NOVARTIS

MYFORTIC® 180 mg / 360 mg

TABLETS

Document type:	Professional Information
Document status:	Final
Release date:	18 September 2026

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SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

Myfortic® 180 tablet

Myfortic® 360 tablet

Mycophenolic acid (as sodium salt) 180 mg or 360 mg

WARNING 1: CONTRAINDICATIONS

MYFORTIC is contraindicated in pregnancy and lactation, and in women of childbearing potential (WOCBP) who are not using highly effective contraception methods (see **section 4.3** and **4.6**).

WARNING 2: IMMUNOSUPPRESSION: RISK OF INFECTIONS AND MALIGNANCY

Immunosuppression caused by MYFORTIC may result in an increased susceptibility to infection and the development of lymphoma and other malignancies, especially of the skin.

Only medical practitioners experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should prescribe MYFORTIC.

Patients receiving MYFORTIC should be managed in facilities equipped with adequate laboratory and supportive medical resources.

The medical practitioner responsible for maintenance therapy should have complete information as required for the follow-up of the patient.

WARNING 3: TERATOGENICITY

MYFORTIC is a potent teratogenic and mutagenic medicine.

Congenital malformations and spontaneous abortions have been reported with the use of MYFORTIC in pregnancy.

Women of childbearing potential (WOCBP) must have two negative medical practitioner or laboratory supervised serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL (IU/L); and the second test should be performed 8-10 days after the first one and 24 hours before MYFORTIC therapy is initiated. Repeat pregnancy tests should be performed during routine follow-up visits.

Women of childbearing potential (WOCBP) should use two reliable forms of contraception simultaneously, including at least one highly effective method, before MYFORTIC therapy is initiated, during therapy, and for 90 days following discontinuation of therapy, unless abstinence is the chosen method of contraception.

Sexually active men are recommended to use condoms during treatment and for 90 days after cessation of treatment. Condom use applies both for reproductively competent and vasectomised men, because the risk associated with the transfer of seminal fluid also apply to men who have had a vasectomy.

Female partners of male patients are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of MYFORTIC.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Myfortic® 180: Each enteric film-coated tablet contains 192,4 mg mycophenolate sodium, which is equivalent to 180 mg mycophenolic acid.

Myfortic® 360: Each enteric film-coated tablet contains 384,8 mg mycophenolate sodium, which is equivalent to 360 mg mycophenolic acid.

Contains sugar:

Myfortic® 180: Lactose 45,0 mg

Myfortic® 360: Lactose 90,0 mg

For full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Myfortic® 180: Lime green, round, bevelled edged film/enteric-coated tablet marked “C” on the one side.

Myfortic® 360: Pale orange-red, ovaloid film/enteric-coated tablet marked “CT” on the one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MYFORTIC is indicated in combination with ciclosporin for microemulsion and corticosteroids for the prevention 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.
- MYFORTIC should be initiated in *de novo* patients within 48 hours following transplantation.
- The recommended dose is 720 mg (four 180 mg or two 360 mg MYFORTIC tablets) administered twice daily (1 440 mg daily dose).
- MYFORTIC can be taken with or without food.
- **MYFORTIC tablets should not be crushed in order to retain the integrity of the enteric coating** (see **section 5.2**).
- Avoid inhalation or direct contact with skin or mucous membrane of the powder, in case of accidental breaking of the MYFORTIC tablets.

Special populations

Elderly population:

No dose adjustment is required in this patient population.

Renal impairment:

No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively (see **section 5.2**). Patients with severe chronic renal impairment (glomerular filtration rate < 25 $mL \cdot min^{-1} \cdot 1{,}73\ m^{-2}$) should be carefully followed up.

Paediatric population:

Safety and efficacy in paediatric patients have not been established.

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

For oral use.

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.
- Pregnancy and lactation (see **section 4.6**).
- MYFORTIC should not be used in women of childbearing potential (WOCBP)

who are not using highly effective contraception methods.

4.4 Special warnings and precautions for use

Patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT)

MYFORTIC is an IMPDH (inosine monophosphate dehydrogenase) inhibitor. 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.

Women of childbearing potential (WOCBP), pregnancy and breastfeeding

Use of MYFORTIC during pregnancy is associated with an increased risk of pregnancy loss including spontaneous abortion and congenital malformations (see **section 4.6**).

It is recommended that MYFORTIC therapy should not be initiated in women of childbearing potential (WOCBP) until a negative pregnancy test has been obtained.

For information on use in pregnancy and contraceptive requirements, (see **section 4.6**).

MYFORTIC should not be used during breastfeeding (see **section 4.6**).

