PROFESSIONAL INFORMATION

WARNING: CARCINOGENICITY

Increased susceptibility to infection and the possible development of lymphoma and other malignancies, especially of the skin, may result from immuno-suppression. Only medical practitioners experienced in immuno-suppressive therapy and management of renal, cardiac or hepatic transplant patients should prescribe MYCOPHENOLATE TEVA. Patients receiving the medicine should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The medical practitioner responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

WARNING: TERATOGENICITY

Mycophenolate is powerfully teratogenic and mutagenic. Congenital malformations and spontaneous abortions have been reported with use of mycophenolate in pregnancy. Women of childbearing potential must have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/ml; the second test should be performed 8-10 days after the first one and immediately before starting treatment with MYCOPHENOLATE TEVA. Repeat pregnancy tests should be performed during routine follow-up visits.

Women of childbearing potential should use two reliable forms of contraception simultaneously, including at least one highly effective method, before beginning MYCOPHENOLATE TEVA therapy, during therapy, and for six weeks following discontinuation of therapy; unless abstinence is the chosen method of contraception.

Sexually active men are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies both for reproductively competent and vasectomised men, because the risks 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 MYCOPHENOLATE TEVA.

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

MYCOPHENOLATE TEVA 500 (film-coated tablets)

MYCOPHENOLATE TEVA 250 (capsules)

Sugar free.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

MYCOPHENOLATE TEVA 500: Each film-coated tablet contains 500 mg mycophenolate mofetil.

MYCOPHENOLATE TEVA 250: Each capsule contains 250 mg mycophenolate mofetil.

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

3. PHARMACEUTICAL FORM:

MYCOPHENOLATE TEVA 500: Pale purple, oval shaped film-coated tablet, debossed with ‘M500’ on one side and plain on the other side.

MYCOPHENOLATE TEVA 250: Hard gelatin capsule size 1, filled with a white to off-white powder. Cap: light blue opaque printed ‘M’ axially in black ink. Body: caramel opaque, printed ‘250’ axially in black ink.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

MYCOPHENOLATE TEVA is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, hepatic or cardiac transplants.

MYCOPHENOLATE TEVA should be used concomitantly with ciclosporin and corticosteroids.

4.2 Posology and method of administration:

Posology:

Dosage for prophylaxis of renal rejection:

Adults: The initial dose of **MYCOPHENOLATE TEVA** should be given orally, within 72 hours following transplantation. The recommended dose is 1,0 g, administered twice a day (daily dose of 2 g) is recommended for renal transplant patients. Although a dose of 1,5 g, administered twice daily (daily dose of 3 g), was used in clinical trials and was shown to be safe and effective, no efficacy advantage could be established for renal transplant patients. Patients receiving 2 g per day of **MYCOPHENOLATE TEVA**, demonstrated an overall better safety profile than patients receiving 3 g per day of **MYCOPHENOLATE TEVA**.

Children (aged 3 months to 18 years): Patients with a body surface area of 1,25 to 1,5 m^2 may be prescribed **MYCOPHENOLATE TEVA** capsules at a dose of 750 mg twice daily (1,5 g daily dose). Patients with a body surface area > 1,5 m^2 may be prescribed **MYCOPHENOLATE TEVA** tablets at a dose of 1 g twice daily (2 g daily dose).

Standard dosage for prophylaxis of cardiac rejection:

Adults: A dose of 1,5 g administered orally, twice a day (daily dose of 3 g), is recommended for use in cardiac transplant patients. The initial dose should be given within 5 days following transplantation.

Children: No data are available for paediatric cardiac transplant patients.

Standard dosage for prophylaxis of hepatic rejection:

Adults: Administration should be initiated as soon as possible after transplantation. A dose of 1,5 g administered orally, twice a day (daily dose of 3 g), is recommended for use in hepatic transplant patients.

Children: No data are available for paediatric hepatic transplant patients.

Standard dosage for treatment of first or refractory renal rejection:

Adults: A dose of 1,5 g administered orally, twice a day (daily dose of 3 g), is recommended for management of first or refractory renal rejection.

Children: No data are available for treatment of first or refractory renal rejection in paediatric renal transplant patients.

Special dosage instructions:

Use in severe renal impairment: In patients with severe chronic renal impairment (glomerular filtration rate < 25 ml/min/1,73 m^2), outside of the immediate post-transplant period, doses greater than 1 g, administered twice a day, should be avoided. These patients should also be carefully observed. No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment.

***Patients with delayed renal graft function post-transplant*:** No dose adjustments are needed in patients experiencing delayed renal graft function post-operatively.

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

Elderly: The recommended dose of 1 g, administered twice a day for renal transplant patients and 1,5 g twice a day for cardiac and hepatic transplant patients, is appropriate for elderly patients. See **section 4.4**.

Other considerations for use:

If neutropenia develops (absolute neutrophil count < 1,3 x 10^3/µl), dosing with **MYCOPHENOLATE TEVA** should be interrupted or the dose reduced.

Method of administration:

MYCOPHENOLATE TEVA tablets and capsules should be taken on an empty stomach.

Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits, **MYCOPHENOLATE TEVA** tablets and capsules should not be crushed or opened, to avoid inhalation or direct contact with skin or mucous membranes of the powder contained in **MYCOPHENOLATE TEVA** tablets/capsules. If such occurs, wash thoroughly with soap and water; rinse eyes with plain water.

4.3 Contraindications:

- Hypersensitivity to mycophenolate mofetil or mycophenolic acid or any of the excipients of **MYCOPHENOLATE TEVA**.
- Pregnancy and breastfeeding.
- Women of childbearing potential not using highly effective methods of contraception.
- Women of childbearing potential without providing a pregnancy test result to rule out unintended use in pregnancy.

4.4 Special warnings and precautions for use:

Malignancies: Patients treated with **MYCOPHENOLATE TEVA** as part of an immuno-suppressive regimen have an increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk seems to be related to both the intensity and duration of immuno-suppression rather than to the use of any specific medicine. (See boxed warning included at the start of the package insert). Lymphoproliferative disease or lymphoma developed in 0,6 % of patients receiving mycophenolate (2 g or 3 g daily) in combination with other immunosuppressants in controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients followed for at least 1 year. Non-melanoma skin carcinomas occurred in 3,6 % of patients; other types of malignancy occurred in 1,1 % of patients.
To minimise any risk of skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using sunscreen with a high protection factor.

Opportunistic infections: Patients on **MYCOPHENOLATE TEVA** are at increased risk of opportunistic infections; the risk increased with total immunosuppressive load. Such infections include latent viral reactivation, such as hepatitis B or hepatitis C reactivation and infections caused by polyomaviruses (BK virus associated nephropathy, JC virus associated progressive multifocal leukoencephalopathy PML). Cases of hepatitis due to reactivation of hepatitis B or hepatitis C have been reported in carrier patients treated with immunosuppressants.

These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. **MYCOPHENOLATE TEVA** 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.

The most common opportunistic infections in patients receiving mycophenolate (2 g or 3 g daily) with other immunosuppressants in controlled clinical trials of renal (2 g data), cardiac and hepatic transplant patients followed for at least 1 year were candida mucocutaneous, cytomegalovirus (CMV) viraemia/syndrome and Herpes simplex. The proportion of patients with CMV viraemia/syndrome was 13,5 %.

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

There have been published reports of bronchiectasis in adults and children who received mycophenolate mofetil as in **MYCOPHENOLATE TEVA** in combination with other immunosuppressants. In some of these cases switching mycophenolate mofetil to another immunosuppressant resulted in improvement in respiratory symptoms. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect on the lung. There have also been isolated reports of interstitial lung disease and pulmonary fibrosis, some of which were fatal (see **section 4.8**). It is recommended that patients who develop persistent pulmonary symptoms, such as cough and dyspnoea, are investigated.

Blood and immune system: Patients treated with **MYCOPHENOLATE TEVA** should be closely monitored for neutropenia. The development of neutropenia can possibly be related to treatment with

MYCOPHENOLATE TEVA, the use of concomitant medicines, viral infections, or a combination of these causes. Cytopenias, including leucopenia, anaemia, thrombocytopenia and pancytopenia, are known risks associated with **MYCOPHENOLATE TEVA** and may lead or contribute to the occurrence of infections and haemorrhages. Agranulocytosis and neutropenia have been reported; therefore, regular monitoring of patients taking **MYCOPHENOLATE TEVA** is advised.

Patients treated with **MYCOPHENOLATE TEVA** should have complete blood counts done, weekly during the first month, twice monthly for the second and third months of treatment, then monthly throughout the first year of treatment.
If neutropenia develops (absolute neutrophil count < 1,3 x 10^3/µl) dosing with **MYCOPHENOLATE TEVA** should be interrupted, or the dose of **MYCOPHENOLATE TEVA** should be reduced, and these patients should be monitored carefully.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate mofetil as in **MYCOPHENOLATE TEVA** in combination with other immunosuppressants. The mechanism for mycophenolate mofetil induced PRCA is unknown. PRCA may resolve with dose reduction or cessation of **MYCOPHENOLATE TEVA** therapy. Changes to **MYCOPHENOLATE TEVA** therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimise the risk of graft rejection (see **section 4.8**).

Isolated cases of abnormal neutrophil morphology, including the acquired Pelger-Huet anomaly, have been observed in patients treated with mycophenolate mofetil. These changes are not associated with impaired neutrophil function. These changes may suggest a ‘left shift’ in the maturity of neutrophils in haematological investigations, which may be mistakenly interpreted as a sign of infection in immunosuppressed patients such as those that receive **MYCOPHENOLATE TEVA**.

Patients treated with **MYCOPHENOLATE TEVA** should be instructed to immediately report any evidence of infection, unexpected bruising, bleeding, or any other manifestation consistent with bone marrow depression that they may experience.

Live vaccinations: Patients should be made aware that during treatment with **MYCOPHENOLATE TEVA**, vaccinations may be less effective and the use of live attenuated vaccines should be avoided due to the increased risk of infection. Influenza vaccination with killed virus may be of value.

