Mycofit 250

(Mycophenolate Mofetil Capsules 250 mg)

Dosage Form

Capsule

Product Description

Light Blue/Peach size '1' hard gelatin capsule imprinting with 'MMF' on cap and '250' on Body and containing white to off white powder.

Route of Administration: Orally.

Pharmacotherapeutic group: Immunosuppressive Agent

ATC code: LO4AA06

Pharmacodynamic properties

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

Following oral administration, Mycophenolate Mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, MPA. As evidenced by suppression of acute rejection following renal transplantation, the immunosuppressant activity of Mycophenolate Mofetil Capsules 250 mg 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 C_{max} was decreased by 40 % in the presence of food. Mycophenolate Mofetil is not measurable systemically in plasma following oral administration. MPA at clinically relevant concentrations is 97 % bound to plasma albumin. 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 is metabolized principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG), which is not pharmacologically active. A negligible amount of drug is excreted as MPA (< 1 % of dose) in the urine. Orally administered radiolabelled Mycophenolate Mofetil results in complete recovery of the administered dose; with 93 % of the administered dose recovered in the urine and 6 % recovered in the faeces. Most (about 87 %) of the administered dose is excreted in the urine as MPAG. At clinically encountered concentrations, MPA and MPAG are not removed by haemodialysis. However, at high MPAG plasma concentrations (> 100µg/ml), small amounts of MPAG are removed. In the early post-transplant period (< 40 days post-

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

Renal impairment:

In a single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate < 25 ml•min^{-1}•1.73 m^{-2}) were 28 – 75 % higher relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. However, the mean single dose MPAG AUC was 3 – 6-fold higher in subjects with severe renal impairment than in subjects with mild renal impairment or normal healthy subjects, consistent with the known renal elimination of MPAG. Multiple dosing of Mycophenolate Mofetil in patients with severe chronic renal impairment has not been studied. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Delayed renal graft function:

In patients with delayed renal graft function post-transplant, mean MPA AUC (0-12h) was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG AUC (0-12h) was 2 – 3-fold higher than in post-transplant patients without delayed graft function. There may be a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. Dose adjustment of Mycophenolate Mofetil Capsules 250 mg 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.

Children and adolescents (aged 2 to 18 years):

Pharmacokinetic parameters were evaluated in 49 paediatric renal transplant patients given 600 mg/m2 Mycophenolate Mofetil orally twice daily. This dose achieved MPA AUC values similar to those seen in adult renal transplant patients receiving Mycophenolate Mofetil Capsules 250 mg at a dose of 1 g 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 patients (≥ 65 years):

Pharmacokinetic behaviour of Mycophenolate Mofetil Capsules 250 mg in the elderly has not been formally evaluated.

Oral contraceptives:

The pharmacokinetics of oral contraceptives was unaffected by coadministration of Mycophenolate Mofetil Capsules 250 mg. A study of the coadministration of Mycophenolate Mofetil Capsules 250 mg (1 g bid) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.15 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) conducted in 18 non-transplant women (not taking other immuno suppressants) over 3 consecutive menstrual cycles showed no clinically relevant influence of Mycophenolate Mofetil Capsules 250 mg

on the ovulation suppressing action of the oral contraceptives. Serum levels of LH, FSH and progesterone were not significantly affected.

Indication

Mycofit Tablets are indicated for the prophylaxis of acute organ rejection in patients receiving allogeneic renal transplants.

Mycofit Tablets are indicated for the prophylaxis of acute organ rejection in patients receiving allogeneic cardiac transplants.

Mycofit Tablets are indicated for the prophylaxis of acute organ rejection in patients receiving allergeneic hepatic transplants.

Mycofit Tablets should be used concomitantly with cyclosporine and corticosteroids. Mycofit Tablets are indicated for induction and maintenance treatment of lupus nephritis.

Mycofit Tablets should be used concomitantly with corticosteroids.

Recommended Dose

Standard dosage for prophylaxis of renal rejection.

A dose of 1g administered twice a day (daily dose of 2 g) is recommended for use in renal transplant patients.

Standard dosage for prophylaxis of cardiac rejection.

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

Standard dosage for prophylaxis of hepatic rejection.

The initial dose of Mycophenolate should be given as soon as possible following transplantation. The recommended dose in hepatic transplant patients is 1.5 g administered twice daily (daily dose of 3 g).

Oral administration.

The initial dose of Mycophenolate should be given as soon as possible following renal or cardiac transplantation.

Induction and maintenance treatment of lupus nephritis.

The recommended dose is 1 g administered twice a day (daily dose of 2 g).

Special dose instructions

Patients with neutropenia If neutropenia develops (absolute neutrophil count

Geriatric Use

The recommended dose of 1 g b.i.d for renal transplant and 1.5 g b.i.d for cardiac or hepatic

transplant patients are appropriate for elderly patients

Renal Impairment

Patients with severe renal impairment

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

No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Patients with delayed renal graft function post-transplant

No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively

Hepatic Impairment

No dose adjustments are needed for renal patients with severe hepatic parenchymal disease. No data are available for cardiac transplant patients with severe hepatic parenchymal disease.

