For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

FENOGRAF 500

1. **Generic Name**

Mycophenolate mofetil Tablets I.P.

2. Qualitative and quantitative composition

Each film coated tablet contains:

Mycophenolate Mofetil IP…….500 mg

Colours: Red Oxide of Iron & Titanium Dioxide I.P.

The excipients used are Microcrystalline Cellulose, Polyvinyl Pyrrolidone, Croscarmellose Sodium, Magnesium Stearate, Hydroxy propyl methyl cellulose, Titanium Dioxide, Red Oxide of Iron, Talc and Polyethylene Glycol

3. Dosage form and strength

Dosage Form: Film Coated Tablets

Strength: 500 mg

4. Clinical particulars

4.1 Therapeutic indication

FENOGRAF 500 is indicated for the prophylaxis of acute organ rejection in patients receiving allogenic hepatic transplantation.

4.2 Posology and method of administration

Treatment with FENOGRAF 500 should be initiated and maintained by appropriately qualified transplant specialists.

Posology

Adults

The recommended oral dose in hepatic transplant patients is 1.5 g administered twice daily (3 g daily dose).

Paediatric population

No data are available for paediatric hepatic transplant patients.

Use in special populations

Elderly

The recommended dose of 1.5 g twice a day for hepatic transplant patients is appropriate for the elderly.

Renal impairment

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

Treatment during rejection episodes

No pharmacokinetic data are available during hepatic transplant rejection.

Paediatric population

No data are available for treatment of first or refractory rejection in paediatric transplant patients.

Method of administration

Oral administration.

Precautions to be taken before handling or administering the medicinal product.

FENOGRAF 500 tablets should not be crushed.

4.3 Contraindications

- FENOGRAF 500 should not be given to patients with hypersensitivity to mycophenolate mofetil, mycophenolic acid or to any of the excipients. Hypersensitivity reactions to FENOGRAF 500 have been observed.
- FENOGRAF 500 should not be given to women of childbearing potential who are not using highly effective contraception.
- FENOGRAF 500 treatment should not be initiated in women of childbearing potential without providing a pregnancy test result to rule out unintended use in pregnancy.
- FENOGRAF 500 should not be used during pregnancy unless there is no suitable alternative treatment to prevent transplant rejection.
- FENOGRAF 500 should not be given to women who are breastfeeding.

4.4 Special warnings and precautions for use

Neoplasms

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including FENOGRAF 500, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As general advice to minimise the risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Infections

Patients treated with immunosuppressants, including FENOGRAF 500, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis. Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation and infections caused by polyomaviruses (BK virus associated nephropathy, JC virus associated progressive multifocal leukoencephalopathy PML). Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.

There have been reports of hypogammaglobulinaemia in association with recurrent infections in patients receiving FENOGRAF 500 in combination with other immunosuppressants. In some of these cases switching FENOGRAF 500 to an alternative immunosuppressant resulted in serum IgG levels returning to normal. Patients on FENOGRAF 500 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 FENOGRAF 500 in combination with other immunosuppressants. In some of these cases switching FENOGRAF 500 to another immunosuppressant resulted in improvement in respiratory symptoms. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect on the lung. There have also been isolated reports of interstitial lung disease and pulmonary fibrosis, some of which were fatal. It is recommended that patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, are investigated.

Blood and immune system

Patients receiving FENOGRAF 500 should be monitored for neutropenia, which may be related to FENOGRAF 500 itself, concomitant medications, viral infections, or some combination of these causes. Patients taking FENOGRAF 500 should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If neutropenia develops (absolute neutrophil count < 1.3 x 10 / μ l), it may be appropriate to interrupt or discontinue FENOGRAF 500.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with FENOGRAF 500 in combination with other immunosuppressants. The mechanism for mycophenolate mofetil induced PRCA is unknown. PRCA may resolve with dose reduction or cessation of FENOGRAF 500 therapy. Changes to FENOGRAF 500 therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimise the risk of graft rejection.

Patients receiving FENOGRAF 500 should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow failure.

Patients should be advised that during treatment with FENOGRAF 500, 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

FENOGRAF 500 has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, haemorrhage and perforation.

FENOGRAF 500 should be administered with caution in patients with active serious digestive system disease.

FENOGRAF 500 is an IMPDH (inosine monophosphate dehydrogenase) inhibitor. Therefore, it should be avoided in patients with rare hereditary deficiency of hypoxanthine guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Interactions

Caution should be exercised when switching combination therapy from regimens containing immunosuppressants, which interfere with MPA enterohepatic recirculation, e.g. ciclosporin, to others devoid of this effect, e.g. tacrolimus, sirolimus, belatacept, or vice versa, as this might result in changes of MPA exposure. Drugs which interfere with MPA's enterohepatic cycle (e.g.cholestyramine, antibiotics) should be used with caution due to their potential to reduce the plasma level and efficacy of FENOGRAF 500. Therapeutic drug monitoring of MPA may be appropriate when switching combination therapy (e.g. from ciclosporin to tacrolimus or vice versa) or to ensure adequate immunosuppression in patients with high immunological risk (e.g. risk of rejection, treatment with antibiotics, addition or removal of an interacting medication).

