renal and urinary disorders	Very common	-
	Common	Renal impairment
General disorders and administration site conditions	Very common	-
	Common	Oedema, pyrexia, chills, pain, malaise, asthenia,
Investigations	Very common	-
	Common	Hepatic enzyme increased, blood creatinine increased, blood lactate dehydrogenase increased, blood urea increased, blood alkaline phosphatase increased, weight decreased

The types of adverse reactions reported during post-marketing with mycophenolate mofetil are similar to those seen in the controlled renal, cardiac and hepatic transplant studies. Additional adverse reactions reported during post-marketing are described below with the frequencies reported within brackets if known.
Gastrointestinal: Gingival hyperplasia, colitis including cytomegalovirus colitis, pancreatitis and intestinal villous atrophy.
Infections: Serious life-threatening infections including meningitis, endocarditis, tuberculosis and atypical mycobacterial infection. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leucoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including mycophenolate mofetil. Agranulocytosis and neutropenia have been reported; therefore, regular monitoring of patients taking mycophenolate mofetil is advised. There have been reports of aplastic anaemia and bone marrow depression in patients treated with mycophenolate mofetil, some of which have been fatal.
Blood and lymphatic system disorder: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil. Isolated cases of abnormal neutrophil morphology, including the acquired Pelger-Huet anomaly, have been observed in patients treated with mycophenolate mofetil. These changes are not associated
Congenital malformations, including reports of multiple malformations, have been observed post-marketing in children of patients exposed to Mycophenolate mofetil in combination with other immunosuppressant's during pregnancy. The following malformations were most frequently reported:
with impaired neutrophil function. These changes may suggest a 'left shift' in the maturity of neutrophils in haematological investigations, which may be mistakenly interpreted as a sign of infection in immunosuppressed patients such as those that receive mycophenolate mofetil.
Hypersensitivity: Hypersensitivity reactions, including angioneurotic oedema and anaphylactic reaction have been reported.

Pregnancy, puerperium and perinatal conditions: Cases of spontaneous abortions have been reported in patients exposed to mycophenolate mofetil, mainly in the first trimester.
Congenital disorders: Congenital malformations have been observed post-marketing in children of patients exposed to mycophenolate mofetil in combination with other immunosuppressants.
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 immunosuppressant's, some of which have been fatal. There have also been reports of bronchiectasis in children and adults (frequency not known).
Immune system disorders: Hypogammaglobulinaemia has been reported in patients receiving mycophenolate mofetil in combination with other immunosuppressants (frequency not known).

OVERDOSE:
Reports of overdoses with mycophenolate mofetil have been received from clinical trials and during post-marketing experience. In many of these cases, no adverse events were reported. In those overdose cases in which adverse events were reported, the events fall within the known safety profile of the medicinal product. It is expected that an overdose of mycophenolate mofetil could possibly result in oversuppression of the immune system and increase susceptibility to infections and bone marrow suppression. If neutropenia develops, dosing with mycophenolate mofetil 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 colestyramine, can remove MPA by decreasing the enterohepatic recirculation of the drug.

PHARMACOLOGICAL PROPERTIES
PHARMACODYNAMICS PROPERTIES:
Therapeutic classification & ATC Codes
Pharmacotherapeutic group: immunosuppressive agents
ATC code: L04AA06
Mechanism of action: Mycophenolate mofetil is the 2-morpholinoethyl ester of MPA. MPA is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase, and therefore inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA.
Because T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines whereas other cell types can utilise salvage pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells.