Contraindication

Hypersensitivity reactions to Mycophenolate Mofetil Capsules 250 mg have been observed. Therefore, Mycophenolate Mofetil Capsules 250 mg is contraindicated in patients with a hypersensitivity to Mycophenolate Mofetil or Mycophenolic acid.

Mycophenolate Mofetil Capsules 250 mg is contraindicated during pregnancy due to its mutagenic and teratogenic potential (see Use in Special Populations: Pregnancy).

Mycophenolate Mofetil Capsules 250 mg is contraindicated in women of childbearing potential not using highly effective contraceptive methods (see Use in Special Populations: Pregnancy).

Mycophenolate Mofetil Capsules 250 mg is contraindicated in women who are breastfeeding (see Use in Special Populations: Breastfeeding).

Warnings & 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 IMMUNOSUPPRESANTS. THESE INFECTIONS MAY LEAD TO SERIOUS, INCLUDING FATAL OUTCOMES.

Patients receiving immunosuppressive regimens involving combinations of drugs, including Mycophenolate Mofetil Capsules 250 mg, 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.

Patients receiving Mycophenolate Mofetil Capsules 250 mg should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

Patients treated with immunosuppressant, including Mycophenolate Mofetil, 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.

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 $<1.3 \times 10^3/\mu l$), 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 immunosuppressants. The mechanism for mycophenolate mofetil induced PRCA is unknown. PRCA may resolve with dose reduction or cessation of Mycophenolate Mofetil therapy. Changes to Mycophenolate Mofetil therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimise the risk of graft rejection.

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. Because 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. On theoretical grounds, 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. It is recommended that Mycophenolate Mofetil should not be administered concomitantly with azathioprine because such concomitant administration has not been studied.

In view of the significant reduction in the AUC of MPA by cholestyramine, caution should be used in the concomitant administration of Mycophenolate Mofetil with medicinal products that interfere with enterohepatic recirculation because of the potential to reduce the efficacy of Mycophenolate Mofetil.

The risk: benefit of mycophenolate mofetil in combination with tacrolimus or sirolimus has not been established.

Interaction with other medicaments

Aciclovir

Higher MPAG and aciclovir plasma concentrations were observed when Mycophenolate Mofetil was administered with aciclovir in comparison to the administration of each drug alone. The changes in MPAG pharmacokinetics (MPAG increased by 8 %) were minimal and are not considered clinically significant. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are aciclovir concentrations, the potential exists for Mycophenolate Mofetil and aciclovir, or its prodrugs, e.g. valaciclovir, to compete for tubular secretion and further increases in concentrations of both drugs may occur.

Antacids with magnesium and aluminum hydroxides

Absorption of Mycophenolate Mofetil was decreased when administered with antacids.

Colestyramine

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

Drugs that interfere with enterohepatic circulation

Caution should be used with drugs that interfere with enterohepatic circulation because of their potential to reduce the efficacy of Mycophenolate Mofetil Capsules 250 mg.

Ciclosporin A

Ciclosporin A pharmacokinetics were unaffected by Mycophenolate Mofetil.

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 Capsules 250 mg 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 are anticipated and Mycophenolate Mofetil Capsules 250 mg dose adjustment is not required. In patients with renal impairment in which Mycophenolate Mofetil Capsules 250 mg and ganciclovir or its prodrugs, e.g. valganciclovir, are co-administered the dose recommendations for ganciclovir should be observed and patients monitored carefully.

Oral contraceptives

The pharmacokinetics and pharmacodynamics of oral contraceptives were unaffected by coadministration of Mycophenolate Mofetil Capsules 250 mg.

Rifampicin

In patients not also taking ciclosporin, concomitant administration of Mycophenolate Mofetil and rifampicin resulted in a decrease in MPA exposure (AUC0-12h) of 18% to 70%. It is recommended to monitor MPA exposure levels and to adjust Mycophenolate Mofetil doses accordingly to maintain clinical efficacy when rifampicin is administered concomitantly.

Sirolimus

In renal transplant patients, concomitant administration of Mycophenolate Mofetil and CsA resulted in reduced MPA exposures by 30-50% compared with patients receiving the combination of sirolimus and similar doses of Mycophenolate Mofetil.

Sevelamer

Decrease in MPA Cmax and AUC0-12 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 is 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 and metronidazole separately

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 their discontinuation. The change in predose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of Mycophenolate Mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

Tacrolimus

In renal transplant patients: Stable renal transplant patients receiving ciclosporin and Mycophenolate Mofetil Capsules 250 mg (1 g BID) showed about a 30 % increase in MPA plasma AUC and about a 20 % decrease in MPAG plasma AUC when ciclosporin was replaced with tacrolimus. MPA Cmax was not affected, while MPAG Cmax was reduced by approximately 20 %. The mechanism of this finding is not well understood. Increased biliary secretion of MPAG accompanied with increased enterohepatic recirculation of MPA may be partly responsible for the finding, since the elevation of MPA concentrations associated with tacrolimus administration was more pronounced in the later portions of the concentration-time profile (4 – 12 hours after dosing). In another study in renal transplant patients, it was shown that the tacrolimus concentration did not appear to be altered by Mycophenolate Mofetil Capsules 250 mg.

