**For the use only 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 tablet

**Strength:** 500 mg

4. **Clinical particulars:**

**4.1 Therapeutic indication:**

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

**4.2 Posology and method of administration:**

Treatment with mycophenolate mofetil should be initiated and maintained by appropriately qualified transplant specialists.

**Posology**

**Use in renal transplant**

Adults

Oral mycophenolate mofetil should be initiated within 72 hours following transplantation. The recommended dose in renal transplant patients is 1 g administered twice daily (2 g daily dose).

Paediatric population aged 2 to 18 years

The recommended dose of mycophenolate mofetil is 600 mg/$m^2$ administered orally twice daily (up to a maximum of 2 g daily). Mycophenolate mofetil tablets should only be prescribed to patients with a body surface area greater than 1.5 $m^2$, at a dose of 1 g twice daily (2 g daily dose). As some adverse reactions occur with greater frequency in this age group compared with adults, temporary dose reduction or interruption may be required; these will need to take into account relevant clinical factors including severity of reaction.

Paediatric population < 2 years

There are limited safety and efficacy data in children below the age of 2 years. These are insufficient to make dose recommendations and therefore use in this age group is not recommended.

**Use in cardiac transplant**

Adults

Oral mycophenolate mofetil should be initiated within 5 days following transplantation. The recommended dose in cardiac transplant patients is 1.5 g administered twice daily (3 g daily dose).

Paediatric population

No data are available for paediatric cardiac transplant patients.

**Use in hepatic transplant**

Adults

Intravenous mycophenolate mofetil should be administered for the first 4 days following hepatic transplant, with oral mycophenolate mofetil initiated as soon after this as it can be tolerated. 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 g administered twice a day for renal transplant patients and 1.5 g twice a day for cardiac or hepatic transplant patients is appropriate for the elderly.

Renal impairment

In renal transplant patients with severe chronic renal impairment (glomerular filtration rate < 25 mL/min/1.73 $m^2$), outside the immediate post-transplant period, doses greater than 1 g administered twice a day should be avoided. These patients should also be carefully observed. No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

Severe hepatic impairment

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

Treatment during rejection episodes

Mycophenolic acid (MPA) is the active metabolite of mycophenolate mofetil. Renal transplant rejection does not lead to changes in MPA pharmacokinetics; dose reduction or interruption of mycophenolate mofetil is not required. There is no basis for mycophenolate mofetil dose adjustment following cardiac transplant rejection. 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

Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits, mycophenolate mofetil tablets should not be crushed.

## 4.3 Contraindications:

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

## 4.4 Special warnings and precautions for use:

Neoplasms

Patients receiving immunosuppressive regimens involving combinations of medicinal products, including Mycophenolate mofetil, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As general advice to 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 Mycophenolate mofetil, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis. Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation and infections caused by polyomaviruses (BK virus associated nephropathy, JC virus associated progressive multifocal leukoencephalopathy PML). Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants. These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.

There have been reports of hypogammaglobulinaemia in association with recurrent infections in patients receiving mycophenolate mofetil in combination with other immunosuppressants. In some of these cases switching mycophenolate mofetil to an alternative immunosuppressant resulted in serum IgG levels returning to normal. Patients on mycophenolate mofetil who develop recurrent infections should have their serum immunoglobulins measured. In cases of sustained, clinically relevant hypogammaglobulinaemia, appropriate clinical action should be considered taking into account the potent cytostatic effects that mycophenolic acid has on T- and B-lymphocytes.

There have been published reports of bronchiectasis in adults and children who received mycophenolate mofetil in combination with other immunosuppressants. In some of these cases switching mycophenolate mofetil to another immunosuppressant resulted in improvement in

respiratory symptoms. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect on the lung. There have also been isolated reports of interstitial lung disease and pulmonary fibrosis, some of which were fatal. It is recommended that patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, are investigated.