It is recommended that FENOGRAF 500 should not be administered concomitantly with azathioprine because such concomitant administration has not been studied.

The risk/benefit ratio of mycophenolate mofetil in combination with sirolimus has not been established.

Special populations

Elderly patients may be at an increased risk of adverse events such as certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared with younger individuals.

Teratogenic Effects

Mycophenolate is a powerful human teratogen. Spontaneous abortion (rate of 45% to 49%) and congenital malformations (estimated rate of 23% to 27%) have been reported following MMF exposure during pregnancy. Therefore, FENOGRAF 500 is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejection. Female patients of childbearing potential should be made aware of the risks and follow the recommendations provided in section 4.6 (e.g. contraceptive methods, pregnancy testing) prior to, during, and after therapy with FENOGRAF 500. 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 FENOGRAF 500 therapy, during therapy, and for six weeks after stopping the therapy, unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred to minimise the potential for contraceptive failure and unintended pregnancy.

For contraception advice for men see section 4.6.

Educational materials

In order to assist patients in avoiding foetal exposure to mycophenolate and to provide additional important safety information, the Marketing Authorisation holder will provide educational materials to healthcare professionals. The educational materials will reinforce the warnings about the teratogenicity of mycophenolate, provide advice on contraception before therapy is started and guidance on the need for pregnancy testing. Full patient information about the teratogenic risk and the pregnancy prevention measures should be given by the physician to women of childbearing potential and, as appropriate, to male patients.

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.

4.5 Drugs interactions

Aciclovir

Higher aciclovir plasma concentrations were observed when mycophenolate mofetil was administered with aciclovir in comparison to the administration of aciclovir 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 aciclovir concentrations, the potential exists for mycophenolate mofetil and aciclovir, or its prodrugs, e.g. valaciclovir, to compete for tubular secretion and further increases in concentrations of both substances may occur.

Antacids and proton pump inhibitors (PPIs)

Decreased MPA exposure has been observed when antacids, such as magnesium and aluminium hydroxides, and PPIs, including lansoprazole and pantoprazole, were administered with FENOGRAF 500. When comparing rates of transplant rejection or rates of graft loss between FENOGRAF 500 patients taking PPIs vs. FENOGRAF 500 patients not taking PPIs, no significant differences were seen. This data support extrapolation of this finding to all antacids because the reduction in exposure when FENOGRAF 500 was co- administered with magnesium and aluminium hydroxides is considerably less than when FENOGRAF 500 was co-administered with PPIs.

Medicinal products that interfere with enterohepatic recirculation (e.g. cholestyramine, ciclosporin A, antibiotics)

Caution should be used with medicinal products that interfere with enterohepatic recirculation because of their potential to reduce the efficacy of FENOGRAF 500.

Cholestyramine

Following single dose administration of 1.5 g of mycophenolate mofetil to normal healthy subjects pre-treated with 4 g 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 FENOGRAF 500.

Ciclosporin A

Ciclosporin A (CsA) pharmacokinetics are unaffected by mycophenolate mofetil.

In contrast, if concomitant CsA 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 FENOGRAF 500 and CsA compared with patients receiving sirolimus or belatacept and similar doses of FENOGRAF 500. Conversely, changes of MPA exposure should be expected when switching patients from CsA to one of the immunosuppressants which does not interfere with MPA´s enterohepatic cycle.

Antibiotics eliminating ®-glucuronidase-producing bacteria in the intestine (e.g. aminoglycoside, cephalosporin, fluoroquinolone, and penicillin classes of antibiotics) may interfere with MPAG/MPA enterohepatic recirculation thus leading to reduced systemic MPA exposure. Information concerning the following antibiotics is available:

Ciprofloxacin or amoxicillin plus clavulanic acid

Reductions in pre-dose (trough) MPA concentrations of 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 predose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of FENOGRAF 500 should not normally be necessary in the absence of clinical evidence of graft

dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

Norfloxacin and metronidazole

As per reported data, in healthy volunteers, no significant interaction was observed when MPA 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 MPA.

Trimethoprim/sulfamethoxazole

No effect on the bioavailability of MPA was observed.

Medicinal products that affect glucuronidation (e.g. isavuconazole, telmisartan)

Concomitant administration of drugs affecting glucuronidation of MPA may change MPA exposure. Caution is therefore recommended when administering these drugs concomitantly with FENOGRAF 500.

Isavuconazole

An increase of MPA $AUC_{0-\infty}$ by 35% was observed with concomitant administration of isavuconazole.

Telmisartan

Concomitant administration of telmisartan and MPA 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 MPA patients with and without concomitant telmisartan medication, no clinical consequences of the pharmacokinetic drug-drug interaction were seen.

Ganciclovir

Based on the results of a reported 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 and ganciclovir, it is anticipated that co-administration of these agents (which compete for mechanisms of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics is anticipated and FENOGRAF 500 dose adjustment is not required. In patients with renal impairment in whom FENOGRAF 500 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.

Rifampicin

Reportedly, in patients not also taking ciclosporin, concomitant administration of mycophenolate and rifampicin resulted in a decrease in MPA exposure (AUC_{0-12h}) of 18% to 70%. It is recommended to monitor MPA exposure levels and to adjust FENOGRAF 500 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 was concomitantly administered with sevelamer without any clinical consequences (i.e. graft rejection). It is recommended, however, to administer FENOGRAF 500 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 with phosphate binders other than sevelamer.

