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

FENOGRAF S

1. **Generic Name:**
   Mycophenolic acid delayed release tablets U.S.P. 360 mg

2. **Qualitative and quantitative composition:**
   FENOGRAF S 360
   Each delayed-release tablet contains:
   Mycophenolic sodium U.S.P
   Equivalent to Mycophenolic Acid 360mg
   Colour: Titanium Dioxide I.P.

   The excipients used are Lactose monohydrate, Crospovidone, Polyvinyl Pyrollidone K 30, Pregelatinised starch, Colloidal silicon dioxide, Magnesium stearate, Triethyl citrate, Titanium dioxide, Talc, Drug Coat L-100, Insta Coat Sol

3. **Dosage form and strength:**
   Dosage form: Delayed Release tablets
   Strength: Fenograf S 360 mg.

4. **Clinical particulars:**

4.1 Therapeutic indication:

For the prophylaxis of acute organ rejection in patients receiving allogenic hepatic transplantation, renal transplantation and cardiac transplantation.

4.2 Posology and method of administration:

Treatment with Mycophenolate Sodium should be initiated and maintained by appropriately qualified transplant specialists.

Posology

The recommended dose is 720 mg administered twice daily (1,440 mg daily dose). This dose of mycophenolate sodium corresponds to 1 g mycophenolate mofetil administered twice daily (2 g daily dose) in terms of mycophenolic acid (MPA) content.

In *de novo* patients, Mycophenolate Sodium should be initiated within 72 hours following transplantation.

Special population

Paediatric population

Insufficient data are available to support the efficacy and safety of Mycophenolate Sodium in children and adolescents. Limited pharmacokinetic data are available for paediatric renal transplant patients.

Older people

The recommended dose in elderly patients is 720 mg twice daily.

Patients with renal impairment

In patients experiencing delayed renal graft function post-operatively, no dose adjustments are needed.

Patients with severe renal impairment (glomerular filtration rate <25 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$) should be carefully monitored and the daily dose of Mycophenolate Sodium should not exceed 1,440 mg.

Patients with hepatic impairment

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

Treatment during rejection episodes

Renal transplant rejection does not lead to changes in mycophenolic acid (MPA) pharmacokinetics; dosage modification or interruption of Mycophenolate Sodium is not required.

Method of administration

Mycophenolate Sodium can be taken with or without food. Patients may select either option but must adhere to their selected option.

In order to retain the integrity of the enteric coating, Mycophenolate Sodium tablets should not be crushed. Where crushing of Mycophenolate Sodium tablets is necessary, avoid inhalation of the powder or direct contact of the powder with skin or mucous membrane. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water. This is due to the teratogenic effects of mycophenolate.

4.3 Contraindications:

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

4.4 Special warnings and precautions for use:

Patients receiving immunosuppressive regimens involving combinations of drugs, including Mycophenolate Sodium, 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.

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

Patients treated with immunosuppressants, including Mycophenolate Sodium, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis. Among the opportunistic infections are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.

There have been reports of hypogammaglobulinaemia in association with recurrent infections in patients receiving Mycophenolate Sodium in combination with other immunosuppressants. In some of

these cases, switching MPA derivatives to an alternative immunosuppressant, resulted in serum IgG levels returning to normal. Patients on Mycophenolate Sodium 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 reports of bronchiectasis in patients who received Mycophenolate Sodium in combination with other immunosuppressants. In some of these cases, switching MPA derivatives 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 been also isolated reports of interstitial lung disease. It is recommended that patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, are investigated for any evidence of underlying interstitial lung disease.

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

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

Patients receiving Mycophenolate Sodium should be monitored for blood disorders (e.g. neutropenia or anemia), which may be related to MPA itself, concomitant medications, viral infections, or some combination of these causes. Patients taking Mycophenolate Sodium should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If blood disorders occur (e.g. neutropenia with absolute neutrophil count $<1.5 \times 10^3/\mu l$ or anemia) it may be appropriate to interrupt or discontinue Mycophenolate Sodium.

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

Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

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

It is recommended that Mycophenolate Sodium not be administered concomitantly with azathioprine because concomitant administration of these drugs has not been evaluated.

Mycophenolic acid (as sodium salt) and mycophenolate mofetil should not be indiscriminately interchanged or substituted because of their different pharmacokinetic profiles.

Mycophenolate Sodium has been administered in combination with corticosteroids and ciclosporin.

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

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

Mycophenolate Sodium 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.

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

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 mycophenolate mofetil exposure during pregnancy. Therefore Mycophenolate Sodium 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 Sodium. 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 Sodium therapy, during therapy and for six weeks after stopping the therapy; unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred to minimise the potential for contraceptive failure and unintended pregnancy.

