MYFORTIC® (Mycophenolic acid): risk of teratogenicity

GUIDE FOR HEALTHCARE PROVIDERS

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Introduction

This Guide has been designed to highlight the risks to babies associated with exposure to mycophenolate during pregnancy and to minimise the number of pregnancies during treatment with this teratogenic medicinal product.

Use this Guide during discussion with the patient and to address any questions or concerns the patient may have.

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.

For further information please refer to the Myfortic Summary of Product Characteristics available at www.medicines.ie or www.hpra.ie

Pregnancy risks associated with mycophenolate

Preclinical Evidence

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

No specific mechanism of teratogenicity and mutagenicity has been identified. However, preclinical tests showed foetal 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.

Clinical evidence in cases of maternal exposure

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 babies born to mothers exposed to mycophenolate during pregnancy is 23% to 27% compared with 4% to 5% in transplantation 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.

In addition 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).

<u>Clinical evidence in cases of paternal exposure</u>

The limited clinical evidence available on paternally-exposed pregnancies does not indicate any increased risk of malformations or miscarriage following paternal exposure to mycophenolate.

Mycophenolate is a powerful teratogen and may potentially be present in semen, however calculations on the amount that could potentially be transferred to a woman suggest it would be at a level unlikely to have an effect. Mycophenolate has been shown to be genotoxic in animal studies at concentrations exceeding the human therapeutic exposures. Thus, the risk of genotoxic effects on sperm cells cannot be completely excluded.

As a precaution male patients and their female partners should be made aware of this potential risk and be recommended reliable contraceptive measures.

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/female partners of male patients) after they stop taking mycophenolate.
- Advise patients taking 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 semen 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.

Before starting treatment with mycophenolate, women of child bearing potential should have two negative serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL to exclude unintended exposure of the embryo to mycophenolate. It is recommended that the second test (when appropriate) should be performed 8 – 10 days after the first one and immediately before starting mycophenolate. 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

Women

Mycophenolate is contraindicated in women of childbearing potential who are not using highly effective contraception. Because of the significant risks of spontaneous abortion and teratogenic potential of mycophenolate, women of childbearing potential should use at least one form of effective contraception before starting mycophenolate therapy, during therapy, and for six weeks after stopping the therapy; unless abstinence is the chosen method of contraception. Two complimentary forms of contraception are more effective and therefore preferred.

Men

In the absence of sufficient data to exclude a risk of harm to the foetus, the following precautionary measures are recommended: sexually active male patients are recommended to use reliable contraception during treatment of the male patient and for at least 90 days after cessation of mycophenolate.

What to do if pregnancy occurs

You should base the course of action following exposure to mycophenolate during pregnancy on the individual patient's benefit-to-risk profile, and determine on a case-by-case basis through a discussion between the treating physician and the patient.

Reporting of suspected adverse events or reactions
Reporting suspected adverse events or reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk profile of the medicinal product. All suspected adverse reactions should be reported to HPRA Pharmacovigilance at www.hpra.ie. Adverse events can also be reported to Novartis preferably at www.novartis.com/report, by emailing drugsafety.dublin@novartis.com or by calling (01) 2080 612.

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