Tacrolimus

In hepatic transplant patients initiated on FENOGRAF 500 and tacrolimus, the AUC and C_{max} of MPA, the active metabolite of MPA, were not significantly affected by co-administration with tacrolimus. In contrast, there was an increase of approximately 20% in tacrolimus AUC when multiple doses of MPA (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 MPA.

Live vaccines

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

Paediatric population

Reportedly, interaction studies have only been performed in adults.

Potential interaction

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.

4.6 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 FENOGRAF 500 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

FENOGRAF 500 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 counselled regarding pregnancy prevention, and planning.

Before starting FENOGRAF 500 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 (because

of the timing of transplant organ availability), 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 (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 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 immunosuppressants other than mycophenolate mofetil).

Congenital malformations, including reports of multiple malformations, have been observed post-marketing in children of patients exposed to FENOGRAF 500 during pregnancy in combination with other immunosuppressants. The following malformations were most frequently reported:

• Abnormalities of the ear (e.g. abnormally formed or absent external ear), external auditory canal artesia (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-Oesophageal malformations (e.g. oesophageal 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.

Reported studies in animals have shown reproductive toxicity.

Breast-feeding

Mycophenolate mofetil has been shown to be excreted in the milk of lactating rats. 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, FENOGRAF 500 is 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. Calculations based on animal data show that the maximum amount of MPA that could potentially be transferred to woman is so low that it would be unlikely to have an effect. Mycophenolate has been shown to be genotoxic in reported animal studies at concentrations exceeding the human therapeutic exposures only 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 with a qualified healthcare professional the potential risks of fathering a child.

4.7 Effects on ability to drive and use machines

FENOGRAF 500 has a moderate influence on the ability to drive and use machines.

FENOGRAF 500 may cause somnolence, confusion, dizziness, tremor or hypotension, and therefore patients are advised to use caution when driving or using machines.

4.8 Undesirable effects

Summary of safety profile

An estimated total of 1557 patients received mycophenolate during five reported clinical trials in the prevention of acute organ rejection. Of these, 991 were included in the three renal studies, 277 were included in one hepatic study, and 289 were included in one cardiac study. Azathioprine was the comparator used in the hepatic and cardiac studies and in two of the renal studies whilst the other renal study was placebo-controlled. Patients in all study arms also received cyclosporine and corticosteroids. The types of adverse reactions reported during post-marketing with mycophenolate are similar to those seen in the controlled renal, cardiac and hepatic transplant studies.

Diarrhoea, leucopenia, sepsis and vomiting were among the most common and/or serious adverse drug reactions associated with the administration of mycophenolate in combination with ciclosporin and corticosteroids. There is evidence of a higher frequency of certain types of infections.

Tabulated list of adverse reactions

The adverse drug reactions (ADRs) from reported clinical trials and post marketing experience are listed in Table 1, by MedDRA system organ class (SOC) along with their frequencies. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). Due to the large differences observed in the frequency of certain ADRs across the different transplant indications, the frequency is presented separately for renal, hepatic and cardiac transplant patients.

Table 1 Summary of adverse drug reactions occurring in patients treated with mycophenolate mofetil reported from clinical trials and post marketing experience

Adverse drug reaction (MedDRA) System Organ Class	**Renal transplant n = 991**	**Hepatic transplant n = 277**	**Cardiac transplant n = 289**
	Frequency	Frequency	Frequency
Infections and infestations			
Bacterial infections	Very Common	Very Common	Very Common
Fungal infections	Common	Very Common	Very Common
Protozoal infections	Uncommon	Uncommon	Uncommon
Viral infections	Very Common	Very Common	Very Common
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Benign neoplasm of skin	Common	Common	Common
Lymphoma	Uncommon	Uncommon	Uncommon
Lymphoproliferative disorder	Uncommon	Uncommon	Uncommon
Neoplasm	Common	Common	Common
Skin cancer	Common	Uncommon	Common
Blood and lymphatic system disorders			
Anemia	Very Common	Very Common	Very Common
Aplasia pure red cell	Uncommon	Uncommon	Uncommon
Bone marrow failure	Uncommon	Uncommon	Uncommon
Ecchymosis	Common	Common	Very Common
Leukocytosis	Common	Very Common	Very Common
Leukopenia	Very Common	Very Common	Very Common
Pancytopenia	Common	Common	Uncommon
Pseudolymphoma	Uncommon	Uncommon	Common
Thrombocytopenia	Common	Very Common	Very Common
Metabolism and nutrition disorders			
Acidosis	Common	Common	Very Common
Hypercholesterolemia	Very Common	Common	Very Common
Hyperglycemia	Common	Very Common	Very Common
Hyperkalemia	Common	Very Common	Very Common
Hyperlipidemia	Common	Common	Very Common
Hypocalcemia	Common	Very Common	Common
Hypokalemia	Common	Very Common	Very Common
Hypomagnesemia	Common	Very Common	Very Common
Hypophosphatemia	Very Common	Very Common	Common
Hyperuricaemia	Common	Common	Very Common
Gout	Common	Common	Very Common
Weight decreased	Common	Common	Common
Confusional state	Common	Very Common	Very Common
Depression	Common	Very Common	Very Common
Insomnia	Common	Very Common	Very Common
Agitation	Uncommon	Common	Very Common
Anxiety	Common	Very Common	Very Common
Thinking abnormal	Uncommon	Common	Common
Nervous system disorders			
Dizziness	Common	Very Common	Very Common