Gastrointestinal disorders**:** Patients with active serious digestive system disease should be treated with caution with **MYCOPHENOLATE TEVA** due to the increased risk of digestive system adverse events, including infrequent cases of gastrointestinal ulceration, haemorrhage or perforation associated with **MYCOPHENOLATE TEVA** administration.
Mouth, oesophageal, gastric, duodenal, and intestinal ulcers often complicated by haemorrhage, as well as hematemesis, melaena, and haemorrhagic forms of gastritis and colitis have been reported. Endoscopic investigation of patients with mycophenolate mofetil-related diarrhoea have revealed isolated cases of intestinal villous atrophy.

MYCOPHENOLATE TEVA should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmillar syndrome as mycophenolic acid (MPA) is a selective, non-competitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH).

Renal impairment: In renal transplant patients with severe chronic renal impairment administration of doses greater than 1 g twice daily should be avoided and they should be carefully monitored. No dosage adjustment is recommended in patients with delayed renal graft function post-transplant, however, they should be carefully monitored as increased mycophenolic acid glucuronide (MPAG)

concentrations have been reported as well as increased incidence of some adverse events (anaemia, thrombocytopenia, hyperkalaemia) as compared with patients without delayed graft function. No data is available for treatment of cardiac transplant patients with severe chronic renal impairment.

Interactions: Caution should be exercised when switching combination therapy from regimens containing immunosuppressants, which interfere with MPA enterohepatic recirculation e.g. ciclosporin to others devoid of this effect e.g. tacrolimus, sirolimus, belatacept, or vice versa, as this might result in changes of MPA exposure. Medicines which interfere with MPA's enterohepatic cycle (e.g. cholestyramine, antibiotics), should be used with caution due to their potential to reduce the plasma level and efficacy of **MYCOPHENOLATE TEVA** (see also **section 4.5**). Therapeutic monitoring of MPA may be appropriate when switching combination therapy (e.g. from ciclosporin to tacrolimus or vice versa) or to ensure adequate immunosuppression in patients with high immunological risk (e.g. risk of rejection, treatment with antibiotics, addition or removal of an interacting medicine).
It is recommended that **MYCOPHENOLATE TEVA** should not be administered concomitantly with azathioprine because such concomitant administration has not been studied.
The risk/benefit ratio of **MYCOPHENOLATE TEVA** in combination with tacrolimus or sirolimus has not been established (see also **section 4.5**).

Paediatrics: The type and frequency of adverse reactions were generally similar to those observed in adult patients at their recommended doses. However, the following treatment-related adverse events were more frequent in the paediatric population, particularly in children under 6 years of age, when compared to adults: diarrhoea, sepsis, leucopenia, anaemia and infection.

Elderly (≥ 65 years): Elderly patients may be at an increased risk of adverse events due to immunosuppression compared to younger individuals.

Elderly patients receiving **MYCOPHENOLATE TEVA** as part of a combination immunosuppressive regimen, may be at increased risk of certain infections (including cytomegalovirus tissue invasive disease) and possibly gastrointestinal haemorrhage and pulmonary oedema, compared to younger individuals.

Teratogenic effects: **MYCOPHENOLATE TEVA** is a powerful human teratogen. Spontaneous abortion (rate of 45-49 %) and congenital malformations (estimated rate of 23-27 %) have been reported following mycophenolate mofetil exposure during pregnancy. It is, therefore, contraindicated in pregnancy. Female patients of childbearing potential should be made aware of the risks and follow the recommendations provided in **section 4.6** prior to, during, and after therapy with **MYCOPHENOLATE TEVA**. Physicians should ensure that women taking **MYCOPHENOLATE TEVA** understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult their physican if there is a possibility of pregnancy.

Contraception: Because of clinical evidence showing a high risk of abortion and congenital malformations when mycophenolate mofetil as in **MYCOPHENOLATE TEVA** 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 (see **section 4.3**) before starting **MYCOPHENOLATE TEVA** 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**).

De novo purine synthesis inhibitors: *De novo* purine synthesis inhibitors-associated acute inflammatory syndrome has been described from post-marketing experience as a paradoxical pro-inflammatory reaction associated with mycophenolate mofetil and mycophenolic acid as in **MYCOPHENOLATE TEVA**, characterised by fever, arthralgia, arthritis, muscle pain and elevated inflammatory markers. Literature case reports showed rapid improvement following discontinuation of the **MYCOPHENOLATE TEVA**.

Additional precautions: Patients should not donate blood during **MYCOPHENOLATE TEVA** therapy or for at least 6 weeks following discontinuation of **MYCOPHENOLATE TEVA**. Men should not donate semen during **MYCOPHENOLATE TEVA** therapy or for 90 days following discontinuation of **MYCOPHENOLATE TEVA**.

4.5 Interaction with other medicines and other forms of interaction:

Immunosupressants such as azathioprine, chlorambucil, corticosteroids, glucocorticoids, ciclophosphamide, mercaptopurine, tacrolimus:

Co-administration with **MYCOPHENOLATE TEVA** may lead to an increased risk of development of lymphomas and other malignancies of the skin or increased susceptibility to infection due to the increase in intensity and duration of immunosuppression.

