


MYCOPHENOLATE REMS

RISKS OF FIRST TRIMESTER PREGNANCY LOSS AND CONGENITAL MALFORMATIONS

MYCOPHENOLATE REMS HEALTHCARE PROVIDERS BROCHURE

For complete safety information, please see *Prescribing Information*, including **Boxed WARNING** and *Medication Guide*, which can be found at www.MycophenolateREMS.com.



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Introducing Mycophenolate REMS

The FDA (Food and Drug Administration) requires a REMS (Risk Evaluation and Mitigation Strategy) to ensure the benefits of taking a drug outweigh the serious risks.

The Mycophenolate REMS has been required by the FDA due to postmarketing reports showing that exposure to mycophenolate during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. While available data are limited, structural malformations occur in approximately 20% of live-born infants exposed in utero to mycophenolate and first trimester pregnancy loss rates are higher.*†

Mycophenolate is available by prescription as:

- CellCept® (mycophenolate mofetil)
- Myfortic® (mycophenolic acid)
- Generic mycophenolate mofetil
- Generic mycophenolic acid

The goal of the Mycophenolate REMS is to mitigate the risk of embryofetal toxicity associated with use of mycophenolate during pregnancy by:

1. Educating healthcare providers (HCPs) on the following:
 - The increased risks of first trimester pregnancy loss and congenital malformations associated with exposure to mycophenolate during pregnancy.
 - The need to counsel females of reproductive potential on the importance of pregnancy prevention and planning when taking mycophenolate.
 - The need to report pregnancies to the Mycophenolate Pregnancy Registry.
2. Informing female patients of reproductive potential who are prescribed mycophenolate about:
 - The increased risks of first trimester pregnancy loss and congenital malformations when taking mycophenolate during pregnancy.
 - The importance of pregnancy prevention and planning when taking mycophenolate.

*Sifontis NM, et al. Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus *Transplantation*. 2006;82:1698-1702.

†Prescribing Information for mycophenolate.

For complete safety information, please see *Prescribing Information*, including **Boxed WARNING and *Medication Guide*, which can be found at www.MycophenolateREMS.com**



Introducing Mycophenolate REMS (cont'd)

All prescribers of mycophenolate and females of reproductive potential, whether or not they plan to get pregnant, should be aware of the risks associated with mycophenolate.

Definitions:

Females of reproductive potential include girls who have entered puberty and all women who have a uterus and have not passed through menopause.

Menopause is the permanent end of menstruation and fertility.

Menopause should be clinically confirmed by a patient's healthcare practitioner. Some commonly used diagnostic criteria include:

1. 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy)
2. Post-surgical from a bilateral oophorectomy

This brochure, the *Mycophenolate REMS Healthcare Provider Brochure*, has been designed to help you understand the components of the Mycophenolate REMS. Included are details on what you can do to help ensure the implementation of the Mycophenolate REMS so that patients understand the risks associated with exposure to mycophenolate during pregnancy.

Increased Risks of First Trimester Pregnancy Loss and Congenital Malformations

Mycophenolate can cause fetal harm when administered to a pregnant female. Exposure to mycophenolate during pregnancy is associated with an increased risk of:

- First trimester pregnancy loss
- Congenital malformations, especially:
 - external ear
 - cleft lip and palate abnormalities
- Anomalies of:
 - the distal limbs
 - heart
 - esophagus
 - kidney
 - nervous system

In December 2006, the National Transplantation Pregnancy Registry (NTPR) published data from prospective cases where 24 female transplant patients reported 33 mycophenolate-exposed pregnancies.* Of these pregnancies, there were:

- 15 spontaneous abortions (45%)
- 18 live-born infants
 - Four of the 18 live-born infants had structural malformations (22%)

Of the 77 females exposed to systemic mycophenolate during pregnancy that were reported in postmarketing data[†] (collected between 1995 and 2007):

- 25 had spontaneous abortions
- 14 had a malformed fetus or infant
 - Six of the 14 malformed offspring had ear abnormalities

The reported malformations were similar to findings in animal reproductive toxicology studies. For comparison, background rate for congenital anomalies in the United States is about 3% and the NTPR data show a rate of 4% to 5% among babies born to organ-transplant patients using other immunosuppressive drugs. Because these postmarketing data are reported voluntarily, it is not always possible to reliably estimate the frequency of particular outcomes.