Headache	Very Common	Very Common	Very Common
Hypertonia	Common	Common	Very Common
Paresthesia	Common	Very Common	Very Common
Somnolence	Common	Common	Very Common
Tremor	Common	Very Common	Very Common
Convulsion	Common	Common	Common
Dysgeusia	Uncommon	Uncommon	Common
Cardiac disorders			
Tachycardia	Common	Very Common	Very Common
Vascular disorders			
Hypertension	Very Common	Very Common	Very Common
Hypotension	Common	Very Common	Very Common
Lymphocele	Uncommon	Uncommon	Uncommon
Venous thrombosis	Common	Common	Common
Vasodilatation	Common	Common	Very Common
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis	Uncommon	Uncommon	Uncommon
Cough	Very Common	Very Common	Very Common
Dyspnea	Very Common	Very Common	Very Common
Interstitial lung disease	Uncommon	Very Rare	Very Rare
Pleural effusion	Uncommon	Very Rare	Very Rare
Pulmonary fibrosis	Very Rare	Uncommon	Uncommon
Gastrointestinal disorders			
Abdominal distension	Common	Very Common	Common
Abdominal Pain	Very Common	Very Common	Very Common
Colitis	Common	Common	Common
Constipation	Very Common	Very Common	Very Common
Decreased appetite	Common	Very Common	Very Common
Diarrhea	Very Common	Very Common	Very Common
Dyspepsia	Very Common	Very Common	Very Common
Esophagitis	Common	Common	Common
Eructation	Uncommon	Uncommon	Common
Flatulence	Common	Very Common	Very Common
Gastritis	Common	Common	Common
Gastrointestinal haemorrhage	Common	Common	Common
Gastrointestinal ulcer	Common	Common	Common
Gingival hyperplasia	Common	Common	Common
Ileus	Common	Common	Common
Mouth ulceration	Common	Common	Common
Nausea	Very Common	Very Common	Very Common
Pancreatitis	Uncommon	Common	Uncommon
Stomatitis	Common	Common	Common
Vomiting	Very Common	Very Common	Very Common
Immune system disorders			
Hypersenstivity	Uncommon	Common	Common
Hypogammaglobulinaemia	Uncommon	Very Rare	Very Rare
Hepatobiliary disorders			

Blood alkaline phosphatase increased	Common	Common	Common
Blood lactate dehydrogenase increased	Common	Uncommon	Very Common
Hepatic enzyme increased	Common	Very Common	Very Common
Hepatitis	Common	Very Common	Uncommon
Hyperbilirubinaemia	Common	Very Common	Very Common
Jaundice	Uncommon	Common	Common
Skin and subcutaneous tissues disorders			
Acne	Common	Common	Very Common
Alopecia	Common	Common	Common
Rash	Common	Very Common	Very Common
Skin hypertrophy	Common	Common	Very Common
Musculoskeletal and connective tissue disorders			
Arthralgia	Common	Common	Very Common
Muscular weakness	Common	Common	Very Common
Renal and urinary disorders			
Blood creatinine increased	Common	Very Common	Very Common
Blood urea increased	Uncommon	Very Common	Very Common
Hematuria	Very Common	Common	Common
Renal impairment	Common	Very Common	Very Common
General disorders and administration site conditions			
Asthenia	Very Common	Very Common	Very Common
Chills	Common	Very Common	Very Common
Edema	Very Common	Very Common	Very Common
Hernia	Common	Very Common	Very Common
Malaise	Common	Common	Common
Pain	Common	Very Common	Very Common
Pyrexia	Very Common	Very Common	Very Common

Note: 991 (2 g / 3 g mycophenolate daily), 289 (3 g mycophenolate daily) and 277 (2 g IV / 3 g oral mycophenolate daily) patients were treated in Phase III studies for the prevention of rejection in renal, cardiac and hepatic transplantation, respectively.

Description of selected adverse reactions

Malignancies

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including FENOGRAF 500, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. Three-year safety data in renal and cardiac transplant patients did not reveal any unexpected changes in incidence of malignancy compared to the 1-year data. Hepatic transplant patients were followed for at least 1 year, but less than 3 years.

Infections

All patients treated with immunosuppressants are at increased risk of bacterial, viral and fungal infections (some of which may lead to a fatal outcome), including those caused by opportunistic agents and latent viral reactivation. The risk increases with total immunosuppressive load. The most serious infections were sepsis, peritonitis, meningitis, endocarditis, tuberculosis and atypical mycobacterial infection. The most common opportunistic infections in patients receiving mycophenolate (2 g or 3 g daily) with other immunosuppressants in reported

controlled clinical trials in renal, cardiac and hepatic transplant patients followed for at least 1 year were candida mucocutaneous, CMV viraemia/syndrome and Herpes simplex. The proportion of patients with CMV viraemia/syndrome was 13.5%. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including mycophenolate.