Blood and immune system

Patients receiving mycophenolate mofetil should be monitored for neutropenia, which may be related to mycophenolate mofetil itself, concomitant medications, viral infections, or some combination of these causes. Patients taking mycophenolate mofetil should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If neutropenia develops (absolute neutrophil count < 1.3 x $10^3$ / μl), it may be appropriate to interrupt or discontinue Mycophenolate mofetil.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil in combination with other 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 receiving mycophenolate mofetil 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 Mycophenolate mofetil, vaccinations may be less effective, and the use of live attenuated vaccines should be avoided. Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

Gastro-intestinal

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

Mycophenolate mofetil should be administered with caution in patients with active serious digestive system disease.

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

**Interactions**

Caution should be exercised when switching combination therapy from regimens containing immunosuppressants, which interfere with MPA enterohepatic recirculation, e.g. 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 Mycophenolate mofetil. 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 mycophenolate mofetil should not be administered concomitantly with azathioprine because such concomitant administration has not been studied.

The risk/benefit ratio of mycophenolate mofetil in combination with 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, mycophenolate mofetil is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejection. Female patients of childbearing potential should be made aware of the risks and follow the recommendations provided (e.g. contraceptive methods, pregnancy testing) prior to, during, and after therapy with Mycophenolate mofetil. Physicians should ensure that women taking mycophenolate understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult their physician if there is a possibility of pregnancy.

Contraception

Because of robust clinical evidence showing a high risk of abortion and congenital malformations when mycophenolate mofetil is used in pregnancy every effort to avoid pregnancy during treatment should be taken. Therefore, women with childbearing potential must use at least one form of reliable contraception before starting mycophenolate mofetil therapy, during therapy, and for six weeks after stopping the therapy, unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred to minimise the potential for contraceptive failure and unintended pregnancy.

For contraception advice for men see section Use in special populations.

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 Drug-Interaction:**

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 Mycophenolate mofetil. When comparing rates of transplant rejection or rates of graft loss between mycophenolate mofetil patients taking PPIs vs. Mycophenolate mofetil 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 mycophenolate mofetil was co-administered with magnesium and aluminium hydroxides is considerably less than when mycophenolate mofetil 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 Mycophenolate mofetil.

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 Mycophenolate mofetil.

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

Ciprofloxacin or amoxicillin plus clavulanic acid

Reductions in pre-dose (trough) MPA concentrations 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 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.

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 mycophenolate mofetil.

Trimethoprim/sulfamethoxazole

No effect on the bioavailability of MPA was observed.

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

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

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 drugdrug 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 mycophenolate mofetil dose adjustment is not required. In patients with renal impairment in whom mycophenolate mofetil and ganciclovir or its prodrugs, e.g. valganciclovir, are co-administered, the dose recommendations for ganciclovir should be observed and patients should be monitored carefully.

Oral contraceptives

The pharmacokinetics and pharmacodynamics of oral contraceptives were unaffected by co-administration of mycophenolate mofetil.

Rifampicin

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 mycophenolate mofetil doses accordingly to maintain clinical efficacy when rifampicin is administered concomitantly.

Sevelamer

Decrease in MPA $C_{max}$ and $AUC_{0-12h}$ by 30% and 25%, respectively, were observed when mycophenolate was concomitantly administered with sevelamer without any clinical consequences (i.e. graft rejection). It is recommended, however, to administer mycophenolate mofetil at least one hour before or three hours after sevelamer intake to minimise the impact on the absorption of MPA. There are no data on mycophenolate with phosphate binders other than sevelamer.

Tacrolimus

In hepatic transplant patients initiated on mycophenolate mofetil 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 Use in special populations

**Women of childbearing potential**

Pregnancy whilst taking mycophenolate must be avoided. Therefore, women of childbearing potential must use at least one form of reliable contraception before starting mycophenolate mofetil therapy, during therapy, and for six weeks after stopping the therapy, unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred.

