Mycophenolate sodium (Myfortic®)
MYCOPHENOLATE GUIDE FOR HEALTHCARE PROVIDERS
Risk of teratogenicity

Introduction

This Guide, the Mycophenolate Guide for Healthcare Providers, has been designed to highlight the risks associated with exposure to mycophenolate during pregnancy, as well as the measures that should be taken to mitigate them. It will facilitate your discussion with the patient and will help you to address any questions or concerns the patient may have.

The purpose of this Guide is to minimise the number of pregnancies during treatment with this teratogenic medicinal product.

Although this Guide presents important information concerning the adverse pregnancy outcomes associated with mycophenolate, please consult the Myfortic Summary of Product Characteristics (SmPC) for full information on mycophenolate.

The teratogenic risks of mycophenolate

Mycophenolate is a powerful teratogen associated with an increased rate of spontaneous abortion and congenital malformation compared with other immunosuppressants. No specific mechanism of teratogenicity and mutagenicity has been identified. However, preclinical tests showed fetal resorptions and malformations in rats and rabbits in the absence of maternal toxicity. Two genotoxicity assays indicated that mycophenolate has the potential to cause chromosomal instability at severely cytotoxic dose levels.

A review of cumulative data of mycophenolate mofetil found that around 45 to 49% of pregnancies in women exposed to mycophenolate resulted in spontaneous abortion, compared with reported frequencies of 12 to 33% in solid organ transplant patients treated with other immunosuppressants. The reported incidence of malformations in the offspring of mothers exposed to mycophenolate during pregnancy is 23 to 27% compared with 4 to 5% in transplant patients treated with other immunosuppressants, and 2 to 3% in the overall population.

Malformations associated with mycophenolate have included abnormalities of the ear, eye and face, congenital heart disease including septal defects, polydactyly or syndactyly, tracheo-oesophageal malformations such as oesophageal atresia, effects on the nervous system such as spina bifida, and renal abnormalities.

Patients at risk of adverse pregnancy outcomes following exposure to mycophenolate include:

- Pregnant patients.
- All female patients of childbearing potential (i.e. girls who have entered puberty and all women who have a uterus and have not passed through menopause).
- Female partners of sexually active men (including vasectomised men) treated with mycophenolate.

Patient counseling

Before initiating or continuing treatment with mycophenolate, female and male patients must be educated about the increased risks of spontaneous abortion and congenital malformations associated with exposure to mycophenolate. You should ensure that women and men taking mycophenolate understand the risk of harm to the foetus, the need for effective contraception, and the need to immediately consult their physician if there is a possibility of pregnancy. The information you share in this discussion will be supported by the Mycophenolate Guide for Patients and the Package Leaflet.

In particular, you should:

- Counsel patients at risk to make sure they understand the risks and the measures required to minimise them.
- Provide female and male patients at risk with the Mycophenolate Guide for Patients, and address any questions or concerns they might have.
- Explain the importance, methods and timing of pregnancy tests prior and during treatment with mycophenolate.
- Provide counseling on the use of effective contraception prior to and during the entire duration of treatment with mycophenolate and for 6 weeks (female patients) or 90 days (male patients) after they stop taking mycophenolate.
- Advise patients using mycophenolate that they must let you know in advance if they are considering becoming pregnant or fathering a child so that you can discuss possible treatment alternatives with them.
- Advise patients treated with mycophenolate not to donate blood during or for 6 weeks after stopping treatment. Male patients should not donate sperm during therapy or for 90 days after stopping treatment.
- Advise patients that this medicine is for their own personal use, they should not give it to anyone else and should return any unused medicine to their pharmacist at the end of treatment

Pregnancy testing

Mycophenolate must not be used during pregnancy unless there is no suitable alternative to prevent transplant rejection.

Before starting treatment with mycophenolate, women of child bearing potential should have a pregnancy test in order to exclude unintended exposure of the embryo to mycophenolate. Two serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL are recommended; whenever feasible, a second test should be performed 8 – 10 days after the first one and immediately before starting mycophenolate mofetil. 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.

Contraceptive requirements

Mycophenolate is contraindicated in women of childbearing potential who are not using highly effective contraception. Because of the teratogenic potential of mycophenolate, women of childbearing potential should use two reliable forms of contraception simultaneously before starting mycophenolate therapy, during therapy, and for six weeks after stopping the 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 for both reproductively competent and vasectomised men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. In addition, female partners of male patients treated with mycophenolate are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of mycophenolate.

