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 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.

Using 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 Summary of Product Characteristics (SmPC) for the respective brand of Mycophenolate mofetil, available at www.hpra.ie for full information on mycophenolate mofetil.

Pregnancy risks associated with mycophenolate

Preclinical evidence

Mycophenolate is a powerful teratogen associated with an increased rate of spontaneous abortion and congenital malformation when compared to 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 show 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 damage 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 transplatation 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.

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).

Clinical evidence in cases of paternal exposure

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 calculation 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 only by small margins. Thus, the risk of genotoxic effects on sperm cells cannot be completed 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 counselling

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 Mofetil Guide for Patients and the Package Leaflet.

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.
- 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 childbearing potential should have two negative serum or urine pregnancy tests with sensitivity of at least 25 mIU/ml to exclude unintended exposure of the embryo to mycophenolate. It is recommended that the second test should be performed 8 to 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

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 must use at least one form of effective contraception before starting mycophenolate therapy, during therapy, and for 6 weeks after stopping the therapy; unless abstinence is the chosen method of contraception.

Two complementary 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 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 mofetil.

What to do if pregnancy occurs

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

Healthcare professionals should report any case of exposure to Mycophenolate mofetil during pregnancy (regardless of the outcome) to the respective Manufacturing Authorisation Holder at the following contact points:

Accord Healthcare Ltd., Medical Information Department, Whiddon Valley Barnstaple, EX32 8NS UK. E-mail: medinfo@accord-healthcare.com Tel: +44 1271 385257	**Clonmel Healthcare Ltd.**, Gurtnafleur Road, Clonmel, Co. Tipperary, E91 D768 Ireland. Email: medicalinformation@clonmel-health.ie Tel: (052) 6177778 Fax: (052) 6177791	**Rowex Ltd.**, Newtown, Bantry, Co. Cork, P75 V009 Ireland. Email: pv@rowa-pharma.ie Tel: (027) 50077 Fax: (027) 50417

Further information

Additional electronic copies of this material are available at www.hpra.ie. Additional hard copies of this material can be requested by contacting the relevant Marketing Authorisation Holder at the following contact points:

Accord Healthcare Ltd., Euro House Euro Business Park Little Island Co. Cork T45 K857 Ireland E-mail: medinfo@accord-healthcare.com Tel: +44 1271 385257	**Clonmel Healthcare Ltd.**, Gurtnafleur Road, Clonmel, Co. Tipperary, E91 D768 Ireland. Email: medicalinformation@clonmel-health.ie Tel: (052) 6177778 Fax: (052) 6177791	**Rowex Ltd.**, Newtown, Bantry, Co. Cork, P75 V009 Ireland. Email: pv@rowa-pharma.ie Tel: (027) 50077 Fax: (027) 50417

Further information about Mycophenolate Mofetil, can be obtained by contacting Medical Information at the respective Marketing Authorisation Holder at the above contact points.

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 balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse events or reactions (see details below).

You can report suspected adverse events directly to:

Accord Healthcare Ltd., Medical Information Department, Whiddon Valley Barnstaple, EX32 8NS UK. E-mail: medinfo@accord-healthcare.com Tel: +44 1271 385257	**Clonmel Healthcare Ltd.**, Gurtnafleur Road, Clonmel, Co. Tipperary, E91 D768 Ireland. Email: medicalinformation@clonmel-health.ie Tel: (052) 6177778 Fax: (052) 6177791	**Rowex Ltd.**, Newtown, Bantry, Co. Cork, P75 V009 Ireland. Email: pv@rowa-pharma.ie Tel: (027) 50077 Fax: (027) 50417

Or alternatively to:

HPRA Pharmacovigilance,
The Health Products Regulatory Authority,
Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2
Telephone: (01) 6764971
Fax: (01) 6762517
Email: medsafety@hpra.ie
Website: www.hpra.ie

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