Malignancies

Patients receiving immunosuppressive regimens involving combinations of medicines, 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.

Infections

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**). Reactivation of hepatitis B (HBV) or hepatitis C (HCV) has been reported in patients treated with MYFORTIC. Monitoring infected patients for clinical and laboratory signs of active HBV or HCV infection is recommended.

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with MYFORTIC (see **section 4.8**). The reported cases generally had risk factors for PML, including immunosuppressant therapies and impairment of immune functions. In immunosuppressed patients, medical practitioners 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**). 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.

Blood dyscrasias

Patients receiving MYFORTIC should be monitored for blood dyscrasias (e.g. neutropenia or anaemia - 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 dyscrasias occur (e.g. neutropenia with absolute neutrophil count < 1,5 x 10^3/µL 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 MYFORTIC in combination with other immunosuppressive agents (see **section 4.8**). The mechanism for MYFORTIC MPA derivatives induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppressive regimen are 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 MYFORTIC therapy. 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 minimise the risk of graft rejection.

Vaccinations

Patients should be advised that during treatment with MYFORTIC, 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.

Gastrointestinal disorders

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.

Combination with other medicines

MYFORTIC has been administered in combination with the following medicines 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.

Sodium warning:

MYFORTIC 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.

Lactose warning:

MYFORTIC tablets contain lactose, which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance e.g., galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take MYFORTIC.

4.5 Interaction with other medicines and other forms of Interaction

Observed interactions resulting in a concomitant use not recommended

Azathioprine:

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

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 **section 4.4**).

Observed interactions to be considered

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 medicines to compete for tubular secretion, resulting in a further increase in the concentration of both MPAG and aciclovir. In this situation patients should be carefully followed up.

Gastroprotective medicines

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. Caution should be used when co-administering antacids (containing magnesium and aluminium hydroxide) with MYFORTIC.

Proton Pump inhibitors:

No changes in the pharmacokinetics of MPA were observed following concomitant administration of MYFORTIC and pantoprazole.

Anticipated interactions to be considered

Cholestyramine and medicines that interfere with enterohepatic circulation:

Due to its capacity to block the enteric circulation of medicines, cholestyramine may decrease the systemic exposure of MPA. Caution should be used when co-administering cholestyramine or medicines 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. However, in patients with renal impairment in which MYFORTIC and ganciclovir are co-administered 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 ciclosporin for microemulsion 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.

Oral contraceptives:

Oral contraceptives undergo oxidative metabolism while MYFORTIC is metabolised by glucuronidation. A clinically significant effect of oral contraceptives on MYFORTIC pharmacokinetics is not anticipated. 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.

Ciclosporin A:

When studied in stable renal transplant patients, ciclosporin A pharmacokinetics were unaffected by steady state dosing of MYFORTIC.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

Effective contraception must be used before beginning MYFORTIC therapy, during therapy, and for six weeks following discontinuation of therapy (see **section 4.5**).

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. MYFORTIC is teratogenic in animals. MYFORTIC therapy should not be initiated until a negative pregnancy test has been obtained. Patients should be instructed to consult their medical practitioner immediately should pregnancy occur.

Congenital malformations that have been reported with MYFORTIC include outer ear and other facial abnormalities including cleft lip and palate, congenital diaphragmatic hernia, anomalies of the distal limbs, heart, oesophagus and kidney. Use of MYFORTIC during pregnancy was also reported to be associated with increased risk of spontaneous abortion.

Breastfeeding

It is not known whether MPA (mycophenolic acid) as contained in MYFORTIC is excreted in human milk.

MYFORTIC should not be used during breastfeeding (see **section 4.4**).

Because many drugs are excreted in human milk, and of the potential for serious adverse reactions in breastfed newborns/infants a decision should be made whether to abstain from breastfeeding while on treatment and during 6 weeks after stopping the treatment or to abstain from using the medicinal product, taking into account the importance of the drug to the mother.

Fertility

Mycophenolate sodium had no effect on fertility of male rats at oral doses up to 40 mg/kg/day. 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 embryo toxicity were already observed.

Male patients

Sexually active men are recommended to use condoms during treatment, and for a total of 13 weeks after their last dose of MYFORTIC. In addition, female partners of the male patients are recommended to use highly effective contraception during treatment of the patient, and for a total of 13 weeks after the patient’s last dose of MYFORTIC.

Semen donation:

Based on animal data, men should not donate semen during therapy and for 90 days following discontinuation of MYFORTIC.

4.7 Effects on ability to drive and use machines

MYFORTIC has minor influence on psychomotor performance but may cause dizziness.