*Sifontis NM, et al. Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus. *Transplantation*. 2006;82:1698-1702.

[†]Prescribing Information for mycophenolate.

Your Role in Mycophenolate REMS

You need to complete the following steps to help ensure the implementation of Mycophenolate REMS with females of reproductive potential:

1. **Document** your Training in the Mycophenolate REMS program
2. **Educate** Females of Reproductive Potential
3. **Obtain** a Signed *Mycophenolate REMS Patient-Prescriber Acknowledgment Form* from Females of Reproductive Potential
4. **Check** Pregnancy Status
5. **Report** any Mycophenolate-Exposed Pregnancies

1. Document your Training in the Mycophenolate REMS

You should become familiar with the risks of embryofetal toxicity associated with mycophenolate and the requirements of Mycophenolate REMS.

As a prescriber of mycophenolate, you should document your training by completing a *Mycophenolate REMS Prescriber Training Confirmation Form* to document that you understand, and will comply with Mycophenolate REMS.

You can submit a prescriber training confirmation form to Mycophenolate REMS by one of several ways:

- Visit www.MycophenolateREMS.com and complete the online form
- Complete a hard copy and submit it via fax to **1-800-617-5768**
- Complete a hard copy and mail it to:
Mycophenolate REMS
200 Pinecrest Plaza
Morgantown, WV 26505-8065
- Call **1-800-617-8191**

This brochure is not a comprehensive description of the risks associated with the use of mycophenolate.

2. Educate Females of Reproductive Potential

■ Educate females about the risks of mycophenolate exposure during pregnancy.

Discuss the increased risks of first trimester pregnancy loss and congenital malformations associated with exposure to mycophenolate during pregnancy with females of reproductive potential before initiating or continuing treatment

The information you share in this discussion will be reinforced by the *Mycophenolate REMS Patient Brochure: What You Need to Know About Mycophenolate*.

■ Provide females of reproductive potential with a *Mycophenolate REMS Overview & Your Birth Control Options* booklet.

Patients need to understand:

- 1) the increased risks of first trimester pregnancy loss and congenital malformations while using mycophenolate
- 2) their birth control options
- 3) their role in the Mycophenolate REMS program

■ Provide pregnancy planning education

- Advise patients using mycophenolate to let you know if they are considering pregnancy.
- Determine whether there are appropriate treatment options with less potential for embryofetal toxicity.
- It is important to optimize the patient's underlying medical condition(s) and nutritional status prior to conception.
- Refer patients for pre-conception counseling and high risk obstetrical care as needed and coordinate care among the patient's established providers.

■ Provide contraception counseling

Unless patients choose not to have sexual intercourse with a man at any time (abstinence), you must instruct them to always use acceptable contraception:

- During entire treatment with mycophenolate
- For 6 weeks after they stop taking mycophenolate

Your Role in Mycophenolate REMS (cont'd)

The following table lists the forms of contraception that are acceptable for use during treatment with mycophenolate. Guide your patients to choose from the following birth control options:

Acceptable Contraception Methods for Females of Reproductive Potential*			
Option 1 Methods to Use Alone	Intrauterine devices (IUDs) Tubal sterilization Patient's partner had a vasectomy		
OR			
Option 2 Choose One Hormone Method AND One Barrier Method	Hormone Methods choose 1		Barrier Methods choose 1
	Estrogen and Progesterone Oral contraceptive pill Transdermal patch Vaginal ring Progesterone-only Injection Implant	AND	Diaphragm with spermicide Cervical cap with spermicide Contraceptive sponge Male condom Female condom
OR			
Option 3 Choose One Barrier Method from each column (<i>must choose two methods</i>)	Barrier Methods choose 1		Barrier Methods choose 1
	Diaphragm with spermicide Cervical cap with spermicide Contraceptive sponge	AND	Male condom Female condom

***Females of reproductive potential** include girls who have entered puberty and all women who have a uterus and have not passed through menopause.

Note: Mycophenolate reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness. Therefore, an additional barrier method of contraception must be used with all hormonal methods.



EMERGENCY CONTRACEPTION

- Patients should also be counseled on the availability of emergency contraception in the event they have intercourse without acceptable contraception or their contraceptive methods fail.
- Patients 17 years and older can purchase emergency contraception over the counter.