PHARMACOKINETIC PROPERTIES:
Absorption: Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete pre systemic metabolism to the active metabolite, MPA. As evidenced by suppression of acute rejection following renal transplantation, the immunosuppressant activity of mycophenolate mofetil is correlated with MPA concentration. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94 % relative to IV mycophenolate mofetil. Food had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g BID to renal transplant patients. However, MPA Cmax was decreased by 40 % in the presence of food. Mycophenolate mofetil is not measurable systemically in plasma following oral administration.
Distribution: As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are usually observed at approximately 6 – 12 hours post-dose. A reduction in the AUC of MPA of approximately 40 % is associated with the co-administration of colestyramine (4 g TID), indicating that there is a significant amount of enterohepatic recirculation. MPA at clinically relevant concentrations is 97 % bound to plasma albumin.
Biotransformation: MPA is metabolised principally by glucuronyl transferase (isoform UGT1A9) to form the inactive phenolic glucuronide of MPA (MPAG). In vivo, MPAG is converted back to free MPA via enterohepatic recirculation. A minor acylglucuronide (AcMPAG) is also formed. AcMPAG is pharmacologically active and is suspected to be responsible for some of MMF's side effects (diarrhoea, leucopenia).
Elimination: A negligible amount of substance is excreted as MPA (<1% of dose) in the urine. Oral administration of radiolabelled mycophenolate mofetil results in complete recovery of the administered dose with 93 % of the administered dose recovered in the urine and 6 % recovered in the feces. Most (about 87 %) of the administered dose is excreted in the urine as MPAG.
At clinically encountered concentrations, MPA and MPAG are not removed by hemodialysis. However, at high MPAG plasma concentrations (> 100µg/ml), small amounts of MPAG are removed. By interfering with enterohepatic circulation of the drug, bile acid sequestrants such as colestyramine, 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. In the early post-transplant period (< 40 days post-transplant), renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30 % lower and Cmax approximately 40 % lower compared to the late post-transplant period (3 – 6 months post-transplant).

SPECIAL POPULATION:
Renal impairment: In a single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate < 25ml/min^{-1} / 1.73m^{-2}) were 28 - 75% higher relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. However, the mean single dose MPAG AUC was 3–6 fold higher in subjects with severe renal impairment than in subjects with mild renal impairment or normal healthy subjects, consistent with the known renal elimination of MPAG. Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.
Delayed renal graft function: In patients with delayed renal graft function post-transplant, mean MPA AUC (0-12h) was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC (0-12h) was 2 – 3-fold higher than in post-transplant patients without delayed graft function. There may be a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of mycophenolate mofetil does not appear to be necessary.
Hepatic impairment: In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease. Effects of hepatic disease on this process probably depend on the particular disease. However, hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.
Paediatric population: Pharmacokinetic parameters were evaluated in 49 paediatric renal transplant patients (aged 2 to 18 years) given 600 mg/m^2 mycophenolate mofetil orally twice daily. This dose achieved MPA AUC values similar to those seen in adult renal transplant patients receiving mycophenolate mofetil at a dose of 1g BID in the early and late post-transplant period. MPA AUC values across age groups were similar in the early and late post-transplant period.
Elderly: Pharmacokinetic behaviour of mycophenolate mofetil in the elderly (• 65years) has not been formally evaluated.
Patients taking oral contraceptives: The pharmacokinetics of oral contraceptives were unaffected by co-administration of mycophenolate mofetil. A study of the co-administration of mycophenolate mofetil (1g BID) and combined oral contraceptives containing ethinylestradiol (0.02mg to 0.04mg) and levonorgestrel (0.05mg to 0.15mg), desogestrel (0.15mg) or gestodene (0.05mg to 0.10mg) conducted in 18 non-transplant women (not taking other immunosuppressant's) over 3 consecutive menstrual cycles showed no clinically relevant influence of mycophenolate mofetil on the ovulation suppressing action of the oral contraceptives.
Serum levels of LH, FSH and progesterone were not significantly affected.

STABILITY
See expiry on the pack

AVAILABILITY
ICOFATE™-M tablets 500mg in a pack of 40's.

INSTRUCTIONS
Dosage as advised by the physician.
To be sold on the prescription of registered medical practitioner.
Tablets should be handled with care and do not crush them.
Keep out of reach of children.
Avoid exposure to heat, light and humidity.
Store between 15 to 30°C.
Improper storage may deteriorate the medicine.
Store in the original package in order to protect from moisture.

Please read the contents carefully before use.
This package insert is regularly reviewed and updated.

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg. Lic. No. 000072

آئیکوفیٹ™-ایم ٹیبلٹ
(مائیکوفینولیٹ موفٹل)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
گولیوں کو احتیاط سے استعمال کریں اور ہرگز نہ چکلیں
بچوں کی پہنچ سے دور رکھیں۔
دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں
ورنہ دوا خراب ہو جائیگی۔
دوا کو کنی سے محفوظ رکھنے کے لیے اسکی اصل پیکنگ میں رکھیں۔