Patients should be cautioned not to drive or use machines until they know how MYFORTIC affects them.

4.8 Undesirable effects

a. Summary of the safety profile

The following side effects cover adverse medicine reactions from two controlled clinical trials.

The very common (≥ 10 %) adverse medicine reactions associated with the administration of MYFORTIC in combination with ciclosporin for microemulsion and corticosteroids, include leucopenia and diarrhoea.

Malignancies:

Patients receiving immunosuppressive regimens involving combinations of medicines, including MPA (mycophenolic acid), are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see **section 4.4***)*.

Overall rates of malignancies observed in MYFORTIC clinical trials are as follows: 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.

Opportunistic infections:

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 medicine 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 medicine reactions:

The table 1 below contains adverse medicine 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.

b. Tabulated summary of adverse drug reactions from clinical trials

Adverse reactions 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 Adverse drug reactions possibly or probably related to MYFORTIC reported in the two phase-III pivotal trials

Infections and infestations	Very common	Viral, bacterial and fungal infections
	Common	Upper respiratory tract infections, pneumonia
	Uncommon	Wound infection, sepsis*, osteomyelitis*

Blood and lymphatic system disorders	Very common	Leucopenia
	Common	Anaemia, thrombocytopenia
	Uncommon	Lymphocele*, lymphopenia*, neutropenia*, lymphadenopathy*
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Tremor, insomnia*
Respiratory, thoracic and mediastinal disorders	Common	Cough, dyspnoea, dyspnoea exertional
	Uncommon	Interstitial lung disease including fatal pulmonary fibrosis, pulmonary congestion*, wheezing*
Gastrointestinal disorders	Very common	Diarrhoea
	Common	Abdominal distension, abdominal pain, constipation, dyspepsia, flatulence, gastritis, loose stools, nausea, vomiting
	Uncommon	Abdominal tenderness, pancreatitis, eructation, halitosis*, ileus*,

		oesophagitis*, peptic ulcer*, subileus*, gastrointestinal haemorrhage, dry mouth*, lip ulceration*, parotid duct obstruction*, gastro-oesophageal reflux disease*, gingival hyperplasia*, peritonitis*
General disorders and administration site conditions	Common	Fatigue, oedema peripheral, pyrexia
	Uncommon	Influenza like illness,oedema lower limb*, pain, rigors*, weakness*
Metabolism and nutrition disorders	Very common	Hypocalcaemia, hypokalaemia, hyperuricaemia
	Common	Hyperkalaemia, hypomagnesaemia
	Uncommon	Anorexia, hyperlipidaemia, diabetes mellitus*, hypercholesterolaemia*, hypophosphataemia

Skin and subcutaneous tissue disorders	Uncommon	Alopecia, contusion*, acne, pruritus
Hepatobiliary disorders	Common	Hepatic function tests abnormal
Vascular disorders	Very common	Hypertension, hypotension
	Common	Aggravated hypertension
Cardiac disorders	Uncommon	Tachycardia, pulmonary oedema*
Eye disorders	Uncommon	Conjunctivitis*, vision blurred*
Musculoskeletal, connective tissue and bone disorders	Common	Arthralgia, asthenia, myalgia
	Uncommon	Back pain*, muscle cramps
Neoplasms benign and malignant	Uncommon	Skin papilloma*, Basal cell carcinoma*, Kaposi's sarcoma*, lymphoproliferative disorder, squamous cell carcinoma*
Psychiatric disorders	Common	Anxiety
	Uncommon	Delusional perception*
Renal and urinary disorders	Common	Increased blood creatinine
	Uncommon	Haematuria*, renal tubular necrosis*, urethral stricture

*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

Immune system disorders:

Hypersensitivity reactions (including anaphylaxis).

Skin and subcutaneous tissue disorders:

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

General disorders and administration site conditions:

De novo purine synthesis inhibitors-associated acute inflammatory syndrome.

The following adverse reactions have not been observed in the context of the two phase-III randomised clinical trials with MYFORTIC, but are attributed to mycophenolic acid compounds as a class effect. The side effects listed below under each system organ class have been reported but frequencies are unknown.

Gastrointestinal disorders:

Colitis, CMV gastritis, intestinal perforation, duodenal ulcers.

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.

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported (see **section 4.4**).

Blood and lymphatic system disorders:

Agranulocytosis, pancytopenia, neutropenia. Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MYFORTIC in combination with other immunosuppressive agents (see **section 4.4**).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity. Symptomatic and supportive management should be used during overdose with MYFORTIC.