3. Obtain a signed *Mycophenolate REMS Patient-Prescriber Acknowledgment Form*

- **Patients and prescribers should sign the patient-prescriber acknowledgment form.**

By signing this form, patients agree that they will comply with Mycophenolate REMS program. For patients who are minors, a legal guardian needs to sign in addition to the patient.

You too, as the prescriber, should sign the form and give a signed copy to the patient.

Retain the original signed copy for your records.

Your Role in Mycophenolate REMS (cont'd)

4. Check Pregnancy Status

You must determine if females of reproductive potential are pregnant:

- One pregnancy test with a sensitivity of at least 25 mIU/mL should be done immediately before starting mycophenolate
- Another pregnancy test with the same sensitivity should be done 8 to 10 days later
- Repeat pregnancy tests should be performed at routine follow-up visits
- Results of all pregnancy tests should be discussed with the patient
 - In the event of a positive pregnancy test, patients should continue to take mycophenolate until a discussion can take place on the risks and benefits of mycophenolate treatment with the patient.
 - The patient should be apprised of the potential hazard to the fetus.
 - In certain situations, you and the patient may decide that the maternal benefits outweigh the risks to the fetus.

5. Report any pregnancies to the Mycophenolate Pregnancy Registry

The Mycophenolate Pregnancy Registry has been established to evaluate mycophenolate-exposed pregnancies and their outcomes. These data will provide an opportunity to learn more about mycophenolate exposure in utero.

Instruct patients to tell you if they get pregnant during treatment with mycophenolate or within 6 weeks following discontinuation of treatment.

If you learn that a patient is pregnant:

- Report the pregnancy to the Mycophenolate Pregnancy
 - By phone: **1-800-617-8191**
 - Online:
www.MycophenolatePregnancyRegistry.com; or
 - By mail:
Mycophenolate Pregnancy Registry
200 Pinecrest Plaza
Morgantown, WV 26505-8065

Reporting a Pregnancy

Patients should be informed that you will report any pregnancies of which you become aware to the Mycophenolate Pregnancy Registry. Provision of patient contact and medical information to the Mycophenolate Pregnancy Registry is covered by an HIPAA waiver.

- Encourage the patient to participate in the Mycophenolate Pregnancy Registry

Mycophenolate REMS Resources

These resources have been developed to help ensure that you and your patients understand the risks associated with exposure to mycophenolate during pregnancy and to comply with the requirements of the Mycophenolate REMS.

These resources, some of which have been described previously, are available either in the

- **Mycophenolate REMS Web Site:**
www.MycophenolateREMS.com

The website provides information about Mycophenolate REMS, including the option to order or download resource materials. All REMS materials for HCPs and patients are available on this website. Prescribers can document their training in the Mycophenolate REMS on this website.

- **Mycophenolate REMS Healthcare Provider Brochure** (this brochure)

- **Mycophenolate REMS Patient Brochure: What You Need to Know About Mycophenolate**

This brochure helps patients understand the increased risks of first trimester pregnancy loss and birth defects with mycophenolate, provides an overview of acceptable forms of contraception, and the Mycophenolate REMS program. You should provide your patient with this brochure.

- **Mycophenolate REMS Patient-Prescriber Acknowledgment Form**

- **Mycophenolate REMS Prescriber Training Confirmation Form**

Prescribers document training in Mycophenolate REMS by completing this form

- **Mycophenolate REMS Center Training Confirmation Form**

Centers document training in Mycophenolate REMS by completing this form

- **Mycophenolate REMS Obstetrician/Gynecologist Referral Template Letters**

These customizable letters available online at Letters can be used by prescribers of mycophenolate to help establish a working relationship with an OB/GYN for patient counseling. There are 2 letter templates—one for contraception counseling and one for pregnancy planning education—that can be customized for your practice and patient before sending to an OB/GYN

- **Medication Guide**

There is a separate Medication Guide for each mycophenolate formulation

- **Mycophenolate Pregnancy Registry Frequently Asked Questions for Patients**

This document answers some common questions about the Mycophenolate Pregnancy Registry in patient-friendly language

Mycophenolate REMS Resources (cont'd)

■ Mycophenolate Pregnancy Registry

The Mycophenolate Pregnancy Registry evaluates mycophenolate-exposed pregnancies and their outcomes. You can contact the Mycophenolate Pregnancy Registry by calling **1-800-617-8191** or visiting www.MycophenolatePregnancyRegistry.com

