NOVARTIS

Drug Regulatory Affairs

MYFORTIC®

(mycophenolic acid as mycophenolate sodium)

180 mg and 360 mg gastro-resistant tablets

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

Author(s): Inna Kissen, Qiaoqian Luethi-Peng, Aurélie Giovannoni

GLC approval: 04 October 2005 amended 26 April 2007, 23 October 2007, 06 May 2008, 07 July 2009 and 02-Feb-2010

Release date: 10-Feb-2010

Tracking Number: 2010-PSB/GLC-0247-s

Document status: Final

Number of pages: 14

1 Name of the medicinal product

MYFORTIC® 180 mg and 360 mg gastro-resistant tablets.

2 Qualitative and quantitative composition

Each gastro-resistant tablet contains 180 mg or 360 mg mycophenolic acid (MPA) as mycophenolate sodium.

For a full list of excipients, see section 6.1.List of excipients.

3 Pharmaceutical form

180 mg Myfortic® tablet comes as a lime green, film-coated, round tablet, with beveled edges and the imprint (debossing) “C” on one side. 360 mg Myfortic tablet come as a pale orange-red, film-coated, ovaloid tablet with imprint (debossing) “CT” on one side.

Information might differ in some countries.

4 Clinical particulars

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Myfortic should be initiated in de-novo patients within 48 hours following transplantation [73]. 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.

Myfortic can be taken with or without food.

Children

Safety and efficacy in paediatric patients have not been established. Limited pharmacokinetic data are available for paediatric renal transplant patients [1] (see section 5.2 Pharmacokinetic properties).

Elderly

No dose adjustment is required in this patient population.

Patients with renal impairment

No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively (see section 5.2 Pharmacokinetic properties) [2]. Patients with severe chronic 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 parenchymal disease [3].

Treatment during rejection episodes

Renal transplant rejection does not lead to changes in mycophenolic acid pharmacokinetics; dosage reduction or interruption of Myfortic is not required.

4.3 Contraindications

Myfortic is contraindicated in patients with a hypersensitivity to mycophenolate sodium, mycophenolic acid or mycophenolate mofetil or to any of the excipients (see section 6.1 List of excipients).

4.4 Special warnings and precautions for use

Myfortic is an IMPDH (inosine monophosphate dehydrogenase) inhibitor [4,5]. On theoretical grounds, therefore, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Use of Myfortic during pregnancy is associated with an increased risk of congenital malformations [79]. Myfortic therapy should not be initiated until a negative pregnancy test has been obtained. For information on use in pregnancy and contraceptive requirements see section 4.6 Pregnancy and lactation.

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 Undesirable effects). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. As general advice to minimize the risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

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

Oversuppression of the immune system increases the susceptibility to infection including opportunistic infections, fatal infections and sepsis (see section 4.8 Undesirable effects).

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with MPA derivatives which include mycophenolate mofetil and mycophenolate sodium (see section 4.8 Undesirable effects). The reported cases generally had risk factors for PML, including immunosuppressant therapies and impairment of immune functions. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated. Polyomavirus associated nephropathy (PVAN), especially due to BK virus infection, should be included in the differential diagnosis in immunosuppressed patients with deteriorating renal function (see section 4.8 Undesirable effects) [82]. Consideration should be given to reducing the total immunosuppression in patients who develop PML or PVAN. In transplant patients, however, reduced immunosuppression may place the graft at risk [80].

Patients receiving Myfortic should be monitored for blood dyscrasias (e.g. neutropenia or anaemia - see section 4.8 Undesirable effects), which may be related to MPA itself, concomitant medications, viral infections, or some combination of these causes. Patients taking Myfortic should have complete blood cell counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If blood dyscrasias occur (e.g. neutropenia with absolute neutrophil count $< 1.5 \times 10^3$ / micro L or anaemia) it may be appropriate to interrupt or discontinue Myfortic.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives in combination with other immunosuppressive agents (see section 4.8 Undesirable effects). The mechanism for MPA derivatives induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppressive regimen is also unknown. However, MPA derivatives may cause blood dyscrasias (see above). In some cases PRCA was found to be reversible with dose reduction or cessation of therapy with MPA derivatives. In transplant patients, however, reduced immunosuppression may place the graft at risk. Changes to Myfortic therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimize the risk of graft rejection [81].