Blood and lymphatic disorders

Cytopenias, including leucopenia, anemia, thrombocytopenia and pancytopenia, are known risks associated with mycophenolate mofetil and may lead or contribute to the occurrence of infections and hemorrhages. Agranulocytosis and neutropenia have been reported; therefore, regular monitoring of patients taking FENOGRAF 500 is advised. There have been reports of aplastic anaemia and bone marrow failure in patients treated with mycophenolate, some of which have been fatal.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate.

Isolated cases of abnormal neutrophil morphology, including the acquired Pelger-Huet anomaly, have been observed in patients treated with mycophenolate. 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 FENOGRAF 500.

Gastrointestinal disorders

The most serious gastrointestinal disorders were ulceration and hemorrhage which are known risks associated with mycophenolate mofetil. Mouth, esophageal, gastric, duodenal, and intestinal ulcers often complicated by hemorrhage, as well as hematemesis, melena, and hemorrhagic forms of gastritis and colitis were commonly reported during the reported pivotal clinical trials.

The most common gastrointestinal disorders, however, were diarrhea, nausea and vomiting. Endoscopic investigation of patients with mycophenolate-related diarrhea have revealed isolated cases of intestinal villous atrophy.

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 trimeste.

Congenital disorders

Congenital malformations have been observed post-marketing in children of patients exposed to mycophenolate 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 in combination with other immunosuppressants, some of which have been fatal. There have also been reports of bronchiectasis in children and adults.

Immune system disorders

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

General disorders and administration site conditions

Edema, including peripheral, face and scrotal edema, was reported very commonly during the pivotal trials. Musculoskeletal pain such as myalgia, and neck and back pain were also very commonly reported.

Special populations

Paediatric population

The type and frequency of adverse reactions in a reported clinical study, which recruited 92 paediatric patients aged 2 to 18 years who were given 600 mg/m mycophenolate mofetil orally twice daily, were generally similar to those observed in adult patients given 1 g mycophenolate twice daily. However, the following treatment-related adverse events were more frequent in the paediatric population, particularly in children under 6 years of age, when compared to adults: diarrhoea, sepsis, leucopenia, anaemia and infection.

Elderly

Elderly patients (≥ 65 years) may generally be at increased risk of adverse reactions due to immunosuppression. Elderly patients receiving FENOGRAF 500 as part of a combination immunosuppressive regimen, may be at increased risk of certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared to younger individuals.

4.9 Overdose

Reports of overdoses with mycophenolate mofetil have been received from reported 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 FENOGRAF 500 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 recirculation of the drug.

5. Pharmacological properties

5.1 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.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressive agents ATC code L04AA06

5.3 Pharmacokinetic properties

Absorption

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 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 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 cholestyramine (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 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 (> 100 μ g/mL), small amounts of MPAG are removed. By interfering with enterohepatic recirculation of the drug, bile acid sequestrants such as cholestyramine, reduce MPA AUC MPA's disposition depends on several transporters. Organic anion-transporting polypeptides (OATPs) and multidrug resistance-associated protein 2 (MRP2) are involved in MPA's disposition; OATP isoforms, MRP2 and breast cancer resistance protein (BCRP) are transporters associated with the glucuronides' biliary excretion. Multidrug resistance protein 1 (MDR1) is also able to transport MPA, but its contribution seems to be confined to the absorption process. In the kidney MPA and its metabolites potently interact with renal organic anion transporters.

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 approximately 40% lower compared to the late post-transplant period (3 – 6 months post-transplant).

Special populations

Renal impairment

In a reported single dose study (6 subjects/group), mean plasma MPA AUC observed in subjects with severe chronic renal impairment (glomerular filtration rate < 25 mL/min 1.73 m^2) were 28 ‑ 75% higher relative to the means observed in normal healthy subjects or subjects with lesser degrees of renal impairment. 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 $AUC_{0\text{-}12h}$ was comparable to that seen in post-transplant patients without delayed graft function. Mean plasma MPAG $AUC_{0\text{-}12h}$ 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 FENOGRAF 500 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

Reportedly, pharmacokinetic parameters were evaluated in 49 paediatric renal transplant patients (aged 2 to 18 years) given 600 mg/m mycophenolate mofetil orally twice daily. This dose achieved MPA AUC values similar to those seen in adult renal transplant patients receiving FENOGRAF 500 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

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

Patients taking oral contraceptives

As per reported data, a study of the co-administration of mycophenolate (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 immunosuppressants) over 3 consecutive menstrual cycles showed no clinically relevant influence of mycophenolate on the ovulation suppressing action of the oral contraceptives. Serum levels of LH, FSH and progesterone were not significantly affected. The pharmacokinetics of oral contraceptives were unaffected by co-administration of mycophenolate.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Reportedly, iin experimental models, mycophenolate mofetil was not tumourigenic. The highest dose tested in the animal carcinogenicity studies resulted in approximately 2 – 3 times the systemic exposure (AUC or C_{max}) observed in renal transplant patients at the recommended clinical dose of 2 g/day and 1.3 – 2 times the systemic exposure (AUC or C_{max}) observed in cardiac transplant patients at the recommended clinical dose of 3 g/day.