Unlike ciclosporin, tacrolimus delays the elimination of **MYCOPHENOLATE TEVA** by impairing the conversion of MPA to MPAG. For patients on tacrolimus, the dose of **MYCOPHENOLATE TEVA** should not exceed 1 g twice a day. Patients should be carefully observed and managed appropriately.

Exposure to tacrolimus concomitantly administered with **MYCOPHENOLATE TEVA** had no effect on the AUC or Cmax of MPA in liver and kidney transplant recipients. In renal transplant patients the tacrolimus concentration did not appear to be altered by **MYCOPHENOLATE TEVA**.

In hepatic transplant patients there was an increase of approximately 20 % in tacrolimus AUC when multiple doses of **MYCOPHENOLATE TEVA** (1,5 g twice daily) were administered to patients taking tacrolimus.

Aciclovir:

May compete with MPAG for tubular secretion, possibly resulting in increased concentrations of both MPAG and the antiviral medicine in the blood. This effect may be compounded in patients with renal insufficiency as MPAG and aciclovir concentrations are increased in the presence of renal impairment. Higher aciclovir plasma concentrations were observed when mycophenolate mofetil as in **MYCOPHENOLATE TEVA** was administered with aciclovir in comparison to the administration of aciclovir alone. The changes in MPAG (the phenolic glucuronide of MPA) pharmacokinetics (MPAG increased by 8 %) were minimal and are not considered clinically significant. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are aciclovir concentrations, the potential exists for **MYCOPHENOLATE TEVA** and aciclovir, or its prodrugs, e.g. valaciclovir, to compete for tubular secretion and further increases in concentrations of both substances may occur.

Ganciclovir:

Based on the results of a single dose administration study of recommended doses of oral mycophenolate mofetil and intravenous ganciclovir and the known effects of renal impairment on the pharmacokinetics of mycophenolate mofetil (see **section 4.2**) and ganciclovir, it is anticipated that co-administration of these medicines (which compete for mechanisms of renal tubular secretion) will result in increases in MPAG and ganciclovir concentration. No substantial alteration of MPA pharmacokinetics is anticipated and **MYCOPHENOLATE TEVA** dose adjustment is not required. In patients with renal impairment in which **MYCOPHENOLATE TEVA** and ganciclovir or its prodrugs, e.g. valganciclovir, are

co-administered the dose recommendations for ganciclovir should be observed and patients monitored carefully.

Antacids and proton pump inhibitors (PPIs):

Decreased mycophenolic acid (MPA) exposure has been observed when antacids, such as magnesium and aluminium hydroxides, and PPIs, including lansoprazole and pantoprazole, were administered with mycophenolate mofetil as in **MYCOPHENOLATE TEVA**. When comparing rates of transplant rejection or rates of graft loss between mycophenolate mofetil patients taking PPIs versus mycophenolate mofetil patients not taking PPIs, no significant differences were seen. This data supports extrapolation of this finding to all antacids because the reduction in exposure when mycophenolate mofetil was co-administered with magnesium and aluminium hydroxides is considerably less than when mycophenolate mofetil was co-administered with PPIs.

Medicines that interfere with enterohepatic recirculation (e.g. cholestyramine, ciclosporin A, antibiotics)

Caution should be used with medicines that interfere with enterohepatic recirculation because of their potential to reduce the efficacy of mycophenolate mofetil as in **MYCOPHENOLATE TEVA**.

Cholestyramine:

Following single dose administration of 1,5 g of mycophenolate mofetil to normal healthy patients pre-treated with 4 g three times a day (TID) of cholestyramine for 4 days, there was a 40 % reduction in the AUC of MPA (see **section 4.4** and **section 5.2**). Caution should be used during concomitant administration because of the potential to reduce efficacy of mycophenolate mofetil.

Ciclosporin A:

Ciclosporin A (CsA) pharmacokinetics are unaffected by mycophenolate mofetil. In contrast, if concomitant CsA treatment is stopped, an increase in MPA AUC of around 30 % should be expected. CsA interferes with MPA enterohepatic recycling, resulting in reduced MPA exposures by 30-50 % in

renal transplant patients treated with mycophenolate mofetil and CsA compared with patients receiving sirolimus or belatacept and similar doses of mycophenolate mofetil (see also **section 4.4**). Conversely, changes of MPA exposure should be expected when switching patients from CsA to one of the immunosuppressants which does not interfere with MPA's enterohepatic cycle.

Antibiotics:

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

Ciprofloxacin and amoxicillin plus clavulanic acid:

Reductions in pre-dose (trough) MPA concentrations of about 50 % have been reported in renal transplant recipients in the days immediately following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. This effect tended to diminish with continued antibiotic use and to cease within a few days of their discontinuation. The change in pre-dose level may not accurately represent changes in overall MPA exposure. Therefore, a change in the dose of **MYCOPHENOLATE TEVA** should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

Norfloxacin and metronidazole:

In healthy volunteers, no significant interaction was observed when mycophenolate mofetil was concomitantly administered with norfloxacin and metronidazole separately. However, norfloxacin and metronidazole combined reduced the MPA exposure by approximately 30 % following a single dose of mycophenolate mofetil.