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

Myfortic has been administered in combination with the following agents in clinical trials: antithymocyte globulin, basiliximab, ciclosporin for microemulsion and corticosteroids. The efficacy and safety of the use of Myfortic with other immunosuppressive agents have not been studied [6,7].

4.5 Interaction with other medicinal products and other forms of interaction

Azathioprine: It is recommended that Myfortic should not be administered concomitantly with azathioprine because such concomitant administration has not been studied (see section 4.4 Special warnings and precautions for use).

Live vaccines: Live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished (see also section 4.4 Special warnings and precautions for use).

Aciclovir: Higher plasma concentrations of both MPAG (mycophenolic acid glucuronide) and aciclovir may occur in the presence of renal impairment. Therefore, the potential exists for these two drugs to compete for tubular secretion, resulting in a further increase in the concentration of both MPAG and aciclovir [8,9]. In this situation patients should be carefully followed up.

Gastroprotective agents

Antacids with magnesium and aluminium hydroxides

The absorption of mycophenolate sodium was decreased when administered with antacids. Concomitant administration of Myfortic and antacids containing magnesium and aluminium hydroxide results in a 37% decrease in MPA systemic exposure and a 25% decrease in MPA maximal concentration [10]. Caution should be used when co-administering antacids (containing magnesium and aluminium hydroxide) with Myfortic.

Proton Pump inhibitors

In healthy volunteers, concomitant administration of MMF 1000 mg and pantoprazole 40 mg twice daily led to a 27% decrease in the MPA AUC and to a 57% decrease in the MPA C_{max}. However, in the same study, no changes in the pharmacokinetics of MPA were observed following concomitant administration of Myfortic and pantoprazole [83].

Cholestyramine and drugs that interfere with enterohepatic circulation: Due to its capacity to block the enteric circulation of drugs, cholestyramine may decrease the systemic exposure of MPA [11,12]. Caution should be used when co-administering cholestyramine or drugs that interfere with enterohepatic circulation because of the potential to reduce the efficacy of Myfortic.

Ganciclovir: MPA and MPAG pharmacokinetics are unaffected by the addition of ganciclovir. The clearance of ganciclovir is unchanged in the setting of therapeutic MPA exposure [14]. However, in patients with renal impairment in which Myfortic and ganciclovir are coadministered the dose recommendations for ganciclovir should be observed and patients monitored carefully.

Tacrolimus: In a calcineurin cross-over study in stable renal transplant patients, steady state Myfortic pharmacokinetics were measured during both Neoral® and tacrolimus treatments. Mean MPA AUC was 19% higher and C_{max} about 20% lower. Conversely mean MPAG AUC and C_{max} were about 30% lower on tacrolimus treatment compared to Neoral® treatment [71,75].

Oral contraceptives: Oral contraceptives undergo oxidative metabolism [15] while Myfortic is metabolized by glucuronidation [12]. A clinically significant effect of oral contraceptives on Myfortic pharmacokinetics is not anticipated [9]. However, given that the long term effect of Myfortic dosing on the pharmacokinetics of oral contraceptives is not known, it is possible that the efficacy of oral contraceptives may be adversely affected (see section 4.6 Pregnancy and lactation).

Ciclosporin A: When studied in stable renal transplant patients, ciclosporin A pharmacokinetics were unaffected by steady state dosing of Myfortic [13].

4.6 Pregnancy and lactation

Pregnancy

Use of Myfortic during pregnancy is associated with an increased risk of congenital malformations. Although there are no adequate and well controlled studies in pregnant women conducted with Myfortic, based on data from the US National Transplant Pregnancy Registry (NTPR), use of mycophenolate mofetil in combination with other immunosuppressants during pregnancy was associated with an increased rate of 22 % (four cases in 18 liveborn with exposure) of congenital malformations, compared to the rate of 4-5% for malformations seen among transplant patients in the NTPR. Congenital malformations that have been reported with mycophenolate mofetil include outer ear and other facial abnormalities including cleft lip and palate, congenital diaphragmatic hernia, anomalies of the distal limbs and heart. Since MMF is converted to MPA following oral or IV administration, the above risks must be taken into account for Myfortic as well. The teratogenic potential of MPA was observed in animal studies (see section 5.3 Preclinical safety data) [79].