Additional precautions

Patients should not donate blood during therapy or for at least 6 weeks following discontinuation of mycophenolate. Men should not donate semen during therapy or for at least 90 days following discontinuation of mycophenolate.

Mycophenolate Sodium contains sodium. This medicinal product contains 13 / 26 mg of sodium per tablet of Mycophenolate Sodium 180 / 360 mg, equivalent to 0.65 / 1.3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Drug-Interaction:

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

Aciclovir and ganciclovir

The potential for myelosuppression in patients receiving both Mycophenolate sodium and aciclovir or ganciclovir has not been studied. Increased levels of mycophenolic acid glucuronide (MPAG) and

aciclovir/ganciclovir may be expected when aciclovir/ganciclovir and Mycophenolate Sodium are administered concomitantly, possibly as a result of competition for the tubular secretion pathway.
The changes in MPAG pharmacokinetics are unlikely to be of clinical significance in patients with adequate renal function. In the presence of renal impairment, the potential exists for increases in plasma MPAG and aciclovir/ganciclovir concentrations; dose recommendations for aciclovir/ganciclovir should be followed and patients carefully observed.

Gastroprotective agents:

Magnesium and aluminium containing antacids:

MPA AUC and Cmax have been shown to decrease by approximately 37% and 25%, respectively, when a single dose of magnesium-aluminium containing antacids is given concomitantly with Mycophenolate Sodium. Magnesium aluminium-containing antacids may be used intermittently for the treatment of occasional dyspepsia. However the chronic, daily use of magnesium-aluminium containing antacids with Mycophenolate Sodium is not recommended due to the potential for decreased mycophenolic acid exposure and reduced efficacy.

Proton pump inhibitors:

In healthy volunteers, no changes in the pharmacokinetics of MPA were observed following concomitant administration of Mycophenolate Sodium and pantoprazole given at 40 mg twice daily during the four previous days. No data are available with other proton pump inhibitors given at high doses.

Oral contraceptives

Interaction studies between MMF and oral contraceptives indicate no interaction. Given the metabolic profile of MPA, no interactions would be expected for Mycophenolate Sodium and oral contraceptives.

Cholestyramine and drugs that bind bile acids

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

Ciclosporin

When studied in stable renal transplant patients, ciclosporin pharmacokinetics were unaffected by steady state dosing of Mycophenolate Sodium. When co-administered with mycophenolate mofetil, ciclosporin is known to decrease the exposure of MPA. When co-administered with Mycophenolate Sodium, ciclosporin may decrease the concentration of MPA as well (by approximately 20%, extrapolated from mycophenolate mofetil data), but the exact extent of this decrease is unknown because such an interaction has not been studied. However, as efficacy studies were conducted in combination with ciclosporin, this interaction does not modify the recommended posology of Mycophenolate Sodium. In case of interruption or discontinuation of ciclosporin, Mycophenolate Sodium dosage should be re-evaluated depending on the immunosuppressive regimen.

Tacrolimus

In a reported calcineurin cross-over study in stable renal transplant patients, steady-state Mycophenolate Sodium pharmacokinetics were measured during both Neoral and tacrolimus treatment. Mean MPA AUC was 19% higher (90% CI: -3, +47), whereas mean MPAG AUC was about 30% lower (90% CI: 16, 42) on tacrolimus compared to Neoral treatment. In addition, MPA AUC intra-subject variability was doubled when switching from Neoral to tacrolimus. Clinicians should note this increase both in MPA AUC and variability, and adjustments to FENOGRAF S dosing

should be dictated by the clinical situation. Close clinical monitoring should be performed when a switch from one calcineurin inhibitor to another is planned.

Live attenuated vaccines

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

4.6 Use in special populations

Women of child-bearing 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 Sodium 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 Sodium is contraindicated during pregnancy unless there is no suitable alternative treatment available to prevent transplant rejection.

Treatment should not be initiated without providing a negative pregnancy test result to rule out unintended use in pregnancy.

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

Before starting Mycophenolate Sodium treatment, women of child bearing 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 Sodium in combination with other immunosuppressants during pregnancy. The following malformations were most frequently reported:

- Abnormalities of the ear (e.g. abnormally formed or absent external), external auditory canal atresia (middle ear);

- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;
- Abnormalities of the eye (e.g. coloboma);
- Congenital heart disease such as atrial and ventricular septal defects;
- Malformations of the fingers (e.g. polydactyly, syndactyly);
- Tracheo-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.

Studies in animals have shown reproductive toxicity.

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 animal studies at concentrations exceeding the human therapeutic exposures by small margins, such that the risk of genotoxic effects on sperm cells cannot completely be excluded.