What to do if pregnancy occurs

Patients must consult their physician immediately should pregnancy occur during treatment with mycophenolate or within 6 weeks after the last dose (within 90 days in case of paternal exposure). It is very important that the patient does not stop mycophenolate without speaking to a physician as transplant patients may risk graft loss.

The correct course of action following exposure to mycophenolate during pregnancy should be based on an assessment of the individual patient's benefit-risk, and determined on a case by case basis through a discussion between the treating physician and the patient.

If you need additional copies of the Patient or HCP Guides contact Novartis Pharma Services Inc., Representative Office Malta on email address novartis.malta@novartis.com, by telephone on +356 21222872 or by mail at P.O. Box 4, Marsa, MRS 1000, Malta to receive hard copies.

Any suspected adverse reactions and medication errors can be reported via the national Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from http://www.medicinesauthority.gov.mt/adrportal and posted to Medicines Authority Post-licensing Directorate, Sir Temi Zammit Buildings, Malta Life Sciences Park, San Gwann SGN 3000 or sent by e-mail to postlicensing.medicinesauthority@gov.mt.

Healthcare professionals may also report any adverse events suspected to be associated with the use of Myfortic to Novartis Pharma Services Inc. Representative Office Malta by phone on 21222872, by fax on 22487219 or e-mail at drug_safety.malta@novartis.com. Healthcare professionals should report any case of exposure to mycophenolate sodium during pregnancy (regardless of outcome) to Novartis.

Myfortic® 180mg and 360mg gastro-resistant tablets

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

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

DOSAGE: Treatment with Myfortic should be initiated and maintained by appropriately qualified transplant specialists. The recommended dose is 720 mg administered twice daily (1,440 mg daily dose). In de novo patients, Myfortic should be initiated within 72 hours following transplantation. Myfortic can be taken with or without food. Patients may select either option but must adhere to their selected option. In order to retain the integrity of the enteric coating, Myfortic tablets should not be crushed. Where crushing of Myfortic tablets is necessary, avoid inhalation of the powder or direct contact of the powder with skin or mucous membrane. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water due to the teratogenic effects of mycophenolate Older people: The recommended dose in elderly patients is 720 mg twice daily

CONTRAINDICATIONS: Hypersensitivity to mycophenolate sodium, mycophenolic acid or mycophenolate mofetil or to any of the excipients ♦ Myfortic is contraindicated in women who are breastfeeding and in women of child bearing potential (WOCBP) not using highly effective contraception methods ♦ Myfortic should not be initiated in women of child bearing potential without providing a pregnancy test result to rule out unintended use in pregnancy. ♦ Myfortic should not be used in pregnancy unless there is no suitable alternative treatment to prevent transplant rejection. ♦Myfortic should not be given to women who are breastfeeding

WARNINGS / PRECAUTIONS: ♦ Patients receiving immunosuppressive regimens involving combinations of drugs, including Myfortic, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. . As general advice to minimise the risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. ♦ Patients receiving Myfortic should be instructed to immediately report any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression. ♦ Patients treated with immunosuppressants, including Myfortic, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis ♦There have been reports of hypogammaglobulinaemia in association with recurrent infections in patients receiving Myfortic in combination with other immunosuppressants. In some of these cases, switching MPA derivatives to an alternative immunosuppressant, resulted in serum IgG levels returning to normal. Patients on Myfortic who develop recurrent infections should have their serum immunoglobulins measured. ♦ There have been reports of bronchiectasis in patients who received Myfortic in combination with other immunosuppressants. In some these cases, switching MPA derivatives to another immunosuppressant, resulted in improvement in respiratory symptoms. The risk of bronchiectasis may be linked to hypogammaglobulinaemia or to a direct effect on the lung. ♦ Reactivation of hepatitis B (HBV) or hepatitis C (HCV) have been reported in patients treated with immunosuppressants, including the mycophenolic acid (MPA) derivatives Myfortic and mycophenolate mofetil (MMF). Monitoring infected patients for clinical and laboratory signs of active HBV or HCV infection is recommended. ♦Cases of pure