Myfortic therapy should not be initiated until a negative pregnancy test has been obtained.

Myfortic should be used in pregnant women only if the potential benefit outweighs the potential risk to the foetus. Patients should be instructed to consult their physician immediately should pregnancy occur.

Effective contraception must be used before beginning Myfortic therapy, during therapy, and for six weeks following discontinuation of therapy (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Lactation

It is not known whether MPA is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from mycophenolate sodium, a decision should be made whether to discontinue the drug or to discontinue nursing while on treatment or within 6 weeks after stopping therapy, taking into account the importance of the drug to the mother.

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 drug reactions from two controlled clinical trials. The trials evaluated the safety of Myfortic and mycophenolate mofetil in 423 de novo and in 322 maintenance renal transplant patients (randomized 1:1); the incidence of adverse events was similar between treatments in each population [6,7].

The very common (≥ 10%) adverse drug reactions associated with the administration of Myfortic in combination with ciclosporin for microemulsion and corticosteroids include leucopenia and diarrhea.

Malignancies

Patient 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 Special warnings and precautions for use). Overall rates of malignancies observed in Myfortic clinical trials are as following: 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% de novo and 1.8% maintenance patients receiving Myfortic for up to 1 year; other types of malignancy occurred in 0.5% de novo and 0.6% maintenance patients [6,70,74].

Opportunistic infections

All transplant patients are at increased risk of opportunistic infections; the risk increased with total immunosuppressive load (see section 4.4 Special warnings and precautions for use). 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 CMV, candidiasis and herpes simplex. The overall rate of CMV infections (serology, viraemia or disease) observed in Myfortic clinical trials was reported in 21.6% of de novo and in 1.9% of maintenance renal transplant patients.

Elderly patients

Elderly patients may generally be at increased risk of adverse drug reactions due to immunosuppression. Elderly patients receiving Myfortic as part of a combination immunosuppressive regimen, did not show an increased risk of adverse reactions, compared to younger individuals in the Myfortic clinical trials.

Other Adverse Drug Reactions

The table 1 below contains adverse drug reactions possibly or probably related to Myfortic reported in the two phase III randomised, double blind, controlled, multi-centre trials: 1 in de novo kidney transplant patients and 1 in maintenance kidney transplant patients, in which Myfortic was administered at a dose of 1,440 mg /day for 12 months together with ciclosporin microemulsion and corticosteroids. It is compiled according to MedDRA system organ class [6,70,74,77].

Adverse reactions (Table 1) are listed according to the following categories: Very common ≥ 10 % (≥ 1/10), Common ≥ 1 % and < 10 % (≥ 1/100 and < 1/10), Uncommon ≥ 0.1 % and < 1 % (≥ 1/1'000 and < 1/100), Rare ≥ 0.01% and < 0.1 % (≥ 1/10'000 and < 1/1'000), Very rare < 0.01 % (< 1/10'000)

Table 1

Infections and infestations		
	Very common	Viral, bacterial and fungal infections
	Common	Upper respiratory tract infections, pneumonia [78]
	Uncommon	Wound infection, sepsis*, osteomyelitis*
Blood and lymphatic system disorders		
	Very common	Leukopenia
	Common	Anaemia, thrombocytopenia
	Uncommon	Lymphocele*, lymphopenia*, neutropenia*, lymphadenopathy*
Nervous system disorders		
	Common	Headache
	Uncommon	Tremor, insomnia*
Respiratory, thoracic and mediastinal disorders		
	Common	Cough
	Uncommon	Pulmonary congestion*, wheezing*
Gastrointestinal disorders		
	Very common	Diarrhea
	Common	Abdominal distension, abdominal pain, constipation, dyspepsia, flatulence, gastritis, loose stools, nausea, vomiting
	Uncommon	Abdominal tenderness, pancreatitis, eructation, halitosis*, ileus*, oesophagitis*, peptic ulcer*, subileus*, tongue discolouration*, gastrointestinal haemorrhage, dry mouth*, lip ulceration*, parotid duct obstruction*, gastro-oesophageal reflux disease*, gingival hyperplasia*, peritonitis*
General disorders and administration site conditions		
	Common	Fatigue, pyrexia
	Uncommon	Influenza like illness, oedema lower limb*, pain, rigors*, thirst*, weakness*
Metabolism and nutrition disorders		
	Uncommon	Anorexia, hyperlipidaemia, diabetes mellitus*, hypercholesterolaemia*, hypophosphataemia
Skin and subcutaneous tissue disorders		
	Uncommon	Alopecia, contusion*
Hepatobiliary disorders		
	Common	Hepatic function tests abnormal
Cardiac disorders		
	Uncommon	Tachycardia, pulmonary oedema*, ventricular extrasystoles*
Eye disorders		
	Uncommon	Conjunctivitis*, vision blurred*
Musculoskeletal, connective tissue disorders		