Therefore, the following precautionary measures are recommended: sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 90 days after cessation of mycophenolate. Male patients of reproductive potential should be made aware of and discuss the potential risks of fathering a child with a qualified health-care professional.

Breastfeeding

MPA is excreted in milk in lactating rats. It is unknown whether Mycophenolate Sodium is excreted in human breast milk. Because of the potential for serious adverse reactions to MPA in breast-fed infants, Mycophenolate Sodium is contra-indicated in women who are breast-feeding.

Fertility

No specific studies with Mycophenolate Sodium in humans have been conducted to evaluate effects on fertility. In a reported study on male and female fertility in rats no effects were seen up to a dose of 40 mg/kg and 20 mg/kg respectively.

4.7 Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machines have been performed. The mechanism of action and pharmacodynamic profile and the reported adverse reactions indicate that an effect is unlikely**.**

4.8 Undesirable effects:

The following undesirable effects cover adverse reactions from reported clinical trials

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. Lymphoproliferative disease or lymphoma developed in 2 de novo (0.9%) patients and in 2 maintenance patients (1.3%) receiving Myfortic for up to 1 year. Non-melanoma skin carcinomas occurred in 0.9% of de novo and 1.8% of maintenance patients receiving Myfortic for up to 1 year; other types of malignancy occurred in 0.5% of de novo and 0.6% of maintenance patients.

Opportunistic infections

All transplant patients are at increased risk of opportunistic infections; the risk increased with total immunosuppressive load. The most common opportunistic infections in patients receiving Mycophenolate mofetil (2 g or 3 g daily) with other immunosuppressants in reported controlled clinical trials of renal transplant patients followed for at least 1 year were cytomegalovirus (CMV), candidiasis and herpes simplex. CMV infection (serology, viraemia or disease) was reported in 21.6% of de novo and in 1.9% of maintenance renal transplant patients.

Older people

Elderly patients may generally be at increased risk of adverse drug reactions due to immunosuppression.

Other adverse reactions

Adverse drug reactions possibly or probably related to Mycophenolate Sodium reported in the reported controlled clinical trials in renal transplant patients, in which Mycophenolate Sodium was administered together with ciclosporin microemulsion and corticosteroids at a dose of 1,440 mg/day for 12 months. It is compiled according to MedDRA system organ class.

Adverse reactions are listed according to the following categories:

Very common	(≥1/10)
Common	(≥1/100 to <1/10)
Uncommon	(≥1/1,000 to <1/100)
Rare	(≥1/10,000 to <1/1,000)
Very rare	(<1/10,000)

Infections and infestations	
Very common:	Viral, bacterial and fungal infections
Common:	Upper respiratory tract infections, pneumonia
Uncommon:	Wound infection, sepsis*, osteomyelitis*
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon:	Skin papilloma*, basal cell carcinoma*, Kaposi´s sarcoma*, lymphoproliferative disorder, squamous cell carcinoma*
Blood and lymphatic system disorders	
Very common:	Leukopenia

Common:	Anaemia, thrombocytopenia
Uncommon:	Lymphopenia*, neutropenia*, lymphadenopathy*
Metabolism and nutrition disorders	
Very common:	Hypocalcemia, hypokalemia, hyperuricemia
Common:	Hyperkalemia, hypomagnesemia
Uncommon:	Anorexia, hyperlipidaemia, diabetes mellitus*, hypercholesterolaemia*, hypophosphataemia
Psychiatric disorders	
Very common:	Anxiety
Uncommon:	Abnormal dreams*, delusional perception*, insomnia*
Nervous system disorders	
Common:	Dizziness, headache
Uncommon:	Tremor
Eye disorders	
Uncommon:	Conjunctivitis*, vision blurred*
Cardiac disorders	
Uncommon:	Tachycardia, ventricular extrasystoles
Vascular disorders	
Very common:	Hypertension
Common:	Hypotension
Uncommon:	Lymphocele*
Respiratory, thoracic and mediastinal disorders	
Common:	Cough, dyspnoea
Uncommon:	Interstitial lung disease, pulmonary congestion*, wheezing*, pulmonary oedema*
Gastrointestinal disorders	
Very common:	Diarrhoea
Common:	Abdominal distension, abdominal pain, constipation, dyspepsia, flatulence, gastritis, nausea, vomiting
Uncommon:	Abdominal tenderness, gastrointestinal haemorrhage, eructation, halitosis*, ileus*, lip ulceration*, oesophagitis*, subileus*, tongue discolouration*, dry mouth*, gastro-oesophageal reflux disease*, gingival hyperplasia*, pancreatitis, parotid duct obstruction*, peptic ulcer*, peritonitis*
Hepato-biliary disorders	
Common:	Liver function tests abnormal
Skin and subcutaneous tissue disorders	
Common:	Acne, pruritus