Two reported genotoxicity assays (*in vitro* mouse lymphoma assay and *in vivo* mouse bone marrow micronucleus test) showed a potential of mycophenolate mofetil to cause chromosomal aberrations. These effects can be related to the pharmacodynamic mode of action, i.e. inhibition of nucleotide synthesis in sensitive cells. Other *in vitro* tests for detection of gene mutation did not demonstrate genotoxic activity.

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. The systemic exposure at this dose represents 2 – 3 times the clinical exposure at the recommended clinical dose of 2 g/day in renal transplant patients and 1.3 – 2 times the clinical exposure at the recommended clinical dose of 3 g/day in cardiac transplant patients. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (including anophthalmia, agnathia, and hydrocephaly) in the first generation offspring in the absence of maternal toxicity. The systemic exposure at this dose was approximately 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

In reported teratology studies in rats and rabbits, foetal resorptions and malformations occurred in rats at 6 mg/kg/day (including anophthalmia, agnathia, and hydrocephaly) and in rabbits at 90 mg/kg/day (including cardiovascular and renal anomalies, such as ectopia cordis and ectopic kidneys, and diaphragmatic and umbilical hernia), in the absence of maternal toxicity. The systemic exposure at these levels is approximately equivalent to or less than 0.5 times the clinical exposure at the recommended clinical dose of 2 g/day for renal transplant patients and approximately 0.3 times the clinical exposure at the recommended clinical dose of 3 g/day for cardiac transplant patients.

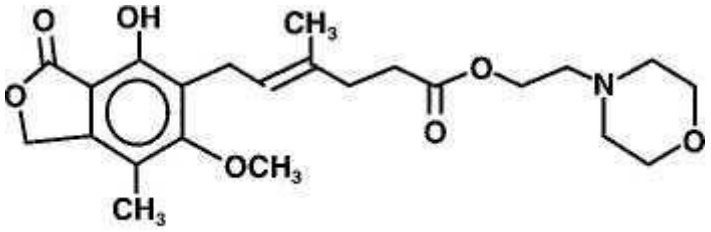
The haematopoietic and lymphoid systems were the primary organs affected in reported toxicology studies conducted with mycophenolate mofetil in the rat, mouse, dog and monkey. These effects occurred at systemic exposure levels that are equivalent to or less than the clinical exposure at the recommended dose of 2 g/day for renal transplant recipients. Gastrointestinal effects were observed in the dog at systemic exposure levels equivalent to or less than the clinical exposure at the recommended dose. Gastrointestinal and renal effects consistent with dehydration were also observed in the monkey at the highest dose (systemic exposure levels equivalent to or greater than clinical exposure). The nonclinical toxicity profile of mycophenolate mofetil appears to be consistent with adverse events observed in human clinical trials which now provide safety data of more relevance to the patient population.

7. Description

Mycophenolate mofetil is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an immunosuppressive agent; inosine monophosphate dehydrogenase (IMPDH) inhibitor.

The chemical name for mycophenolate mofetil (MMF) is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4 hexenoate. It

has molecular formula of C23H31NO7, a molecular weight of 433.5, and the following structural formula:



Mycophenolate mofetil is a white or almost white crystalline powder. It is freely soluble in acetone; sparingly soluble in anhydrous ethanol; practically insoluble in water.

Mycophenolate Mofetil Tablets are pale brown coloured, oblong shaped, slightly biconvex film coated tablets with scored in the middle on one side. The excipients used are Microcrystalline Cellulose, Polyvinyl Pyrrolidone, Croscarmellose Sodium, Magnesium Stearate, Hydroxy propyl methyl cellulose, Titanium Dioxide, Red Oxide of Iron, Talc and Polyethylene Glycol

8. Pharmaceutical particulars

8.1 Incompatibilities
Not applicable.

8.2 Shelf-life
Do not use later than the date of expiry.

8.3 Packaging information
FENOGRAF 500 is available in blister Strips of 10 tablets.

8.4 Storage and handing instructions
Store at a temperature not exceeding 30°C, protected from light and moisture.
Keep out of reach of children.

9 Patient counselling information

FENOGRAF 500

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• **This medicine has been prescribed for you only.** Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1.What FENOGRAF 500 is and what it is used for

9.2.What you need to know before you take FENOGRAF 500

9.3.How to take FENOGRAF 500

9.4.Possible side effects

9.5.How to store FENOGRAF 500

9.6.Contents of the pack and other information

9.1 What FENOGRAF 500 is and what it is used for

FENOGRAF 500 contains mycophenolate mofetil.

• This belongs to a group of medicines called “immunosuppressants”.

FENOGRAF 500 is used to prevent your body rejecting a transplanted liver.

9.2 What you need to know before you take FENOGRAF 500

WARNING

Mycophenolate causes birth defects and miscarriage. If you are a woman who could become pregnant, you must provide a negative pregnancy test before starting treatment and must follow the contraception advice given to you by your doctor.

Your doctor will speak to you and give you written information, particularly on the effects of mycophenolate on unborn babies. Read the information carefully and follow the instructions.

If you do not fully understand these instructions, please ask your doctor to explain them again before you take mycophenolate. See also further information in this section under “Warnings and precautions” and “Pregnancy and breast-feeding”.