	Uncommon	Arthritis*, back pain*, muscle cramps
Neoplasms benign and malignant		
	Uncommon	Skin papilloma* Basal cell carcinoma*, Kaposi's sarcoma*, lymphoproliferative disorder, squamous cell carcinoma*
Psychiatric disorders		
	Uncommon	Abnormal dreams*, delusional perception*
Renal and urinary disorders		
	Common	Increased blood creatinine
	Uncommon	Hematuria*, renal tubular necrosis*, urethral stricture
Reproductive system and breast disorders		
	Uncommon	Impotence*

* 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

Rash has been identified as an adverse drug reaction from post-approval clinical trials, post marketing surveillance and spontaneous reports [84].

The following adverse reactions are attributed to MPA derivatives as a class effect [16-20]:

Infections and Infestations: Serious, sometimes life-threatening infections, including meningitis, infectious endocarditis, tuberculosis, and atypical mycobacterial infection. Polyomavirus associated nephropathy (PVAN), especially due to BK virus infection [82]. Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported (see section 4.4 Special warnings and precautions for use)[80].

Blood and lymphatic system disorders: Neutropenia, pancytopenia. Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives in combination with other immunosuppressive agents (see section 4.4 Special warnings and precautions for use) [81].

Gastrointestinal disorders: Colitis, oesophagitis (including CMV-colitis and -oesophagitis), CMV gastritis, pancreatitis, intestinal perforation, gastrointestinal haemorrhage, gastric ulcers, duodenal ulcers, ileus.

4.9 Overdose

There has been no reported experience of overdosage of Myfortic in humans.

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 [21,22]. This is in large part due to the very high plasma protein binding of MPA, 97% [23]. By interfering with enterohepatic circulation of MPA, bile acid sequestrants, such as cholestyramine, may reduce the systemic MPA exposure [11,12].

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressant (ATC code L04 A A06)

MPA inhibits the proliferation of T- and B lymphocytes more potent than other cells because in contrast to other cell types that can utilise purine salvage pathways [24,25] the lymphocyte proliferation is critically dependent on de novo synthesis. Thus the mode of action is complementary to calcineurin inhibitors which interfere with cytokine transcription and resting T-lymphocytes [26,27].

5.2 Pharmacokinetic properties

Absorption

Following oral administration, mycophenolate sodium is extensively absorbed [12,28]. Consistent with its enteric coated design, the time to maximal concentration of MPA was approximately 1.5 to 2 hours [12]. In vitro studies demonstrated that the enteric coated formulation of Myfortic prevents the release of MPA under acidic conditions as in the stomach [29].

In stable renal transplant patients on ciclosporin for microemulsion based immunosuppression, the gastrointestinal absorption of MPA was 93% and the absolute bioavailability was 72% [28]. Myfortic pharmacokinetics are dose proportional and linear over the studied dose range of 180 to 2,160 mg [1]. Compared to the fasting state, administration 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) [30] which is the most relevant pk parameter linked to efficacy [31]. However there was a 33% decrease in the maximal concentration of MPA (C_{max}) [30].

Distribution

The volume of distribution at steady state for MPA is 50 litres [28]. Both mycophenolic acid and mycophenolic acid glucuronide are highly protein bound, 97% and 82%, respectively [23]. The free MPA concentration may increase under conditions of decreased protein binding sites (uraemia, hepatic failure, hypoalbuminemia, concomitant use of drugs with high protein binding). This may put patients at increased risk of MPA-related adverse effects [23,31-33].