Uncommon:	Alopecia
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia
Common:	Myalgia
Uncommon:	Arthritis*, back pain*, muscle cramps
Renal and urinary disorders	
Common:	Blood creatinine increased
Uncommon:	Haematuria*, renal tubular necrosis*, urethral stricture
Reproductive system and breast disorders	
Uncommon:	Impotence*
General disorders and administration site conditions	
Common:	Asthenia, Fatigue, oedema peripheral, pyrexia
Uncommon:	Influenza like illness, oedema lower limb*, pain, rigors*, thirst*, weakness*
Injury, poisoning and procedural complications	
Uncommon:	Contusion*

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

Note: renal transplant patients were treated with 1,440 mg Mycophenolate Sodium daily up to one year. A similar profile was seen in the *de novo* and maintenance transplant population although the incidence tended to be lower in the maintenance patients.
Rash and agranulocytosis have been identified as adverse drug reactions from post marketing experience.
The following additional adverse reactions are attributed to MPA derivatives as a class effect:

Infections and infestations:
Serious, life-threatening infections, including meningitis, infectious endocarditis, tuberculosis, and atypical mycobacterial infection. 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 Sodium.

Blood and lymphatic system disorders:
Neutropenia, pancytopenia.
Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives.

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

Respiratory, thoracic and mediastinal disorders:
There have been isolated reports of interstitial lung disease in patients treated with Mycophenolate Sodium in combination with other immunosuppressants. There have also been reports of bronchiectasis in combination with other immunosuppressants.
Isolated cases of abnormal neutrophil morphology, including the acquired Pelger-Huet anomaly, have been observed in patients treated with MPA derivatives. 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 Sodium.

Gastrointestinal disorders:
Colitis, CMV gastritis, intestinal perforation, gastric ulcers, duodenal ulcers.

Pregnancy, puerperium and perinatal conditions:
Cases of spontaneous abortion have been reported in patients exposed to mycophenolate 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.

General disorders and administration site conditions:
De novo purine synthesis inhibitors-associated acute inflammatory syndrome with frequency uncommon has been described from post-marketing experience as a paradoxical proinflammatory reaction associated with mycophenolate mofetil and mycophenolic acid, characterised by fever, arthralgia, arthritis, muscle pain and elevated inflammatory markers. Literature case reports showed rapid improvement following discontinuation of the medicinal product.

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:
There have been reports of intentional or accidental overdoses with Mycophenolate Sodium, whereas not all patients experienced related adverse events.
In those overdose cases in which adverse events were reported, the events fall within the known safety profile of the class (mainly blood dyscrasias, sepsis…).
Although dialysis may be used to remove the inactive metabolite MPAG, it would not be expected to remove clinically significant amounts of the active moiety MPA. This is in large part due to the very high plasma protein binding of MPA, 97%. By interfering with enterohepatic circulation of MPA, bile acid sequestrants, such as cholestyramine, may reduce the systemic MPA exposure.

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
Pharmacodynamic properties are not available for mycophenolate mofetil.

5.3 Pharmacokinetic properties:

Absorption

Following oral administration, mycophenolate sodium is extensively absorbed. Consistent with its enteric coated design, the time to maximal concentration (Tmax) of MPA was approximately 1.5-2 hours. Approximately 10% of all morning pharmacokinetic profiles showed a delayed Tmax, sometimes up to several hours, without any expected impact on 24 hour/daily MPA exposure.

In stable renal transplant patients on ciclosporin-based immunosuppression, the gastrointestinal absorption of MPA was 93% and the absolute bioavailability was 72%. Mycophenolate sodium pharmacokinetics are dose proportional and linear over the studied dose range of 180 to 2,160 mg.

Compared to the fasting state, administration of a single dose of mycophenolate sodium 720 mg with a high fat meal (55 g fat, 1,000 calories) had no effect on the systemic exposure of MPA (AUC), which is the most relevant pharmacokinetic parameter linked to efficacy. However there was a 33% decrease in the maximal concentration of MPA (Cmax). Moreover, Tlag and Tmax were on average 3-5 hours delayed, with several patients having a Tmax of >15 hours. The effect of food on mycophenolate sodium may lead to an absorption overlap from one dose interval to another. However, this effect was not shown to be clinically significant.

Distribution

The volume of distribution at steady state for MPA is 50 litres. Both mycophenolic acid and mycophenolic acid glucuronide are highly protein bound (97% and 82%, respectively). The free MPA concentration may increase under conditions of decreased protein binding sites (uraemia, hepatic failure, hypoalbuminaemia, concomitant use of drugs with high protein binding). This may put patients at increased risk of MPA-related adverse effects.