red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives (which include mycophenolate mofetil and mycophenolate sodium) in combination with other immunosuppressants. ♦ Patients receiving Myfortic should be monitored for blood disorders (e.g neutropenia or anemia - see section 4.8), which may be related to MPA itself, concomitant medications, viral infections, or some combination of these causes. Patients taking Myfortic should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. ♦ Patients should be advised that during treatment with MPA vaccinations may be less effective and the use of live attenuated vaccines should be avoided. ♦ Because MPA derivatives have been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration and haemorrhage and perforation, Myfortic should be administered with caution in patients with active serious digestive system disease. ♦ It is recommended that Myfortic not be administered concomitantly with azathioprine because concomitant administration of these drugs has not been evaluated. ♦Mycophenolic acid (as sodium salt) and mycophenolate mofetil should not be indiscriminately interchanged or substituted because of their different pharmacokinetic profiles. ♦ Myfortic contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. ♦The concomitant administration of Myfortic and drugs which interfere with enterohepatic circulation, for example cholestyramine or activated charcoal, may result in sub-therapeutic systemic MPA exposure and reduced efficacy. ♦Myfortic is an IMPDH (inosine monophosphate dehydrogenase) inhibitor. Therefore, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome. ♦Myfortic therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning Myfortic therapy, during therapy and for six weeks following therapy discontinuation. ♦ Mycophenolate is a powerful human teratogen. Spontaneous abortion and congenital malformations have been reported following mycophenolate mofetil exposure during pregnancy. Therefore Myfortic is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejection. Female and male patients of reproductive potential should be made aware of the risks and follow the recommendations provided ♦Because of the genotoxic and teratogenic potential of Myfortic, women with childbearing potential should use two reliable forms of contraception simultaneously before starting Myfortic therapy, during therapy, and for six weeks after stopping the therapy; unless abstinence is the chosen method of contraception. ♦Patients should not donate blood during therapy or for at least 6 weeks following discontinuation of mycophenolate. Men should not donate semen during therapy or for at least 90 days following discontinuation of mycophenolate. ♦Sexually active men are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomized men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. In addition, female partners of male patients treated with Myfortic are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of Myfortic.

INTERACTIONS: ♦The potential for myelosuppression in patients receiving both Myfortic and aciclovir or ganciclovir has not been studied. ♦Magnesium aluminium-containing antacids may be used intermittently for the treatment of occasional dyspepsia. However the chronic, daily use of magnesium-aluminium containing antacids with Myfortic is not recommended due to the potential for decreased

mycophenolic acid exposure and reduced efficacy. ♦Caution should be used when co-administering drugs or therapies that may bind bile acids, for example bile acid sequestrates or oral activated charcoal, because of the potential to decrease MPA exposure and thus reduce the efficacy of Myfortic ♦ Live vaccines should not be given to patients with an impaired immune response. The antibody response to other vaccines may be diminished

ADVERSE REACTIONS: ♦Very common: Viral, bacterial and fungal infections; Leukopenia; Hypocalcemia, hypokalaemia, hyperuricaemia; Anxiety; Hypertension; Diarrhoea; Arthralgia ♦Common: Upper respiratory tract infections, pneumonia; Anaemia, thrombocytopenia; Hyperkalaemia, hypomagnesaemia; Dizziness, headache; Hypotension; Cough, dyspnoea; Abdominal distension, abdominal pain, constipation, dyspepsia, flatulence, gastritis, nausea, vomiting; Liver function tests abnormal; Acne, pruritus; Myalgia; Blood creatinine increased; Asthenia, Fatigue, oedema peripheral, pyrexia♦ Uncommon: Wound infection, sepsis, osteomyelitis; Skin papilloma, basal cell carcinoma, Kaposi´s sarcoma, lymphoproliferative disorder, squamous cell carcinoma; Lymphopenia, neutropenia, lymphadenopathy; Anorexia, hyperlipidaemia, diabetes mellitus, hypercholesterolaemia, hypophosphataemia; Abnormal dreams, delusional perception, insomnia; Tremor; Conjunctivitis, vision blurred; Tachycardia, ventricular extrasystoles; Lymphocele; Interstitial lung disease, pulmonary congestion, wheezing, pulmonary oedema; Abdominal tenderness, gastrointestinal haemorrhage, eructation, halitosis, ileus, lip ulceration, oesophagitis, subileus, tongue discolouration, dry mouth, gastro-oesophageal reflux disease, gingival hyperplasia, pancreatitis, parotid duct obstruction, peptic ulcer, peritonitis; Alopecia; Arthritis, back pain, muscle cramps; Haematuria, renal tubular necrosis, urethral stricture; Impotence; Influenza like illness, oedema lower limb, pain, rigors, thirst, weakness; Contusion. For a full list of Adverse reactions, please refer to the SmPC.

LEGAL CATEGORY:POM

PACK SIZES: 120 gastro-resistant tablets

MARKETING AUTHORISATION HOLDER: Novartis Pharmaceuticals UK Ltd, Frimley Business Park, Frimley, Camberley, Surrey GU16 7SR, United Kingdom.

MARKETING AUTHORISATION NUMBER: MA088/04901, 088/04902

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available upon request from: Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel +356 21222872

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