If blood dyscrasias occur (e.g. neutropenia with absolute neutrophil count < 1,5 x 10^3 / µL or anaemia) it may be appropriate to interrupt or discontinue MYFORTIC (see **section 4.4***).*

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

A 34. Other

Pharmacotherapeutic group: immunosuppressant, ATC code: L04AA06

Mycophenolic acid (MPA) inhibits the proliferation of T- and B lymphocytes more potently than other cells because in purines in contrast to other cell types that can utilise salvage pathways, 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.

5.2 Pharmacokinetic properties

Absorption:

Following oral administration, mycophenolate sodium is extensively absorbed. The time to maximal concentration of MPA was approximately 1,5 to 2 hours which is consistent with the enteric-coated design. In vitro studies demonstrated that the enteric-coated formulation of mycophenolate sodium prevents the release of MPA under acidic conditions (e.g. in the stomach).

In stable renal transplant patients on ciclosporin for microemulsion based immunosuppression, the gastrointestinal absorption of MPA was 93 % and the absolute bioavailability was 72 %. Mycophenolate pharmacokinetics are dose proportional and linear over the studied dose range of 180 to 2 160 mg. Compared to the fasting state, administration of the enteric coated 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 (C_{max}).

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 medicines with high protein binding). This may put patients at increased risk of MPA-related adverse effects.

Metabolism:

The half-life of MPA is 11,7 hours and the clearance is 8,6 L/hr. 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 biologic activity. In stable renal transplant patients on ciclosporin for microemulsion based immunosuppression, approximately 28 % of the oral mycophenolate dose is converted to MPAG by pre-systemic metabolism. The half-life of MPAG is longer than that of MPA, approximately 15,7 hours and its clearance is 0,45 L/hr.

Elimination:

Although small amounts of MPA are present in the urine (< 3,0 %), 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 to 8 hours after mycophenolate dosing a second peak of MPA concentration can be measured, consistent with reabsorption of the deconjugated MPA.

Pharmacokinetics in renal transplant patients on ciclosporin for microemulsion based immunosuppression:

The table below shows the mean pharmacokinetic parameters for MPA following the administration of mycophenolate. 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)**	**T_{max} (hr)**	**C_{max} (ug/mL)**	**AUC 0-∞ (ug*hr/mL)**
	720 mg	2	26,1 (12,0)	66,5 (22,6)
Adult multiple dose x 6 days BID n =12	**Dose (oral)**	**T_{max} (hr)**	**C_{max} (ug/mL)**	**AUC 0-12 (ug*hr/mL)**
	720 mg	2	37,0 (13,3)	67,9 (20,3)
Adult multiple dose x 28 days BID n = 36	**Dose (oral)**	**T_{max} (hr)**	**C_{max} (ug/mL)**	**AUC 0-12 (ug*hr/mL)**
	720 mg	2,5	31,2	71,2 (26,3)

			(18,1)	
Adult chronic, multiple dosing BID n = 48	**Dose**	**T_{max} (hr)**	**C_{max} (ug/mL)**	**AUC 0-12 (ug*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)

Renal Insufficiency:

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 Insufficiency:

There are no studies in hepatic insufficiency.

Paediatrics:

Limited data are available on the use of mycophenolate sodium in children.

Gender:

There are no clinically significant gender differences in MYFORTIC pharmacokinetics.

Elderly:

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: maize starch, povidone (K-30), crospovidone, lactose, colloidal silicon dioxide and magnesium stearate.

Tablet coating: hypromellose phthalate/ hydroxypropylmethylcellulose phthalate, titanium dioxide, iron oxide yellow and indigotine.

Contains sugar: Lactose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

The tablets should be protected from moisture.

Store in the original package and container.

6.5 Nature and contents of container

The tablets are packed in PA/AL/PVC (polyamide/ aluminium/ polyvinylchloride) and aluminium foil blister packs of 20’s, 50’s, 100’s, 120’s or 250’s.

The outer carton is a printed cardboard box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd.

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg

2090

Tel. (011) 347 6600

8 REGISTRATION NUMBER(S)

Myfortic® 180: 37/34/0158

Myfortic® 360: 37/34/0159

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 April 2012

10 DATE OF REVISION OF THE TEXT

18 September 2026

® Registered trademark

MYFORTIC® 180		**MYFORTIC® 360**	
Namibia: 15/34/0073	NS2	Namibia: 15/34/0074	NS2
Botswana: BOT1101803A	S2	Botswana: BOT1101804A	S2

Manufacturer:

Novartis Pharma Produktions GmbH

Oeflingerstrasse 44, 79664 Wehr, Germany