**Pregnancy**

Mycophenolate mofetil is contraindicated during pregnancy unless there is no suitable alternative treatment to prevent transplant rejection. Treatment should not be initiated without providing a negative pregnancy test result to rule out unintended use in pregnancy.

Female patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations at the beginning of the treatment and must be counselled regarding pregnancy prevention, and planning.

Before starting mycophenolate mofetil 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 MYCOPHENOLATE MOFETIL 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, mycophenolate mofetil 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:**

Mycophenolate mofetil has a moderate influence on the ability to drive and use machines.

**4.8 Undesirable effects:**

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

*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 postmarketing 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 patient.

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 |

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|---|---|---|---|
| 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 Mycophenolate mofetil, 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 1year 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 mycophenolate mofetil 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 Mycophenolate mofetil.

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 trimester.

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 mycophenolate mofetil 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.

**Reporting of side effects:**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

**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 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 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 (> 100μg/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 Cmax 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 MYCOPHENOLATE MOFETIL does not appear to be necessary.

Hepatic impairment

In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease. Effects of hepatic disease on this process probably depend on the particular disease. However, hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, may show a different effect.

Paediatric population

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

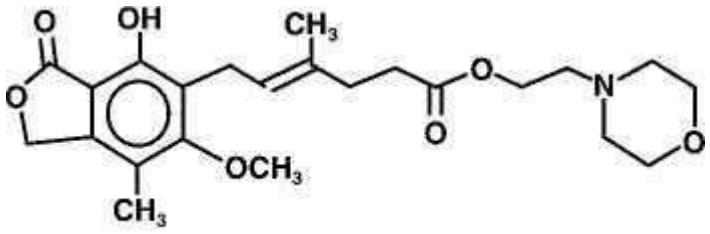
Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. The systemic exposure at this dose represents 2 – 3 times the clinical exposure at the recommended clinical dose of 2 g/day in renal transplant patients and 1.3 – 2 times the clinical exposure at the recommended 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 reported 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-(1,3dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4 hexenoate. It has molecular formula of $C_{23}H_{31}NO_7$, 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:**

MYCOPHENOLATE MOFETIL is available in blister Strips of 10 tablets.

**8.4 Sorage 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**

**Package leaflet: Information for the user**

**FENOGRAF 500**

**Mycophenolate mofetil tablets I.P.**

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. See section 4.

**What is in this leaflet?**

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

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

FENOGRAF 500is a medicine that is used to suppress immune activity.

The active substance in this medicine is called mycophenolate mofetil.

FENOGRAF 500is used to prevent your body rejecting a transplanted kidney, heart or liver. It is used in combination with other medicines with a similar function (i.e. ciclosporin and corticosteroids).

## 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, contraception and breast-feeding".

**Do not take FENOGRAF 500**

- if you are allergic to mycophenolate mofetil, mycophenolic acid or any of the other ingredients of 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.

**PRECAUTIONS**

**Talk to your doctor or pharmacist** before starting treatment with FENOGRAF 500.

- if you experience any evidence of infection (e.g. fever, sore throat), unexpected bruising and/or bleeding.
- if you have or ever have had any problems with your digestive system, e.g. stomach ulcers.
- if you are planning to become pregnant, or if you get pregnant while you or your partner are taking FENOGRAF 500.

FENOGRAF 500 reduces your body's defence mechanism. Because of this, there is an increased risk of skin cancer, Therefore you should limit your exposure to sunlight and ultraviolet (UV) light by wearing appropriate protective clothing and using a sunscreen with a high protection factor.

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 500and for at least 90 days after stopping treatment.

Children and adolescents

FENOGRAF 500 is used in children and adolescents (aged 2 to 18) to prevent a body rejecting a transplanted kidney. FENOGRAF 500should not be used in children and adolescents (aged 2 to 18) for heart or liver transplantation.

FENOGRAF 500should not be used at all in children under 2 years old.