Biotransformation

MPA is metabolised principally by glucuronyl transferase to form the phenolic glucuronide of MPA, mycophenolic acid glucuronide (MPAG). MPAG is the predominant metabolite of MPA and does not manifest biological activity. In stable renal transplant patients on ciclosporin-based immunosuppression, approximately 28% of the oral mycophenolate sodium dose is converted to MPAG by presystemic metabolism. The half-life of MPAG is longer than that of MPA, approximately 16 hours, and its clearance is 0.45 l/h.

Elimination

The half-life of MPA is approximately 12 hours and the clearance is 8.6 l/h. Although negligible amounts of MPA are present in the urine (<1.0%), the majority of MPA is eliminated in the urine as MPAG. MPAG secreted in the bile is available for deconjugation by gut flora. The MPA resulting from this deconjugation may then be reabsorbed. Approximately 6-8 hours after mycophenolate sodium dosing a second peak of MPA concentration can be measured, consistent with reabsorption of the deconjugated MPA. There is large variability in the MPA trough levels inherent to MPA preparations, and high morning trough levels (C0 > 10 µg/ml) have been observed in approximately 2% of patients treated with mycophenolate sodium. However, across studies, the AUC at steady state (0-12h) which is indicative of the overall exposure showed a lower variability than the one corresponding to Ctrough.

Pharmacokinetics in renal transplant patients on ciclosporin-based immunosuppression

Shown are mean pharmacokinetic parameters for MPA following the administration of Mycophenolate Sodium. In the early post transplant period, mean MPA AUC and mean MPA C_{max} were approximately one-half of the values measured six months post transplant.

Mean (SD) pharmacokinetic parameters for MPA following oral administration of FENOGRAF S to renal transplant patients on ciclosporin-based immunosuppression

Adult chronic, multiple dosing 720 mg BID (Study ERLB 301) n=48	**Dose**	**T_{max}* (h)**	**C_{max} (µg/ml)**	**AUC 0-12 (µg x h/ml)**
14 days post-transplant	720 mg	2	13.9 (8.6)	29.1 (10.4)
3 months post -transplant	720 mg	2	24.6 (13.2)	50.7 (17.3)
6 months post-transplant	720 mg	2	23.0 (10.1)	55.7 (14.6)
Adult chronic, multiple dosing 720 mg BID 18 months post-transplant (Study ERLB 302) n=18	Dose	T_{max}* (h)	C_{max} (µg/ml)	AUC 0-12 (µg x h/ml)
	720 mg	1.5	18.9 (7.9)	57.4 (15.0)
Paediatric 450 mg/m^2 single dose (Study ERL 0106) n=16	Dose	T_{max}* (h)	C_{max} (µg/ml)	AUC o-∞ (µg x h/ml)
	450 mg/m^2	2.5	31.9 (18.2)	74.5 (28.3)

* median values

Special populations

Renal impairment

MPA pharmacokinetics appeared to be unchanged over the range of normal to absent renal function. In contrast, MPAG exposure increased with decreased renal function; MPAG exposure being approximately 8 fold higher in the setting of anuria. Clearance of either MPA or MPAG was unaffected by haemodialysis. Free MPA may also significantly increase in the setting of renal failure. This may be due to decreased plasma protein binding of MPA in the presence of high blood urea concentration.

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 and adolescents

Limited data are available on the use of Mycophenolate Sodium in children and adolescents. In Table 2 above the mean (SD) MPA pharmacokinetics are shown for stable paediatric renal transplant patients (aged 5-16 years) on ciclosporin-based immunosuppression. Mean MPA AUC at a dose of 450 mg/m^2 was similar to that measured in adults receiving 720 mg Mycophenolate Sodium. The mean apparent clearance of MPA was approximately 6.7 l/h/m^2.

Gender

There are no clinically significant gender differences in Mycophenolate Sodium pharmacokinetics.

Older people

Pharmacokinetics in the elderly have not formally been studied. MPA exposure does not appear to vary to a clinically significant degree by age.

6. Nonclinical properties:

The haematopoetic and lymphoid system were the primary organs affected in repeated-dose toxicity studies conducted with mycophenolate sodium in rats and mice. Aplastic, regenerative anemia was identified as being the dose-limiting toxicity in rodents exposed to MPA. Evaluation of myelograms showed a marked decrease in erythroid cells (polychromatic erythroblasts and normoblasts) and a dose-dependent enlargement of the spleen and increase in extramedullary hematopoiesis. These effects occurred at systemic exposure levels which are equivalent to or less than the clinical exposure at the recommended dose of 1.44 g/day of Mycophenolate Sodium in renal transplant patients.