Biotransformation

The half life of MPA is 11.7 hours and the clearance is 8.6 L/hr [28]. MPA is metabolized principally by glucuronyl transferase to form the phenolic glucuronide of MPA, mycophenolic acid glucuronide (MPAG) [24,33,34] MPAG is the predominant metabolite of MPA and does not manifest biologic activity [35,36]. In stable renal transplant patients on ciclosporin for microemulsion based immunosuppression, approximately 28% of the oral Myfortic dose is converted to MPAG by presystemic metabolism [28]. The half life of MPAG is longer than that of MPA, approximately 15.7 hours and its clearance is 0.45 L/hr [12,28].

Elimination

Although negligible amounts of MPA are present in the urine (< 1.0%), the majority of MPA is eliminated in the urine as MPAG [37-39]. MPAG secreted in the bile is available for deconjugation by gut flora. The MPA resulting from this deconjugation may then be reabsorbed [40]. Approximately 6 to 8 hours after Myfortic dosing a second peak of MPA concentration can be measured, consistent with reabsorption of the deconjugated MPA [12,28].

Pharmacokinetics in Renal Transplant Patients on ciclosporin for microemulsion based immunosuppression [72,76]

Shown in the following table are mean pharmacokinetic parameters for MPA following the administration of Myfortic. Single dose Myfortic pharmacokinetics predict multiple dose and chronic dosing Myfortic pharmacokinetics. In the early post transplant period, mean MPA AUC and mean MPA C_{max} was approximately one-half of that measured six months post transplant.

Mean (SD) Pharmacokinetic Parameters for MPA Following Oral Administration of Myfortic to Renal Transplant Patients on Ciclosporin for Microemulsion Based Immunosuppression

Adult single dose n = 24	Dose (oral)	Tmax(hrs)	Cmax (microgram/mL)	AUC 0-∞ (microgram*hr/mL)
	720 mg	2	26.1 (12.0)	66.5 (22.6)
Adult Multiple dose x 6 days BID n=12	Dose (oral)	Tmax (hrs)	Cmax (microgram/mL)	AUC 0-12 (microgram*hr/mL)
	720 mg	2	37.0 (13.3)	67.9 (20.3)
Adult Multiple dose x 28 days BID n = 36 [72,76]	Dose (oral)	Tmax (hrs)	Cmax (microgram/mL)	AUC 0-12 (microgram*hr/mL)
	720 mg	2.5	31.2(18.1)	71.2(26.3)
Adult Chronic, multiple dosing BID (Study ERLB 301) n=48	Dose	Tmax (hrs)	Cmax (microgram/mL)	AUC 0-12 (microgram*hr/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)
Paediatric single dose n=10	Dose	Tmax (hrs)	Cmax (microgram/mL)	AUC 0-∞ (microgram*hr/mL)
	450 mg/m^2	2-2.5	31.9 (18.2)	76.2 (25.2)

Renal Insufficiency

MPA pharmacokinetic appeared to be unchanged over the range of normal to absent renal function [2]. In contrast, MPAG exposure increased with decreased renal function; MPAG exposure being approximately 8 fold higher in the setting of anuria [2]. Clearance of either MPA or MPAG was unaffected by haemodialysis [17]. Free MPA may also significantly increase in the setting of renal failure [41,42]. This may be due to decreased plasma protein binding of MPA in the presence of high blood urea concentration [42].

Hepatic Insufficiency

In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease [42]. 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 [39].

Paediatrics

Limited data are available on the use of Myfortic in children [43]. In the table above the mean (SD) MPA pharmacokinetics are shown for stable paediatric renal transplant patients on ciclosporin microemulsion based immunosuppression [43]. Increased variability of MPA C_{max} and AUC were noted in these paediatric patients compared to adult renal transplant patients [12,43]. Mean MPA AUC at this dose was higher than typically measured in adults receiving 720 mg Myfortic. The mean apparent clearance of MPA was approximately 7.7 L/hr [3]. A Myfortic dose of 200 to 300 mg/m^2 would be expected to result in a MPA AUC of 30 to 50 micrograms hr/mL [43].

Gender

There are no clinically significant gender differences in Myfortic pharmacokinetics [44].

Elderly

Based on preliminary data MPA exposure does not appear to vary to a clinically significant degree by age [44].

5.3 Preclinical safety data

The haematopoetic and lymphoid system were the primary organs affected in toxicology studies conducted with mycophenolate sodium in rats and mice. 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.