Other medicines and FENOGRAF 500

**Tell your doctor or pharmacist** if you are taking, have recently taken or might take any other medicines. If you answer yes to any of the following questions talk to your doctor before you start to take FENOGRAF 500:

Are you taking any medicines containing:

- azathioprine or other immunosuppressive agents (which are sometimes given to patients after a transplant operation),
- cholestyramine (used to treat patients with high blood cholesterol),
- rifampicin (antibiotic),
- antacids or proton pump inhibitors (used for acid problem in your stomach such as indigestion),
- phosphate binders (used in patients with chronic kidney failure to reduce the absorption of phosphate),
- antibiotics (used to treat bacterial infections),
- isavuconazole (used to treat fungal infections),
- telmisartan (used to treat high blood pressure) o or any other medicines (including those you can buy without a prescription) that your doctor does not know about?

Do you need to receive vaccines (live vaccines)? Your doctor will have to advise you what is indicated for you.

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 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 or pharmacist for advice before taking this medicine. Your doctor will talk to you about the risk 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 Myfenax 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 500if you are breast-feeding. This is because small amounts of the medicine can pass into the mother's milk.

Driving and using machines

FENOGRAF 500has 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 this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.**

Your treatment is started and monitored by a doctor who is specialised in transplants.

The usual way to take FENOGRAF 500is as follows:

**Kidney Transplant**

Adult

The first dose will be given within 72 hours after the transplant operation. The recommended daily dose is 4 tablets (2 g of the active ingredient) taken as 2 separate doses. This means taking 2 tablets separate doses. This means taking 2 tablets in the morning then 2 tablets in the evening.

Children and adolescents (aged 2 to 18)

The dose given will vary depending on the size of the child, Your doctor will decide the most appropriate dose based on body surface area (Height and Weight). The recommended dose is 600 $mg/m^2$ taken twice a day.

**Heart Transplant**

Adults

The first dose will be given 5 days following the transplant operation. The recommended daily dose is 6 tablets (3 g of the active ingredient) taken as 2 separate doses. This means taking 3 tablets in the morning then 3 tablets in the evening.

Children

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

**Liver Transplant**

Adults

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

Children

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

**Method and route of administration**

Swallow your tablets whole with a glass of water. You can take them with or without food. Do not break or crush them.

Treatment will continue for you as long as you need immunosuppression to prevent your body from rejecting your transplanted organ.

**If you take more FENOGRAF 500than you should**

It is important not to take too many tablets. Contact your nearest hospital Accident and Emergency department or a doctor for advice if you have swallowed more tablets than you have been told to take or if you think a child has swallowed any.

**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 forgotten dose.

**If you stop taking FENOGRAF 500**

Do not stop taking FENOGRAF 500because you feel better. It is important to take the medicine for as long as the doctor has told you to. Stopping your treatment with FENOGRAF 500may increase the chance of rejection of your transplanted organ. Do not stop taking your medicine unless your doctor tells you to.

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

## 9.4 Possible side effects

Like all medicines, this medicine 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 black or bloody stool or if you vomit blood or dark particles that look like coffee grounds. These may be signs of bleeding in the stomach or intestines.
- 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, angioeodema)

The frequency of certain side effects is dependent on the transplanted organ, i.e. some side effects can occur more or less often depending on whether this medicinal product is being taken to prevent your body from rejecting a transplanted heart or a transplanted kidney. For the sake of clarity each side effect is always listed under its highest frequency.