For more information about Mycophenolate REMS and for all resource materials

- Visit www.MycophenolateREMS.com
- Call **1-800-617-8191**

Additional Resources

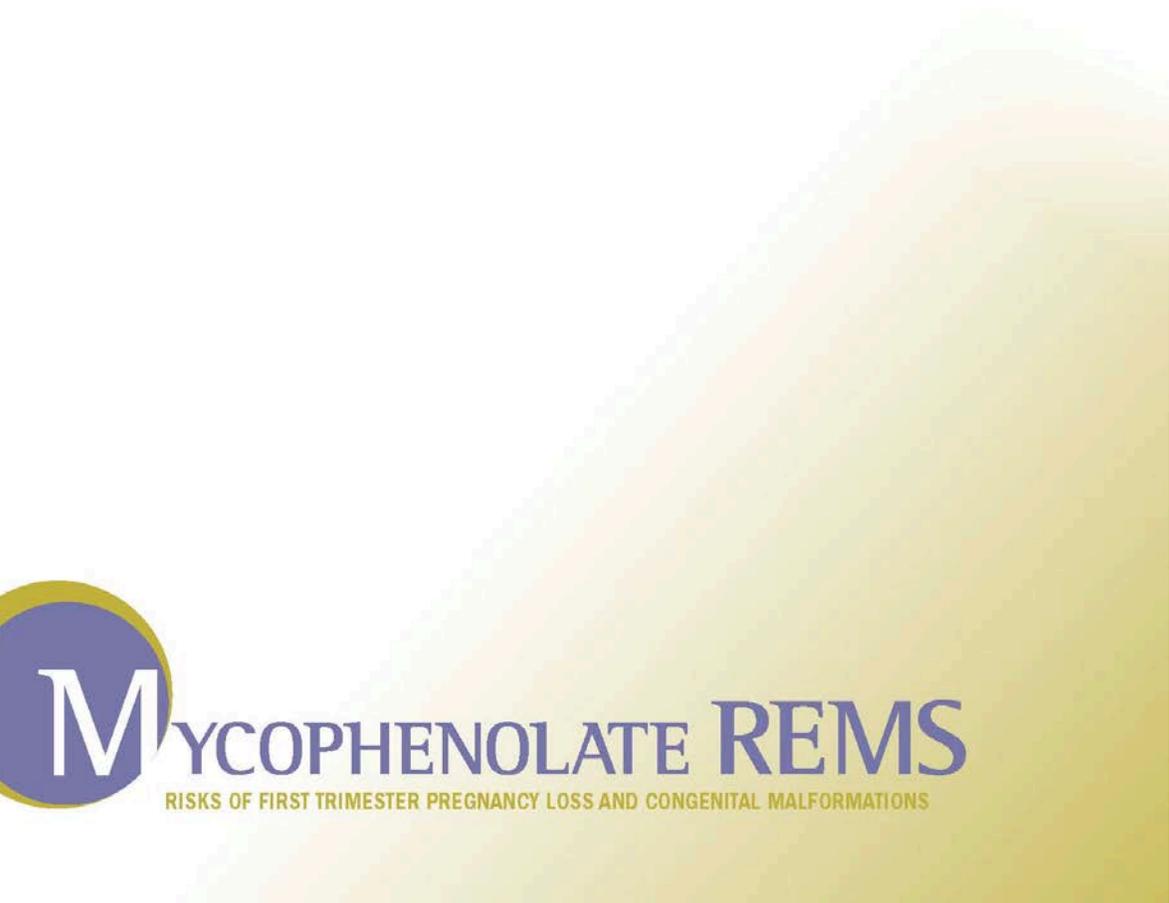
FOR MORE INFORMATION ABOUT CONTRACEPTION*

- Association of Reproductive Health Professionals: www.arhp.org
- Planned Parenthood: www.plannedparenthood.org

FOR MORE INFORMATION ABOUT BIRTH DEFECTS*

- Centers for Disease Control and Prevention: www.cdc.gov

*Mycophenolate REMS is neither affiliated with nor an endorser of these organizations. The information provided by Mycophenolate REMS or these organizations is meant for informational purposes only, and is not intended to replace your medical advice to your patients.



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