1. NAME OF THE MEDICINAL PRODUCT

Myfortic® 180 mg gastro-resistant tablets

Myfortic® 360 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 192.4 and 384.8 mycophenolate sodium equivalent to 180 mg or 360 mg mycophenolic acid.

Excipients:

Each Myfortic 180 mg tablet contains 45 mg lactose anhydrous and 13 mg sodium.

Each Myfortic 360 mg tablet contains 90 mg lactose anhydrous and 26 mg sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant Tablets
Myfortic 180mg is a lime green, gastro-resistant film-coated round tablet, with bevelled edges and the imprint (debossing) “C” on one side.
Myfortic 360mg is a pale orange-red, gastro-resistant film-coated, ovaloid tablet with imprint (debossing) “CT” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Myfortic is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adult patients receiving allogeneic renal transplants.

4.2 Posology and method of administration

Posology

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

The recommended dose is 720 mg (four 180 mg or two 360 mg Myfortic gastro-resistant tablets) administered twice daily (1,440 mg daily dose). In patients receiving mycophenolate mofetil (MMF) 2 g, treatment can be replaced by 720 mg administered twice daily (1,440 mg daily dose) of Myfortic.

For additional information about the corresponding therapeutic doses of mycophenolate sodium and mycophenolate mofetil, see sections 4.4 and 5.2.

In *de novo* patients, Myfortic should be initiated within 48 hours following transplantation.

Special population

Paediatric population
Insufficient data are available to support the efficacy and safety of Myfortic in children and adolescents. Limited pharmacokinetic data are available for paediatric renal transplant patients (see section 5.2).

Geriatric patients

No dose adjustment is required in this patient population.

Patients with renal impairment
In patients experiencing delayed renal graft function post-operatively, no dose adjustments are needed (see section 5.2).
Patients with severe renal impairment (glomerular filtration rate <25 ml · min^{-1} · 1.73 m^{-2}) should be carefully followed up.

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 reduction or interruption of Myfortic is not required.

Method of administration
Myfortic can be taken with or without food. Patients may select either option but must adhere to their selected option (see section 5.2).

In order to retain the integrity of the enteric coating, Myfortic tablets should not be crushed. Where crushing of Myfortic 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

Myfortic should not be used in patients with hypersensitivity to mycophenolate sodium, mycophenolic acid or mycophenolate mofetil or to any of the excipients listed in section 6.1.

Myfortic should not be used in women of child bearing potential (WOCBP) who are not using highly effective contraception methods.

Myfortic should not be initiated in women of child bearing potential without providing a pregnancy test result to rule out unintended use in pregnancy (see section 4.6).

Myfortic should not be used in pregnancy unless there is no suitable alternative treatment to prevent transplant rejection (see section 4.6).

Myfortic should not be given to women who are breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

Patients receiving immunosuppressive regimens involving combinations of drugs, including Myfortic, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.8). 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 Myfortic 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 Myfortic, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis (see section 4.8). 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. Mycophenolic acid has a cytostatic effect on B- and T-lymphocytes, therefore an increased severity of COVID-19 may occur, and appropriate clinical action should be considered.

There have been reports of hypogammaglobulinaemia in association with recurrent infections in patients receiving Myfortic 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 Myfortic 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 Myfortic 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 (see section 4.8). 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 Myfortic 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 Myfortic therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimise the risk of graft rejection (see Section 4.8).

Patients receiving Myfortic should be monitored for blood disorders (e.g. neutropenia or anemia - see section 4.8), which may be related to MPA itself, concomitant medications, viral infections, or some combination of these causes.

Patients taking Myfortic 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 x 10^3/µl or anemia) it may be appropriate to interrupt or discontinue Myfortic.

Patients should be advised that during treatment with MPA vaccinations may be less effective and the use of live attenuated vaccines should be avoided (see section 4.5).

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, Myfortic should be administered with caution in patients with active serious digestive system disease.

It is recommended that Myfortic 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.

Myfortic 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 Myfortic with other immunosuppressive agents (for example, tacrolimus) have not been studied.
The concomitant administration of Myfortic and drugs which interfere with enterohepatic circulation, for example cholestyramine or activated charcoal, may result in sub-therapeutic systemic MPA exposure and reduced efficacy.

Myfortic 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.

Myfortic therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning Myfortic therapy, during therapy and for six weeks following therapy discontinuation (see section 4.6).

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, Myfortic is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejection. Female patients of childbearing potential should be made aware of the risks and follow the recommendations provided in section 4.6 (e.g., contraceptive methods, pregnancy testing) prior to, during, and after therapy with Myfortic. 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 (see section 4.6)

For patients who are considering pregnancy, consider alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of Myfortic should be discussed with the patient.

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 (section 4.3) before starting Myfortic therapy, during therapy and for six weeks after stopping the therapy, unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred to minimise the potential for contraceptive failure and unintended pregnancy.

For contraception advice for men see section 4.6.

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.

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

Excipients with known effect:
Myfortic contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

Aciclovir and ganciclovir
The potential for myelosuppression in patients receiving both Myfortic 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 Myfortic 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 C_{max} have been shown to decrease by approximately 37% and 25%, respectively, when a single dose of magnesium-aluminium containing antacids is given concomitantly with Myfortic. 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 Myfortic 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 Myfortic 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 Myfortic 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 Myfortic.