Gastrointestinal effects were observed in the dog at systemic exposure levels equivalent to or less than the clinical exposure at the recommended doses.

The non-clinical toxicity profile of mycophenolic acid (as sodium salt) 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.

Three genotoxicity assays (*in vitro* mouse lymphoma assay, micronucleus test in V79 Chinese hamster cells and *in vivo* mouse bone marrow micronucleus test) showed a potential of mycophenolic acid 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.

Mycophenolic acid (as sodium salt) was not tumourigenic in rats and mice. The highest dose tested in the animal carcinogenicity studies resulted in approximately 0.6-5 times the systemic exposure (AUC or C_{max}) observed in renal transplant patients at the recommended clinical dose of 1.44 g/day.

Mycophenolic acid (as sodium salt) had no effect on fertility of male or female rats up to dose levels at which general toxicity and embryotoxicity were observed.

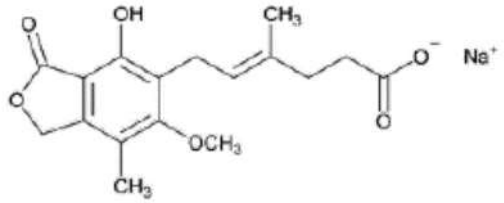
In a reported teratology study performed with mycophenolic acid (as sodium salt) in rats, at a dose as low as 1 mg/kg, malformations in the offspring were observed, including anophthalmia, exencephaly and umbilical hernia. The systemic exposure at this dose represents 0.05 times the clinical exposure at the dose of 1.44 g/day of Mycophenolate Sodium.

In a reported pre- and postnatal development study in rat, mycophenolic acid (as sodium salt) caused developmental delays (abnormal pupillary reflex in females and preputial separation in males) at the highest dose of 3 mg/kg that also induced malformations.

Mycophenolic acid (as sodium salt) showed a phototoxic potential in an *in vitro* 3T3 NRU phototoxicity assay.

7. Description:

Mycophenolate Sodium is 4-Hexenoic acid, 6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, monosodium salt, (E)-;Sodium (E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroiso benzofuran-5-yl)-4-methylhex-4-enoate. The empirical formula is $C_{17}H_{19}NaO_6$ and its molecular weight is 342.32 g/mol. The chemical structure of Mycophenolate Sodium is:



FENOGRAF S 360 is a white colored, circular, biconvex, enteric coated tablets and plain on both sides. The excipients used are Lactose monohydrate, Crospovidone, Polyvinyl Pyrollidone K 30, Pregelatinised starch, Colloidal silicon dioxide, Magnesium stearate, Triethyl citrate, Titanium dioxide, Talc, Drug Coat L-100, Insta Coat Sol

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 S 360 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

Package leaflet: Information for the user
FENOGRAF S
Mycophenolate Sodium Delayed Release Tablets

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 9.4.

What is in this leaflet?

9.1 What FENOGRAF S is and what it is used for

FENOGRAF S contains a substance called mycophenolic acid. This belongs to a group of medicines called immunosuppressants.

FENOGRAF S is used to stop the body's immune system from rejecting a kidney transplant. It is used together with other medicines containing ciclosporin and corticosteroids.

9.2 What you need to know before you take FENOGRAF S

Do not take FENOGRAF S

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 S:

- if you are allergic to mycophenolic acid, mycophenolate sodium, mycophenolate mofetil 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 Contraception in women and men).
- if you are breast-feeding (see also "Pregnancy and breast-feeding").

If any of the above apply to you, tell your doctor without taking FENOGRAF S.

Warning and precautions

Talk to your doctor or pharmacist before taking FENOGRAF S:

- if you have or have ever had serious digestive problems, such as stomach ulcer.
- if you have a rare hereditary enzyme deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) such as Lesch-Nyhan or Kelley-Seegmiller syndrome.

You should also be aware that:

- FENOGRAF S lowers the skin´s level of protection from the sun. This increases the risk of skin cancer. You should limit your exposure to sunlight and ultraviolet (UV) light by covering exposed skin areas as much as possible and regularly applying sunscreen with a high protective factor. Ask your doctor for advice on protection from the sun.
- if you already had hepatitis B or C, FENOGRAF S may increase the risk of these diseases re-appearing. Your doctor may perform blood analysis and check for symptoms of these diseases. If you experience any symptoms (yellow skin and eyes, nausea, loss of appetite, dark urine) you should tell your doctor immediately.
- if you get a persistent cough or become breathless, especially when taking other immunosuppressants, you should tell your doctor straight away.
- your doctor may want to check your blood level of antibodies during treatment with FENOGRAF S particularly when the infections recur, especially if you are also taking other immunosuppressants, and will tell you whether you can continue taking FENOGRAF S.
- if you get any signs of infection (such as fever or a sore throat) or unexpected bruising or bleeding you should tell your doctor straight away.
- your doctor may want to check your white blood cell count during treatment with FENOGRAF S, and will tell you whether you can continue taking FENOGRAF S.
- the active substance, mycophenolic acid, is not the same as other similar-sounding medicines such as mycophenolate mofetil. You should not switch between medicines unless your doctor tells you to.
- use of FENOGRAF S in pregnancy may harm the foetus (see also "Pregnancy and breast-feeding") and increase the risk of pregnancy loss (spontaneous abortion).