Trimethoprim/sulfamethoxazole:

No effect on the bioavailability of MPA was observed.

Medicines that affect glucuronidation (e.g. isavuconazole, telmisartan):

Concomitant administration of medicines affecting glucuronidation of MPA may change MPA exposure. Caution is therefore recommended when administering these medicines concomitantly with **MYCOPHENOLATE TEVA**.

Isavuconazole:

An increase of MPA AUC(0-∞) by 35 % was observed with concomitant administration of isavuconazole.

Telmisartan:

Concomitant administration of telmisartan and mycophenolate mofetil resulted in an approximately 30 % decrease of MPA concentrations. Telmisartan changes MPA's elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression, which in turn results in an enhanced UGT1A9 expression and activity. When comparing rates of transplant rejection, rates of graft loss or adverse event profiles between mycophenolate mofetil patients with and without concomitant telmisartan, no clinical consequences of the pharmacokinetic medicine interaction were seen.

Oral contraceptives:

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

Rifampicin:

It has been observed that concomitant administration of **MYCOPHENOLATE TEVA** and rifampicin resulted in a decrease in MPA exposure (AUC_{0-12h}) of 18 % - 70 %. It is therefore recommended to monitor MPA exposure levels and to adjust **MYCOPHENOLATE TEVA** doses accordingly to maintain clinical efficacy when rifampicin is administered concomitantly.

Sevelamer:

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

Probenecid or medicines that undergo renal tubular secretion:

Renal tubular secretion may be inhibited by probenecid and result in increased plasma concentrations of the metabolites of mycophenolate; other medicines known to undergo renal tubular secretion may also compete with MPAG to raise plasma concentrations of either medicines undergoing renal tubular secretion. Concomitant administration of sevelamer and **MYCOPHENOLATE TEVA** in adults and paediatric patients decreased the MPA Cmax and AUC(0-12) by 30 % and 25 % respectively. The data suggests that sevelamer and other calcium free phosphate binders preferentially should be given 2 hours after **MYCOPHENOLATE TEVA** intake to minimise the impact on the absorption of MPA.

Live vaccines:

Live vaccines should be avoided in patients with an impaired immune response as there is an increased risk of infection. The antibody response to other vaccines may be diminished. See **section 4.4**.

4.6 Fertility, pregnancy and lactation:

MYCOPHENOLATE TEVA is contraindicated in pregnancy and in breastfeeding mothers.

MYCOPHENOLATE TEVA therapy must not be initiated until a negative pregnancy test has been obtained to rule out unintended use in pregnancy.

Women of childbearing potential should use two reliable forms of contraception simultaneously, including at least one highly effective method, before beginning **MYCOPHENOLATE TEVA** therapy, during therapy, and for six weeks following discontinuation of therapy; unless abstinence is the chosen method of contraception. Two complementary forms of contraception simultaneously are preferred.

Sexually active men are recommended to use condoms during treatment with **MYCOPHENOLATE TEVA** and for at least 90 days after cessation of **MYCOPHENOLATE TEVA** treatment. Condom use applies both for reproductively competent and vasectomised men; because the risks 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 **MYCOPHENOLATE TEVA**.
(See boxed warning at the start of this leaflet).

Patients should be instructed to consult their medical practitioner immediately should pregnancy occur.

Female patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations at the beginning of **MYCOPHENOLATE TEVA** treatment and must be counselled regarding pregnancy prevention and planning.
Before starting **MYCOPHENOLATE TEVA**, women of childbearing potential should have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/ml in order to exclude unintended exposure of the embryo to mycophenolate. It is recommended that the second test should be performed 8-10 days after the first test. For transplants from deceased donors, if it is not possible to perform two tests 8-10 days apart before treatment starts (because of the timing of transplant organ availability), a pregnancy test must be performed immediately before starting treatment and a further test performed 8-10 days later.

Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported). Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.

MYCOPHENOLATE TEVA is powerfully teratogenic and mutagenic.

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

The following malformations were reported:

- facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits
- abnormalities of the ear (e.g. abnormally-formed or absent external/middle ear), external auditory canal atresia (middle ear) and eye (e.g. coloboma, microphthalmos)
- malformations of the fingers (e.g. polydactyly, syndactyly, brachydactyly)
- cardiac abnormalities such as atrial and ventricular septal defects
- 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.

Breastfeeding:

Mycophenolate mofetil as in **MYCOPHENOLATE TEVA** has been shown to be excreted in the milk of lactating rats. It is not known whether this substance is excreted in human milk. Because of the potential

for serious adverse reactions to **MYCOPHENOLATE TEVA** in breastfed infants, **MYCOPHENOLATE TEVA** is contraindicated in breastfeeding mothers (see **section 4.3**).

Men:

Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to mycophenolate mofetil as in **MYCOPHENOLATE TEVA**.

Mycophenolic acid (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 TEVA**. Male patients of reproductive potential should be made aware of and discuss with a qualified healthcare professional the potential risks of fathering a child.

4.7 Effects on ability to drive and use machines:

MYCOPHENOLATE TEVA frequently causes dizziness and somnolence and may also cause confusion, tremor and hypotension. Therefore, patients should be advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether **MYCOPHENOLATE TEVA** affects their ability to perform these activities.