**Other side effects**

**Very common (may affect more than 1 in 10 people)**

- Bacterial, viral and/or fungal infections
- Serious infection which may affect the whole body
- Decrease in the number of white blood cells, platelets or red blood cells, which can result in increased risk of infections, bruising, bleeding, breathlessness and weakness
- Bleeding underneath the skin
- Increase in the number of white blood cells
- Too much acid in the body

- High level of cholesterol and/or lipids in the blood
- High level of sugar in the blood
- High level of potassium in the blood, low level of potassium, magnesium, calcium, and/or phosphate in the blood
- High level of uric acid in the blood, gout
- Feeling restless, abnormalities of thought, perception and levels of awareness, depression, feeling anxious, difficulty in sleeping
- Increased tension of the muscles, shaking, sleepiness, feeling dizzy, headache, tingling, pricking or numbness
- Faster heart beat
- Low/high blood pressure, widening of blood vessels
- Accumulation of fluid in the lung, shortness of breath, cough
- Bloated belly
- Vomiting, stomach pain, diarrhea, feeling sick
- Constipation, indigestion, wind (flatulence)
- Decreased appetite
- Changes in different laboratory parameters
- Inflammation of the liver, yellowing of the skin and whites of the eyes
- Growth of the skin, rash, acne
- Muscle weakness
- Joint pain
- Kidney problems
- Blood in the urine
- Fever, feeling of coldness, pain, feeling of weak and feeble
- Fluid retention in the body
- Part of an internal organ or tissue bulging through a weak spot in the abdominal muscles

**Common (may affect up to 1 in 10 people)**

- Skin cancer, non-cancerous growth of the skin
- Abnormal and excessive growth of tissue
- Decrease in the number of blood cells
- Benign enlargement of the lymph nodes
- Inflammatory changes of the skin (pseudolymphoma)
- Decreased weight
- Abnormal thinking
- Fit
- Distortion of the sense of the taste
- Blood clot that forms within a vein
- Inflammation of the colon which causes abdominal bloated belly
- Vomiting, stomach pain, diarrhea, feeling sick
- Constipation, indigestion, wind(flatulence)
- Decreased appetite
- Changes in different laboratory parameters
- Inflammation of the liver, yellowish of the skin and whites of the eyes
- Growth of the skin, rash, acne
- Pain or diarrhea (sometimes cused by cytomegalovirus), ulcer of the mouth and/or stomach and/or duodenum, inflammation of the stomach, oesophagus and/or mouth and lips belching

- hair loss
- feeling unwell
- overgrowth of the gum tissue
- inflammation of the pancrease which causes severe pain in the abdomen and back.

**Uncommon (may affect up to 1 in 100 people)**

- protozoal infections
- proliferation of the lymphatic tissue, including
- insufficient production of red blood cells
- serious diseases of the bone marrow . accumulation of lymphatic fluid within the body
- 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.
- decrease in the amount of antibodies in the blood
- severe reduction in the number of certain white blood cells (possible symptoms are fever, sore throat, frequent infections) (agranulocytosis)

**Not known (frequency cannot be estimated from the available data)**

- alterations of the inner wall of the small intestine (intestinal villous atrophy)
- serious inflammation of the membrane that covers the brain and spinal cord
- serious inflammation of the heart and its valves
- bacterial infections usually resulting in a serious lung disorder (tuberculosis, atypical mycobacterial infection)
- serious disease of the kidney (BK virus associated nephropathy)
- serious disease of the central nervous system (JC virus associated progressive multifocal leucoencephalopathy)
- decrease in the number of certain white blood cells (neutropenia)
- change of the shape of certain white blood cells

Do not stop taking your medicine unless you have discussed this with your doctor first.

**Reporting of side effects:**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of

Torrent Pharma available at:

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

**9.5 How to store FENOGRAF 500**

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

**9.6 Contents of the pack and other information**

The active constituent is FENOGRAF 500(500 mg)
Colour: 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

FENOGRAF 500is available in blister Strips of 10 tablets

**10. Details of manufacturer**

**Manufactured by:**

The Madras Pharmaceuticals

137-B, Old Mahabalipuram Road,

Karapakkam, Chennai – 600096,

Tamil Nadu

**11. Details of permission or licence number with date**

Mfg. Licence No. : 247 issued on 02/04/2018

**12. Date of revision**

**July 2021**

MARKETED BY


TORRENT PHARMACEUTICALS LTD.

**IN/FENOGRAF 500mg/July-21/06/PI**