Other medicines and FENOGRAF S
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines, including medicines obtained without a prescription.

In particular, you should talk to your doctor if you are taking any of the following:

- other immunosuppressant medicines such as azathioprine or tacrolimus.
- medicines used to treat high blood cholesterol levels such as cholestyramine.
- activated charcoal used to treat digestive problems such as diarrhoea, upset stomach, and gas.
- antacids that contain magnesium and aluminium.
- medicines used to treat viral infections such as aciclovir or ganciclovir.

You should also tell your doctor if you plan to have any vaccinations.

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

FENOGRAF S with food and drink

FENOGRAF S can be taken with or without food. You need to choose whether to take your tablets with or without food and then take them in the same way each day. This is to make sure that the same amount of your medication is absorbed into your body each day.

Older people

Elderly people (age 65 years or older) can take FENOGRAF S without any need to adjust the usual recommended dose.

Children and adolescents
The use of FENOGRAF S in children and adolescents is not recommended due to lack of data.

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 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 mycophenolate 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 S if you are breast-feeding. This is because small amounts of the medicine can pass into the mother's milk.

Contraception in women taking FENOGRAF S

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

- Before you start taking FENOGRAF S
- During your entire treatment with FENOGRAF S
- For 6 weeks after you stop taking FENOGRAF S.

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 S

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

Driving and using machines
FENOGRAF S has not been shown to affect your ability to drive or use machines.

FENOGRAF S contains sodium

This medicinal product contains 13 mg of sodium per tablet of FENOGRAF S 180 mg, equivalent to 0.65 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

9.3 How to take FENOGRAF S

Always take FENOGRAF S exactly as your doctor has told you. FENOGRAF S will only be prescribed for you by a doctor with experience in treating transplant patients. Check with your doctor or pharmacist if you are not sure.

How much to take

The recommended daily dose of FENOGRAF S is 1440 mg (8 tablets of FENOGRAF S 180 mg). This is taken as 2 separate doses of 720 mg each (4 tablets of FENOGRAF S 180 mg). Take your tablets in the morning and in the evening.
The first dose of 720 mg will be given within 72 hours after transplantation.

If you have severe kidney problems
Your daily dose should not be more than 1440 mg (8 tablets of FENOGRAF S 180 mg).

Taking FENOGRAF S

- Swallow the tablets whole with a glass of water.
- Do not break or crush the tablets.
- Do not take any tablets that are broken or split.
- Treatment will continue for as long as you need immunosuppression to stop your body rejecting your transplant.

If you take more FENOGRAF S than you should

If you take more FENOGRAF S than you should, or if someone else has taken your tablets, talk to a doctor or go to a hospital straight away. Medical attention may be necessary. Take the tablets with you and show them to your doctor or to the hospital staff. If you have run out of tablets, take the empty packaging with you.

If you forget to take FENOGRAF S

If you forget to take FENOGRAF S, take it as soon as you remember unless it is almost time for your next dose. Then take your next dose at the usual time. Ask your doctor for advice. Do not take a double dose to make up for a forgotten dose.

If you stop taking FENOGRAF S

Do not stop taking FENOGRAF S unless your doctor tells you to. Stopping FENOGRAF S may increase the chance of your body rejecting your kidney transplant.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Elderly patients may experience more side effects due to a reduced immune defence.
Immunosuppressants, including FENOGRAF S, reduces your body´s own defence mechanisms to stop you rejecting your transplanted organ. Consequently your body will not be as good as normal at fighting infections. So if you are taking FENOGRAF S, you may therefore catch more infections than usual such as infections of the brain, skin, mouth, stomach and intestines, lungs and urinary tract.
Your doctor will perform regular blood tests to monitor any changes in the number of your blood cells or in the levels of substances carried in your blood, such as sugar, fat and cholesterol.