4.8 Undesirable effects:

The principal adverse reactions associated with the administration of **MYCOPHENOLATE TEVA** include diarrhoea, leucopenia, sepsis and vomiting and there is evidence of a higher frequency of certain types of infections. See **section 4.4**.

The following has been reported for **MYCOPHENOLATE TEVA** when used in combination with ciclosporin and corticosteroids:

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE EVENTS**
Infections and infestations	*Frequent*	Sepsis, gastrointestinal candidiasis, urinary tract infection, herpes simplex, herpes zoster, pneumonia, influenza, respiratory tract infection, respiratory moniliasis, gastrointestinal infection, candidiasis, gastroenteritis, infection, bronchitis, pharyngitis, sinusitis, fungal skin infections, skin candida, vaginal candidiasis, rhinitis, abscess, cellulitis, bacterial infections, fungal infections, viral infections
	Less frequent	Protozoal infections
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	*Frequent*	Skin cancer, benign neoplasm of skin, non-melanoma skin carcinomas, cysts (including lymphocele and hydrocele)
	Less frequent	Lymphoma, lymphoproliferative disorder
Blood and lymphatic system disorders	*Frequent*	Leucopenia, thrombocytopenia, anaemia (including hypochromic anaemia), pancytopenia, leucocytosis,

		haemorrhage, ecchymosis, polycythaemia, petechial, increased prothrombin time, increased thromboplastin time
	Less frequent	Pure red cell aplasia, bone marrow failure, pseudolymphoma
Immune system disorders	*Frequent*	Hypersensitivity
	Less frequent	Hypogammaglobulinaemia
Endocrine disorders	*Frequent*	Diabetes mellitus, parathyroid disorder (elevated PTH level), Cushing's syndrome, hypothyroidism
Metabolism and nutrition disorders	*Frequent*	Acidosis, hyperkalaemia, hypokalaemia, hyperglycaemia, hypomagnesaemia, hypocalcaemia, hypercholesterolaemia, hyperlipidaemia, hypophosphataemia, hyperuricaemia, gout, anorexia, weight decreased, elevated blood urea, elevated creatinine, elevated enzyme levels (lactic dehydrogenase, AST and ALT), hypervolaemia, hyponatraemia, hypoproteinaemia, dehydration, alkalosis, hypochloraemia, hypoxia, respiratory acidosis, thirst
Psychiatric disorders	*Frequent*	Agitation, confusional state, depression, anxiety, abnormal thinking, insomnia, emotional lability, hallucinations, delirium, psychosis
Nervous system disorders	*Frequent*	Convulsion, hypertonia, tremor, somnolence, myasthenic syndrome, dizziness, headache,

		paraesthesia, dysgeusia, neuropathy, vertigo, hyperaesthesia
Eye disorders	*Frequent*	Amblyopia, cataract, conjunctivitis, abnormal vision, eye haemorrhage
Ear and labyrinth disorders	*Frequent*	Ear pain, deafness, tinnitus
Cardiac disorders	*Frequent*	Tachycardia, dysrhythmia, bradycardia, cardiac failure, pericardial effusion, angina pectoris, atrial fibrillation, cardiac arrest, pulmonary hypertension
Vascular disorders	*Frequent*	Hypotension, hypertension, vasodilatation, postural hypotension, thrombosis, syncope, vasospasm, increased venous pressure
	Less frequent	Lymphocele
Respiratory, thoracic and mediastinal disorders	*Frequent*	Pleural effusion, dyspnoea, cough, asthma, atelectasis, pulmonary oedema,
	Less frequent	Bronchiectasis, interstitial lung disease, pulmonary fibrosis
Gastrointestinal disorders	*Frequent*	Vomiting, abdominal pain, diarrhoea, nausea, gastrointestinal haemorrhage, peritonitis, ileus, colitis, gastric ulcer, duodenal ulcer, gastritis, oesophagitis, stomatitis, constipation, dyspepsia, flatulence, enlarged abdomen, hernia, oral moniliasis, cholangitis, gingivitis, gum hyperplasia, melaena, dysphagia, mouth ulceration, rectal disorder, decreased appetite, abdominal distension
	Less frequent	Eructation, pancreatitis

Hepatobiliary disorders	*Frequent*	Hepatitis, jaundice, hyperbilirubinaemia, ascites, blood alkaline phosphatase increased, hepatic enzyme increased, blood lactate dehydrogenase increased
Skin and subcutaneous tissue disorders	*Frequent*	Skin hypertrophy (including actinic keratosis), rash, acne, alopecia, pruritus, sweating, hirsutism, skin ulcer, facial oedema
Musculoskeletal and connective tissue disorders	*Frequent*	Arthralgia, pelvic pain, neck pain, leg cramps, myalgia, osteoporosis, muscular weakness
Renal and urinary disorders	*Frequent*	Renal impairment, haematuria, renal tubular necrosis, abnormal kidney function (decrease in renal function, elevated serum creatinine), oliguria, albuminuria, dysuria, hydronephrosis, pyelonephritis, urinary frequency, nocturia, renal failure, urinary incontinence, urinary retention, scrotal oedema, blood creatinine increased, blood urea increased, renal impairment
Reproductive system and breast disorders	*Frequent*	Impotence
General disorders and administration site conditions	*Frequent*	Oedema, pyrexia, chills, pain (includes abdominal, back and chest), malaise, asthenia, pallor, hernia
	Less frequent	*De novo* purine synthesis inhibitors-associated acute inflammatory syndrome.