Do not take FENOGRAF 500:

- If you are allergic (hypersensitive) to mycophenolate mofetil, mycophenolic acid or any of the other ingredients in this medicine
- If you are a woman who could be pregnant and you have not provided a negative pregnancy test before your first prescription as mycophenolate causes birth defects and miscarriage.
- If you are pregnant or planning to become pregnant or think you may be pregnant
- If you are not using effective contraception (see Pregnancy, contraception and breast-feeding).
- If you are breast-feeding.

Do not take this medicine if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking FENOGRAF 500.

Warnings and precautions

Talk to your doctor straight away before starting treatment with FENOGRAF 500:

- If you have a sign of infection such as a fever or sore throat
- If you have any unexpected bruising or bleeding
- If you have ever had a problem with your digestive system such as a stomach ulcer
- If you are planning to become pregnant or if you get pregnant while you or partner are taking FENOGRAF 500.

If any of the above apply to you (or you are not sure), talk to your doctor straight away before starting treatment with FENOGRAF 500.

The effect of sunlight

FENOGRAF 500 reduces your body’s defences. As a result, there is an increased risk of skin cancer. Limit the amount of sunlight and UV light you get. Do this by:

• wearing protective clothing which also covers your head, neck, arms and legs

• using a sunscreen with a high protection factor.

Other medicines and FENOGRAF 500

Please tell your doctor if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, such as herbal medicines. This is because FENOGRAF 500 can affect the way some other medicines work. Also other medicines can affect the way FENOGRAF 500 works.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines before you start FENOGRAF 500:

- azathioprine or other medicines which suppress your immune system – given after a transplant operation
- cholestyramine – used to treat high cholesterol
- rifampicin – an antibiotic used to prevent and treat infections such as tuberculosis (TB)
- antacids or proton pump inhibitors – used for acid problems in your stomach such as indigestion
- phosphate binders – used by people with chronic kidney failure to reduce how much phosphate gets absorbed into their blood.
- antibiotics – used to treat bacterial infections
- isavuconazole – used to treat fungal infections
- telmisartan – used to treat high blood pressure

Vaccines

If you need to have a vaccine (a live vaccine) while taking FENOGRAF 500, talk to your doctor first. Your doctor will have to advise you on what vaccines you can have.

You must not donate blood during treatment with FENOGRAF 500 and for at least 6 weeks after stopping treatment. Men must not donate semen during treatment with FENOGRAF 500 and for at least 90 days after stopping treatment.

FENOGRAF 500 with food and drink

Taking food and drink has no effect on your treatment with FENOGRAF 500.

Pregnancy, contraception and breast-feeding

Contraception in women taking FENOGRAF 500

If you are a woman who could become pregnant you must use an effective method of contraception with FENOGRAF 500. This includes:

• Before you start taking FENOGRAF 500

• During your entire treatment with FENOGRAF 500

• For 6 weeks after you stop taking FENOGRAF 500.

Talk to your doctor about the most suitable contraception for you. This will depend on your individual situation. Two forms of contraception are preferable as this will reduce the risk of unintended pregnancy. **Contact your doctor as soon as possible, if you think your**

contraception may not have been effective or if you have forgotten to take your contraceptive pill.

You are a woman who is not capable of becoming pregnant if any of the following applies to you:

- You are post-menopausal, i.e. at least 50 years old and your last period was more than a year ago (if your periods have stopped because you have had treatment for cancer, then there is still a chance you could become pregnant)
- Your fallopian tubes and both ovaries have been removed by surgery (bilateral salpingo-oophorectomy)
- Your womb (uterus) has been removed by surgery (hysterectomy)
- Your ovaries no longer work (premature ovarian failure, which has been confirmed by a specialist gynaecologist)
- You were born with one of the following rare conditions that make pregnancy impossible: the XY genotype, Turner's syndrome or uterine agenesis
- You are a child or teenager who has not started having periods.

Contraception in men taking FENOGRAF 500

The available evidence does not indicate an increased risk of malformations or miscarriage if the father takes mycophenolate. However, a risk cannot be completely excluded. As a precaution you or your female partner are recommended to use reliable contraception during treatment and for 90 days after you stop taking FENOGRAF 500.

If you are planning to have a child, talk to your doctor about the potential risks and alternative therapies.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Your doctor will talk to you about the risks in case of pregnancy and the alternatives you can take to prevent rejection of your transplant organ if:

- You plan to become pregnant.
- You miss or think you have missed a period, or you have unusual menstrual bleeding, or suspect you are pregnant.
- You have sex without using an effective method of contraception.

If you do become pregnant during the treatment with mycophenolate, you must inform your doctor immediately. However, keep taking FENOGRAF 500 until you see him or her.

Pregnancy

Mycophenolate causes a very high frequency of miscarriage (50%) and of severe birth defects (23- 27 %) in the unborn baby. Birth defects which have been reported include anomalies of ears, of eyes, of face (cleft lip/palate), of development of fingers, of heart, oesophagus (tube that connects the throat with the stomach), kidneys and nervous system (for example spina bifida (where the bones of the spine are not properly developed). Your baby may be affected by one or more of these.

If you are a woman who could become pregnant, you must provide a negative pregnancy test before starting treatment and must follow the contraception advice given to you by your doctor. Your doctor may request more than one test to ensure you are not pregnant before starting treatment.