Other interactions:

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

Live vaccines

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

Pregnancy and Lactation

It is recommended that Mycophenolate Mofetil Capsules 250 mg therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning Mycophenolate Mofetil Capsules 250 mg therapy, during therapy, and for six weeks following discontinuation of therapy. Patients should be instructed to consult their physician immediately should pregnancy occur.

The use of Mycophenolate Mofetil Capsules 250 mg is not recommended during pregnancy and should be reserved for cases where no more suitable alternative treatment is available. Mycophenolate Mofetil Capsules 250 mg should be used in pregnant women only if the potential benefit outweighs the potential risk to the foetus. There are no adequate data from the use of Mycophenolate Mofetil Capsules 250 mg in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Mycophenolate Mofetil Capsules 250 mg 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 Mycophenolate Mofetil Capsules 250 mg, 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 Mycophenolate Mofetil Capsules 250 mg. 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 contraception during treatment and for total of 90 days after the last dose of Mycophenolate Mofetil Capsules 250 mg.

Congenital malformations, including multiple malformations have been reported post-marketing in children of patients exposed to Mycophenolate in combination with other immune suppressants 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 immune suppressants 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 immune suppressants. Studies in animals have shown reproductive toxicity.

Breastfeeding

Mycophenolate Mofetil Capsules 250 mg 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.

Side effects/Adverse Reactions

The following undesirable effects cover adverse reactions from post-marketing experience: 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.

System Organ Class		**Adverse Drug Reactions**
Infections and infestations	Very common	Sepsis, gastrointestinal candidiasis, urinary tract infection, herpes simplex, herpes zoster
	Common	Pneumonia, influenza, respiratory tract infection, respiratory moniliasis, gastrointestinal infection, candidiasis, gastroenteritis, infection, bronchitis, pharyngitis, sinusitis, fungal skin infection, skin candida, vaginal candidiasis, rhinitis
Neoplasms benign, malignant and unspecified (incl cysts and polyps	Very common	-
	Common	Skin cancer, benign neoplasm of skin
Blood and lymphatic system disorders	Very common	Leucopenia, thrombocytopenia, anaemia

	Common	Pancytopenia, leucocytosis
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 disorder	Very common	-
	Common	Tachycardia
Vascular disorders	Very common	-
	Common	Hypotension, hypertension, vasodilatation
Respiratory, thoracic and mediastinal disorders	Very common	-
	Common	Pleural effusion, dyspnoea, cough
Gastrointestinal disorders	Very common	Vomiting, abdominal pain, diarrhoea, nausea
	Common	Gastrointestinal haemorrhage, peritonitis, ileus, colitis, gastric ulcer, duodenal ulcer, gastritis, oesophagitis, stomatitis, constipation, dyspepsia, flatulence, eructation
Hepatobiliary disorders	Very common	-
	Common	Hepatitis, jaundice, hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Very common	-
	Common	Skin hypertrophy, rash, acne, alopecia
Muscoskeletal and connective tissue disorder	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

Gastrointestinal:

Gingival hyperplasia, colitis including cytomegalovirus colitis, pancreatitis, and intestinal villous atrophy.

Disorders related to immunosuppression:

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 multifocalleucoencephalopathy (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 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.

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.

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

General disorders and administration site conditions

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.

Adverse Drug Reactions post-marketing experience:

Congenital Disorders

Congenital malformations have been reported post-marketing in children of patients exposed to Mycophenolate in combination with other immune suppressants 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).

Signs & Symptoms of overdose and Treatment

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 over suppression 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 cholestyramine, can remove MPA by decreasing the enterohepatic re-circulation of the drug.

Effects on Ability to Drive and Use Machine

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.

Storage Conditions

Do not store above 30°C. Store in the original package in order to protect from moisture.

Keep out of reach and sight of children

Packaging

Mycophenolate Mofetil Capsules 250 mg is packed in PVC/PVdC-Alu Blister of 10 capsules. Each Carton contains 3 blisters (3 x 10 Capsules), 5 blisters (5 x 10 Capsules) and 10 blisters (10 x 10 Capsules).

Shelf life

36 months

Manufactured by:

INTAS PHARMACEUTICALS LTD.

Matoda-382 210, Dist.: Ahmedabad. INDIA

Product Registration Holder:

Jetpharma Sdn Bhd

No.13, Jalan Rajawali 2,

Bandar Puchong Jaya

47100 Puchong

Selangor, Malaysia

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