Investigations	*Frequent*	Increased hepatic enzyme, increased blood creatinine, increased blood lactate dehydrogenase, increased blood urea, increased blood alkaline phosphatase, decreased weight, increased weight

Post-marketing experience:

The following undesirable effects cover adverse reactions from post-marketing experience. The types of adverse reactions reported during post-marketing with mycophenolate are similar to those seen in the controlled renal, cardiac and hepatic transplant studies. Additional adverse reactions reported during post-marketing are described below.

Gastrointestinal: colitis including cytomegalovirus colitis, pancreatitis and intestinal villous atrophy.

Disorders related to immunosuppression: serious life-threatening infections including meningitis, endocarditis, tuberculosis and atypical mycobacterial infection.

Agranulocytosis and neutropenia have been reported; therefore regular monitoring of patients taking **MYCOPHENOLATE TEVA** is advised. There have been reports of aplastic anaemia and bone marrow depression in patients treated with mycophenolate, some of which have been fatal.

Congenital disorders: congenital malformations including ear malformations in offspring of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy.

Hypersensitivity: hypersensitivity reactions, including angioedema and anaphylactic reactions have been reported.

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. Healthcare professionals are asked to

report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form', found under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8.

4.9 Overdose:

Overdosage with **MYCOPHENOLATE TEVA** may result in over suppression of the immune system and increase susceptibility to infections and bone marrow suppression. If neutropenia develops, dosing with **MYCOPHENOLATE TEVA** should be interrupted or the dose reduced (see **section 4.4**).

MPA cannot be removed by haemodialysis. However, at high MPAG plasma concentrations (> 100 mg/ml) small amounts of MPAG are removed. MPA can be removed by bile acid sequestrants, such as cholestyramine which would increase excretion of **MYCOPHENOLATE TEVA**.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 32.16 Other (Immuno-suppressants)

ATC code: N06DA04

Mechanism of action:

Mycophenolate mofetil (MMF) is a prodrug that is rapidly hydrolysed to the active metabolite, mycophenolic acid (MPA), which is a selective, non-competitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH). IMPDH is an important enzyme in the *de novo* pathway of guanine nucleotide synthesis.

B and T lymphocytes are highly dependent on this pathway for cell proliferation, while other cell types can use salvage pathways. MPA therefore selectively inhibits lymphocyte proliferation and functions, including antibody formation, cellular adhesion and migration. The cytostatic effects of MPA on lymphocytes are reversed by the addition of guanosine or deoxyguanosine. MPA also suppresses antibody formation by B-lymphocytes.

MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells, and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection.

Mycophenolate mofetil does not inhibit early events in the activation of human peripheral blood mononuclear cells, such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but does block the coupling of these events to DNA synthesis and proliferation.

5.2 Pharmacokinetic properties:

Absorption:

After oral administration, mycophenolate mofetil undergoes extensive absorption and rapid and complete metabolism to the active metabolite, MPA. MPA, in turn, is metabolised to the inactive phenolic glucuronide MPAG.

The parent mycophenolate mofetil is cleared within a few minutes from the blood. The half-life of MPA is about 16 hours.

The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94 % relative to intravenous mycophenolate mofetil. Mycophenolate mofetil can be measured systemically during intravenous infusion; however, after oral administration it is below the limit of quantification (0,4 µg/ml). Immediately post-transplant (< 40 days) renal, cardiac and hepatic transplant patients had mean MPA AUCs approximately 30 % lower and Cmax approximately 40 % lower compared to the late post-transplant period (3 to 6 months post-transplant). MPA AUC levels obtained following administration of 1 g twice daily intravenous mycophenolate mofetil at the recommended infusion rate to renal patients in the immediate post-transplant phase are comparable to those observed following oral dosing. In hepatic transplant patients, administration of 1 g twice daily intravenous mycophenolate mofetil followed by 1,5 g twice daily oral mycophenolate mofetil resulted in MPA AUC values similar to those found in renal transplant patients administered 1 g mycophenolate mofetil twice daily.

Food had no effect on the extent of absorption of mycophenolate mofetil when administered at doses of 1,5 g twice daily to renal transplant patients. However, the maximum plasma concentrations of MPA were decreased by 40 % in the presence of food.

Distribution and protein binding:

An observed secondary peak in plasma MPA concentrations that occurs 6 to 12 hours after a dose as well as the co-administration of cholestyramine which results in an approximately 40 % decrease in MPA concentrations, suggest that enterohepatic recirculation is involved.

The mean apparent volume of distribution in healthy volunteers is approximately 3,6 litre per kg of body weight (L/kg). Mean blood compared to plasma ratios of radioactivity concentrations indicate that MPA and mycophenolic acid glucuronide (MPAG), the phenolic glucuronide metabolite, do not extensively distribute into the cellular fractions of blood. MPA is highly protein bound to plasma albumin (97 % at clinically relevant concentrations) and MPAG is 82 % at concentration ranges normally seen in stable renal transplant patients.