The non-clinical toxicity profile of mycophenolate sodium appears to be consistent with adverse events observed in humans exposed to MPA, which now provide safety data of more relevance to the patient population (see section 4.8 Undesirable effects).

Mycophenolate sodium had no effect on fertility of male rats at oral doses up to 40 mg/kg/day [47,48]. The systemic exposure at this dose represents approximately 9 times the clinical exposure at the tested clinical dose of 1.44 g of Myfortic per day. No effects on female fertility were seen up to a dose of 20 mg/kg, a dose at which maternal toxicity and embryotoxicity were already observed [49].

In a teratology study performed with mycophenolate sodium in rats, at a dose as low as 1 mg/kg, malformations in the offspring were observed, including anophthalmia, exencephaly and umbilical hernia [50]. 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 Pregnancy and

lactation). There are no relevant qualitative or quantitative differences in the teratogenic potential of mycophenolate sodium and mycophenolate mofetil.

Single oral doses of MPA are moderately well tolerated in rats (LD_{50} of 350 to 700 mg/kg), well tolerated in mice or monkeys (LD_{50} of more than 1,000 mg/kg), and extremely well tolerated in rabbits (LD_{50} of more than 6,000 mg/kg) [45,46,50].

The genotoxic potential of mycophenolate sodium was determined in five assays. MPA was genotoxic in the mouse lymphoma/thymidine kinase assay, the micronucleus test in V79 Chinese hamster cells and the in vivo mouse micronucleus assay. Mycophenolate sodium was not genotoxic in the bacterial mutation assay or the chromosomal aberration assay in human lymphocytes [51-66]. The lowest dose showing genotoxic effects in a mouse bone marrow micronucleus resulted in approximately 3 times the systemic exposure (AUC or C_{max}) observed in renal transplant patients at the tested clinical dose of 1.44 g of Myfortic per day. There are no relevant qualitative or quantitative differences in the genotoxic potential of mycophenolate sodium and mycophenolate mofetil. It is probable that the mutagenic activity observed was due to a shift in the relative abundance of the nucleotides in the cellular pool used for DNA synthesis.

In a 104-week oral carcinogenicity study in rats, mycophenolate sodium at daily doses up to 9 mg/kg was not tumorigenic. The highest dose tested resulted in approximately 0.6 to 1.2 times the systemic exposure observed in renal transplant patients at the recommended dose of 1.44 g/day [67]. Similar results were observed in a parallel study in rats performed with mycophenolate mofetil [68]. In a 26-week oral carcinogenicity assay in a $P53^{\pm}$ (heterozygous) transgenic mouse model, mycophenolate sodium at daily doses up to 200 mg/kg was not tumorigenic [69]. The highest dose tested was 200 mg/kg, resulting in approximately 5 times the systemic exposure observed in renal transplant patients (1.44 g/day).

6 Pharmaceutical particulars

6.1 List of excipients

Maize starch; povidone (K-30); crospovidone; lactose; colloidal silicon dioxide; magnesium stearate.

The gastro resistant tablet coating consist of hypromellose phthalate/ hydroxypropylmethylcellulose phthalate; titanum dioxide; iron oxide yellow; indigotin.

Information might differ in some countries.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 month.

Information might differ in some countries.

6.4 Special precautions for storage

Do not store above 30°C. Myfortic 180 mg and 360 mg gastro-resistant tablets should be protected from moisture and light. Store in the original package and container.

Information might differ in some countries.

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

6.5 Nature and contents of container

Myfortic 180 mg and 360 mg gastro-resistant tablets:

1 carton contains 20 tablets

1 carton contains 50 tablets

1 carton contains 100 tablets

1 carton contains 120 tablets

1 carton contains 250 tablets

The tablets are packed in aluminium blister pack of 10 tablets.

Information might differ in some countries.

6.6 Instructions for use and handling [77]

Myfortic tablets should not be crushed in order to remain the integrity of the enteric coating (see section 5.2 Pharmacokinetic properties).

Mycophenolate sodium has demonstrated teratogenic effects in rats and rabbits (see section 4.6. Pregnancy and lactation). Avoid inhalation or direct contact with skin or mucous membrane of the powder, in case of crushing Myfortic tablets is necessary.

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