Ciclosporin
When studied in stable renal transplant patients, ciclosporin pharmacokinetics were unaffected by steady state dosing of Myfortic. When co-administered with mycophenolate mofetil, ciclosporin is known to decrease the exposure of MPA. When co-administered with Myfortic, 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 Myfortic. In case of interruption or discontinuation of ciclosporin, Myfortic dosage should be re-evaluated depending on the immunosuppressive regimen.

Tacrolimus
In a calcineurin cross-over study in stable renal transplant patients, steady-state Myfortic 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 Myfortic 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 Fertility, pregnancy and lactation

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 (section 4.3) before starting Myfortic 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

Myfortic 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 Myfortic 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 Myfortic 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 (see section 5.3).

<u>Men</u>

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
Limited data shows that mycophenolic acid is excreted in human milk. Because of the potential for serious adverse reactions to MPA in breast-fed infants, Myfortic is contra-indicated in women who are breast-feeding (see section 4.3).

Fertility

No specific studies with Myfortic in humans have been conducted to evaluate effects on fertility. In a 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 (see section 5.3).

4.7 Effects on ability to drive and use machines

Myfortic has minor influence on the ability to drive and use machines.

4.8 Undesirable effects

The following undesirable effects cover adverse drug reactions from clinical trials:

Malignancies
Patients receiving immunosuppressive regimens involving combinations of drugs, including MPA, are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see section 4.4). 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 (see section 4.4). The most common opportunistic infections in *de novo* renal transplant patients receiving Myfortic with other immunosuppressants in controlled clinical trials of renal transplant patients followed for 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 drug reactions
Table 1 below contains adverse drug reactions possibly or probably related to Myfortic reported in the controlled clinical trials in renal transplant patients, in which Myfortic 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)

Table 1

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 Myfortic 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.

Adverse drug reactions from post-marketing experience:

Blood and lymphatic system disorders: Agranulocytosis

Immune system disorders: Hypersensitivity reactions (including anaphylaxis)

Skin and subcutaneous tissue disorders: Rash

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.

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 Myfortic (see section 4.4).

Blood and lymphatic system disorders:
Neutropenia, pancytopenia.
Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives (see section 4.4).

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

Respiratory, thoracic and mediastinal disorders:
There have been isolated reports of interstitial lung disease in patients treated with Myfortic 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 Myfortic.

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 (see section 4.6).

Congenital disorders:
Congenital malformations have been observed post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants (see section 4.6).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il and to Novartis using the following email address: safetydesk.israel@novartis.com

4.9 Overdose

There have been reports of intentional or accidental overdoses with Myfortic, 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…) (see sections 4.4 and 4.8).

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 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressant, ATC code: L04AA06

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 utilize salvage pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, mycophenolate sodium is extensively absorbed. Consistent with its enteric coated design, the time to maximal concentration (T_{max}) of MPA was approximately 1.5-2 hours. Approximately 10% of all morning pharmacokinetic profiles showed a delayed T_{max}, 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%. Myfortic 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 Myfortic 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 (C_{max}). Moreover, T_{lag} and T_{max} were on average 3-5 hours delayed, with several patients having a T_{max} of >15 hours. The effect of food on Myfortic 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 Myfortic 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 Myfortic 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 (C_0 > 10 µg/ml) have been observed in approximately 2% of patients treated with Myfortic. 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 C_{trough}.

Pharmacokinetics in renal transplant patients on ciclosporin-based immunosuppression
Shown in Table 2 are mean pharmacokinetic parameters for MPA following the administration of Myfortic. 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.

Table 2 Mean (SD) pharmacokinetic parameters for MPA following oral administration of Myfortic 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

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 Myfortic 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 Myfortic. The mean apparent clearance of MPA was approximately 6.7 l/h/m^2.

Gender
There are no clinically significant gender differences in Myfortic 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.

5.3 Preclinical safety data

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 Myfortic 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 human clinical trials which now provide safety data of more relevance to the patient population (see section 4.8).

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 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 Myfortic (see section 4.6).

In a 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Lactose, anhydrous
Crospovidone
Povidone (K-30)
Maize starch
Silica, colloidal anhydrous
Magnesium stearate
The gastro-resistant tablet coating of Myfortic 180 consist of Hypromellose phthalate; Titanium dioxide (CI 77891, E-171); Iron oxide yellow (CI 77492, E-172); indigotine (Indigo carmine) (F,D & C Blue, E132).

The gastro-resistant tablet coating of Myfortic 360 consist of Hypromellose phthalate; Titanium dioxide (CI 77891, E-171); Iron oxide yellow (CI 77492, E-172); Iron oxide red (CI 77491, E-172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

The tablets are packed in polyamide/aluminium/PVC/aluminium blister packs in quantity of 120 tables per carton.

6.6 Special precautions for disposal and other handling

In order to retain the integrity of the enteric coating, Myfortic tablets should not be crushed (see section 4.2).

Mycophenolic acid has demonstrated teratogenic effects (see section 4.6). Where crushing of Myfortic tablets is necessary, avoid inhalation of the powder or direct contact of the powder with skin or mucous membrane.

Myfortic must be kept out of the reach and sight of children.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. REGISTRATION HOLDER and IMPORTER:

Novartis Israel Ltd., P.O.B 7126, Tel Aviv

8. REGISTRATION NUMBER/S:
128-30-30715
128-33-30716

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