Some effects could be serious:

- signs of infection including fever, chills, sweating, feeling tired, drowsy, or lack of energy. If you are taking FENOGRAF S you may be more likely to get viral, bacterial and fungal infections than usual. Such infections could affect various parts of your body, but the parts most commonly affected are the kidneys, bladder, upper and/or lower airways.
- vomiting blood, black or bloody stools, stomach or intestinal ulcer.
- swelling of your glands, development of a new skin growth or enlargement of an existing skin growth, or changes in an existing mole. As can happen in patients taking immunosuppressants, a very small number of FENOGRAF S patients have developed cancer of the skin or lymph nodes.

If you experience any of the above after taking FENOGRAF S, talk to your doctor straight away.

Other side effects may include:

- Very common (affecting more than 1 in 10 patients)
- low level of white blood cells
- low level of calcium in the blood (hypocalcaemia)
- low level of potassium in the blood (hypokalemia)
- high level of uric acid in the blood (hyperuricemia)
- high blood pressure (hypertension)
- anxiety
- diarrhoea
- pain in joints (arthralgia)

Common (affecting less than 1 in 10 patients)

- low level of red blood cells which can result in tiredness, breathlessness and looking pale (anaemia)
- low level of blood platelets which can result in unexpected bleeding and bruising (thrombocytopenia)

- high level of potassium in the blood (hyperkalemia)
- low level of magnesium in the blood (hypomagnesemia)
- dizziness
- headache
- cough
- low blood pressure (hypotension)
- shortness of breath (dyspnoea)
- abdominal or stomach pain, inflammation of the lining of the stomach, abdominal bloating, constipation, indigestion, wind (flatulence), loose stools, feeling sick (nausea), being sick (vomiting)
- tiredness, fever
- abnormal results of liver or kidney function tests
- respiratory infections
- acne
- weakness (asthenia)
- muscle pain (myalgia)
- swollen hands, ankles or feet (oedema peripheral)
- itching

Uncommon (affecting less than 1 in 100 patients)

- fast heart beat (tachycardia) or irregular heart beat (ventricular extrasystoles), fluid in the lungs (pulmonary oedema)
- a growth that looks like a sac (cyst) containing fluid (lymph) (lymphocele)
- trembling, difficulty in sleeping
- redness and swelling of eyes (conjunctivitis), blurred vision
- wheezing
- belching, bad breath, bowel blockage (ileus), lip ulcers, heartburn, tongue discolouration, dry mouth, inflammation of the gums, inflammation of the pancreas leading to severe upper stomach pain (pancreatitis), blockage of the salivary glands, inflammation of the inner lining of the abdomen (peritonitis)
- infection of the bones, blood and the skin
- blood in urine, damage to the kidney, pain and difficulty passing urine
- hair loss, skin bruising
- inflammation of the joints (arthritis), back pain, muscle cramps
- loss of appetite, increased level of lipids (hyperlipidemia), sugar (diabetes), cholesterol
- (hypercholesterolemia), or decreased level of phosphate in the blood (hypophosphatemia)
- signs of flu (such as tiredness, chills, sore throat, aching joints or muscles), swelling of ankles and feet, pain, rigors, feeling thirsty or weak
- strange dreams, believing things that aren´t true (delusions)
- inability to get or keep an erection
- cough, difficulty breathing, painful breathing (possible symptoms of interstitial lung disease)

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

- rash
- fever, sore throat, frequent infections (possible symptoms of lack of white cells in the blood) (agranulocytosis)

Other side effects reported with medicines similar to FENOGRAF S

Additional side effects have been reported with the group of medicines that FENOGRAF S belongs to: inflammation of the colon (large intestine), inflammation of the stomach lining caused by cytomegalovirus, development of a hole in the intestinal wall, resulting in severe abdominal pain with possible bleeding, stomach or duodenal ulcers, a low level of specific white blood cells or of all blood cells, serious infections such as inflammation of the heart and its valves and of the membrane that covers the brain and spinal cord, shortness of breath, cough, which can be due to bronchiectasis (a condition in which the lung airways are abnormally dilated) and other less common bacterial infections usually resulting in a serious lung disorder (tuberculosis and atypical mycobacterial infection). Talk to your doctor if you develop a persistent cough or breathlessness.

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 S

- Keep this medicine out of the sight and reach of children.
- Do not use FENOGRAF S after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
- This medicine does not require any special temperature storage conditions.
- Store FENOGRAF S in the original package in order to protect it from moisture.
- Do not use FENOGRAF S if you notice that the pack is damaged or shows signs of tampering.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

9.6 Contents of the pack and other information

What FENOGRAF S contains

- The active substance is mycophenolic acid (as mycophenolate sodium). Each tablet of FENOGRAF S contains 360 mg of mycophenolic acid.

What FENOGRAF S looks like and contents of the pack

FENOGRAF S 360 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