At higher MPAG concentrations, (e.g. in patients with renal impairment or delayed graft function), binding of MPA may be reduced as a result of competition between MPA and MPAG for binding sites.

Metabolism:

Mycophenolate mofetil is hydrolysed pre-systemically and completely to the active metabolite, MPA, which is then primarily metabolised by glucuronyl transferase, to the inactive phenolic glucuronide (MPAG). In vivo, MPAG is converted to free MPA via enterohepatic recirculation.

Mean apparent half-life of MPA is approximately 17,9 hours and plasma clearance is approximately 193 ml per minute after oral administration.

Excretion:

Renal clearance is 93 % (less than 1 % as MPA and 87 % as MPAG) and occurs by renal tubular secretion and glomerular filtration. Faecal clearance is 6 %.

MPA and MPAG are usually not removed by haemodialysis, although small amounts of MPAG are removed at high plasma MPAG concentrations (> 100 mcg per ml.

Special populations:

Patients with severe renal impairment:

In a single dose study (6 patients/group), mean plasma MPA AUC after a single oral dose in patients with severe chronic renal impairment (glomerular filtration rate < 25 ml/min/1,73 m^2), was 28 to 75 % higher than that observed in normal healthy volunteers or patients with lesser degrees of renal impairment. In addition, the mean single-dose plasma MPAG AUC was 3 to 6 fold higher in patients with severe renal impairment than in patients with mild renal impairment or normal healthy patients, consistent with the known renal elimination of MPAG.

Patients with delayed renal graft function post-transplant:

In patients with delayed renal graft function post-transplant, mean MPA AUC (0-12 h) was comparable to that seen in post-transplant patients without delayed renal graft function. Mean plasma MPAG AUC (0-12 h) was 2 to 3 fold higher than in post-transplant patients without delayed renal graft function. In patients with primary renal non-functioning graft following renal transplantation, plasma concentrations of MPAG accumulated; accumulation of MPA, if any, was much smaller.

Patients with hepatic impairment:

In volunteers with alcoholic cirrhosis, hepatic MPA glucuronidation processes were relatively unaffected by hepatic parenchymal disease. Hepatic disease with predominantly biliary damage, such as primary biliary cirrhosis, has not been established.

Children aged > 18 years:

Pharmacokinetic parameters in paediatric renal transplant patients (ranging from 1 to 18 years of age) given 600 mg/m^2 mycophenolate mofetil orally twice daily achieved MPA AUC values similar to those seen in adult renal transplant patients receiving mycophenolate mofetil at a dose of 1 g twice daily in the early and late post-transplant period. MPA AUC values across age groups were similar in the early and late post-transplant period.

Elderly:

Pharmacokinetics in the elderly has not been formally evaluated.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

MYCOPHENOLATE TEVA 500:

Croscarmellose sodium, magnesium stearate, microcrystalline cellulose and povidone.

The tablet coating Opadry purple consists of: hypromellose 6cP, indigo carmine aluminium lake FD&C blue (E132), iron oxide black (E172), iron oxide red (E172), polyethylene glycol, talc and titanium dioxide.

MYCOPHENOLATE TEVA 250:

Croscarmellose sodium, magnesium stearate, povidone, pregelatinised starch.

The capsule shell cap consists of indigo carmine (E132), titanium dioxide (E171), gelatin and the capsule shell body consists of red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171) and gelatin.

Black ink contains shellac, black iron oxide (E172), propylene glycol and potassium hydroxide.

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

36 months.

6.4 Special precautions for storage:

Store at or below 25 °C.

Keep in the original package and protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits, **MYCOPHENOLATE TEVA** capsules should not be opened or crushed. Avoid inhalation, or direct contact with skin or mucous membranes, of the powder contained in **MYCOPHENOLATE TEVA** capsules. If such contact occurs, wash thoroughly with soap and water, rinse eyes with plain water.

Do not use the medicine after the expiry date that has been printed on the container.

6.5 Nature and contents of container:

MYCOPHENOLATE TEVA 500:

Transparent PVC/PVDC-aluminium blisters. Each blister strip contains 10 tablets.

Pack size 50: 5 blister strips packed in an outer carton.

Pack size 150: 15 blister strips packed in an outer carton.

MYCOPHENOLATE TEVA 250:

Transparent PVC/PVDC-aluminium blisters. Each blister strip contains 10 capsules

Pack size 100: 10 blister strips packed in an outer carton.

Pack size 300: 30 blister strips packed in an outer carton.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd,

Maxwell Office Park,

Magwa Crescent West,

Waterfall City,

Midrand,

Gauteng,

South Africa

8. REGISTRATION NUMBER:

MYCOPHENOLATE TEVA 500: 45/32.16/1086

MYCOPHENOLATE TEVA 250: 46/32.16/0322

9. DATE OF FIRST AUTHORISATION:

11 June 2018

10. DATE OF REVISION OF TEXT:

29 March 2022