MYCOPHENOLATE MOFETIL

GUIDE FOR HEALTHCARE PROFESSIONALS

INFORMATION ABOUT RISK OF TERATOGENICITY

This is risk minimisation material and is provided as a collaborative project between Accord Healthcare Ltd., Clonmel Healthcare Ltd., and Rowex Ltd. For further information, please refer to the Summary of Product Characteristics (SmPC) for the respective medicinal product from the relevant Marketing Authorisation Holder available at www.hpra.ie

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Introduction

This guide, the Mycophenolate Mofetil Guide for Healthcare Professionals, has been prepared in order 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 discussions with your patient and will help you to address any questions or concerns your 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 Summary of Product Characteristics (SmPC) for the respective brand of Mycophenolate mofetil, available at www.hpra.ie for full information on mycophenolate mofetil.

The teratogenic risks of mycophenolate

Mycophenolate is a powerful teratogen associated with an increased rate of spontaneous abortion and congenital malformation when compared to other immunosuppressants. Because of this, mycophenolate is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejections.

There has been no specific mechanism of teratogenicity and mutagenicity 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 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.

Congenital malformations, including reports of multiple malformations, have been observed post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy**.** The following malformations were most frequently reported:

- Abnormalities of the ear (e.g. abnormally formed or absent external/middle ear), external auditory canal atresia;
- Congenital heart disease such as atrial and ventricular septal defects;
- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;
- Abnormalities of the eye (e.g. coloboma);
- Malformations of the finger (e.g. polydactyl, syndactyl);
- Tracheo-Oesophageal malformations (e.g. oesophageal atresia);
- Nervous system malformations such as spina bifida;
- Renal abnormalities.

Additionally, there have been isolated reports of the following malformations:

- Microphthalmia;
- Congenital choroid plexus cyst;
- Septum pellucidum agenesis;
- Olfactory nerve agenesis.

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 counselling

Education of male and female patients about the increased risks of spontaneous abortion and congenital malformations associated with exposure to mycophenolate is necessary before initiating or continuing treatment with mycophenolate. It should be ensured 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 Mofetil Guide for Patients and the Package Leaflet of the respective brand of mycophenolate mofetil prescribed for the patient.

In particular, you should:

- Counsel at-risk patients to ensure they understand the risks and the measures required to minimise them.
- Provide female and male patients at risk with the Mycophenolate Mofetil Guide for Patients and address any questions or concerns they might have.
- Explain the importance, methods and timing of pregnancy tests prior to, and during, treatment with mycophenolate.
- Provide counselling 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/female partners of 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 possible treatment alternatives can be discussed with them.
- Patients treated with mycophenolate should be advised 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 treatment should not be initiated in women of childbearing potential without providing a pregnancy test result to rule out unintended use in pregnancy.

Prior to treatment initiation 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; the 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. Should pregnancy occur, patients should be instructed to consult with their physician immediately.

Contraceptive requirements

Mycophenolate is contraindicated in women of childbearing potential who are not using highly effective contraception. Due to 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.

It is recommended that sexually active men 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.

Action in case of the occurrence of pregnancy

Should pregnancy occur during treatment with mycophenolate or within 6 weeks after the last dose (within 90 days in case of paternal exposure), patients must consult their physician immediately. It is very important that the patient is aware not to 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.

ADR Reporting

Suspected Adverse Drug Reactions or medication errors should be reported to the Malta Medicines Authority via the ADR reporting form, available online at http://www.medicinesauthority.gov.mt/adrportal.

The ADR reporting form can be sent by post to Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 or via email to postlicensing.medicinesauthority@gov.mt.

Alternatively, adverse drug reactions can also be reported to Central Procurement & Supplies Unit, (Head Office),UB002, Industrial Estate, San Gwann - SGN3000 or via email: info.cpsu@gov.mt.