Breast-feeding

Do not take FENOGRAF 500 if you are breast-feeding. This is because small amounts of the medicine can pass into the mother's milk.

Driving and using machines

FENOGRAF 500 has a moderate influence on your ability to drive or use any tools or machines. If you feel drowsy, numb or confused, talk to your doctor or nurse and do not drive or use any tools or machines until you feel better.

9.3 How to take FENOGRAF 500

Always take FENOGRAF 500 exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

How much to take

Treatment will continue for as long as you need to prevent you from rejecting your transplant organ.

Adults

- The first dose of oral FENOGRAF 500 will be given to you at least 4 days after the transplant operation and when you are able to swallow oral medicines.
- The daily dose is 6 tablets (3 g of the medicine) taken as 2 separate doses.
- Take 3 tablets in the morning and then 3 tablets in the evening.

Children

• There is no information for the use of FENOGRAF 500 in children with a liver transplant.

Taking the medicine

- Swallow your tablets whole with a glass of water.
- Do not break or crush them.

If you take more FENOGRAF 500 than you should

If you take more FENOGRAF 500 than you should, talk to a doctor or go to a hospital straight away. Also do this if someone else accidentally takes your medicine. Take the medicine pack with you.

If you forget to take FENOGRAF 500

If you forget to take your medicine at any time, take it as soon as you remember. Then continue to take it at the usual times. Do not take a double dose to make up for a missed dose.

If you stop taking FENOGRAF 500

Do not stop taking FENOGRAF 500 unless your doctor tells you to. If you stop your treatment you may increase the chance of rejection of your transplanted organ.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, FENOGRAF 500 can cause side effects, although not everybody gets them.

Talk to a doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

- you have a sign of infection such as a fever or sore throat
- you have any unexpected bruising or bleeding
- you have a rash, swelling of your face, lips, tongue or throat, with difficulty breathing - you may be having a serious allergic reaction to the medicine (such as anaphylaxis, angioedema).

Usual problems

Some of the more usual problems are diarrhoea, fewer white cells or red cells in your blood, infection and vomiting. Your doctor will do regular blood tests to check for any changes in:

• the number of your blood cells or signs of infections.

Children may be more likely than adults to have some side effects. These include diarrhoea, infections, fewer white cells and fewer red cells in the blood.

Fighting infections
FENOGRAF 500 reduces your body's defences. This is to stop you rejecting your transplant. As a result, your body will not be as good as normal at fighting infections. This means you may catch more infections than usual. This includes infections of the brain, skin, mouth, stomach and gut, lungs and urinary system.

Lymph and skin cancer
As can happen in patients taking this type of medicine (immune-suppressants), a very small number of FENOGRAF 500 patients have developed cancer of the lymphoid tissues and skin.

General unwanted effects
You may get general side effects affecting your body as a whole. These include serious allergic reactions (such as anaphylaxis, angioedema), fever, feeling very tired, difficulty sleeping, pains (such as stomach, chest, joint or muscle), headache, flu symptoms and swelling.

Other unwanted effects may include:

Skin problems such as:

• acne cold sores, shingles, skin growth hair loss, rash, itching.

Urinary problems such as:

• blood in the urine.

Digestive system and mouth problems such as:

• swelling of the gums and mouth ulcers,

• inflammation of the pancreas, colon or stomach,

• gastrointestinal disorders including bleeding,

• liver problems,

• diarrhoea, constipation, feeling sick (nausea), indigestion, loss of appetite, flatulence.

Nervous system problems such as:

• feeling dizzy, drowsy or numb,

• tremor, muscle spasms, convulsions,

• feeling anxious or depressed changes in your mood or thoughts.

Heart and blood vessel problems such as:

• change in blood pressure, accelerated heartbeat, widening of blood vessels.

Lung problems such as:

• pneumonia, bronchitis,

• shortness of breath, cough, which can be due to bronchiectasis (a condition in which the lung airways are abnormally dilated) or pulmonary fibrosis (scarring of the lung). Talk to your doctor if you develop a persistent cough or breathlessness,

• fluid on the lungs or inside the chest,

• sinus problems.

Other problems such as:

• weight loss, gout, high blood sugar, bleeding, bruising.

9.5 How to store FENOGRAF 500

• Keep out of the sight and reach of children.

• Do not use the tablets after the expiry date.

• Do not store above 30°C. Keep in outer carton in order to protect from light.

• Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

9.6 Contents of the pack and other information
What FENOGRAF 500 film coated tablet contains

The active substance is mycophenolate mofetil.

The other ingredients are Microcrystalline Cellulose, Polyvinyl Pyrrolidone, Croscarmellose Sodium, Magnesium Stearate, Hydroxy propyl methyl cellulose, Titanium Dioxide, Red Oxide of Iron, Talc and Polyethylene Glycol.

10 Details of manufacturer
The Madras Pharmaceuticals
137-B, Old Mahabalipuram Road,
Karapakkam, Chennai – 600096,
Tamil Nadu

11. Details of permission or licence number with date
Mfg. Lic. No. : 247 issued on 02/04/2018

12. Date of revision
APR-2020

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/FENOGRAF 500 500mg/APR-20/05/PI