MYCOPHENOLATE REMS

HEALTHCARE PROVIDER BROCHURE

What you need to know about mycophenolate use, first trimester pregnancy loss, and congenital malformations.

What is my role in the Mycophenolate REMS?	
1	Document your training in the Mycophenolate REMS
2	Educate Females of Reproductive Potential on the increased risks of mycophenolate
3	Check pregnancy status of patients
4	Reassess treatment options for patients who are considering becoming pregnant
5	Report any pregnancies to the Mycophenolate Pregnancy Registry

For complete safety information and a comprehensive description of the increased risks associated with mycophenolate, please see *Prescribing Information*, including Boxed WARNING and *Medication Guide*, which can be found at **www.MycophenolateREMS.com**

MYCOPHENOLATE AND INCREASED RISKS OF EMBRYOFETAL TOXICITY

There are increased risks of first trimester pregnancy loss and congenital malformations associated with mycophenolate. As a healthcare provider, here is what you should know.

MYCOPHENOLATE PREGNANCY RISKS

- 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, but not limited to:
    - the distal limbs, heart, esophagus, kidney, nervous system

MYCOPHENOLATE REMS

- The Food and Drug Administration (FDA) requires a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of taking a drug outweigh the serious risks.
- The Mycophenolate REMS is required due to post marketing reports showing that exposure to mycophenolate during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations.
- Mycophenolate is available by prescription as:
  - CellCept® (mycophenolate mofetil), Myfortic® (mycophenolic acid), Generic mycophenolate mofetil, Generic mycophenolic acid.

DATA INSIGHTS

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†:

- 25 had spontaneous abortions
- 14 had a malformed fetus or infant, of which six had ear abnormalities

While available data are limited, structural malformations occur in approximately 20% of live-born infants exposed in utero to mycophenolate. First trimester pregnancy loss rates have been reported to be approximately 45%*†.

HEALTHCARE PROVIDER INFORMATION

- All prescribers of mycophenolate and females of reproductive potential, whether or not they plan to get pregnant, should be aware of the increased risks associated with mycophenolate.
- Females of reproductive potential include girls who have entered puberty and all women who have a uterus and ovaries and have not passed through menopause.
- Menopause is the permanent end of menstruation and fertility, and should be clinically confirmed by a patient's healthcare practitioner. Commonly used diagnostic criteria include:
  - 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or therapy)
  - Post-surgical from a bilateral oophorectomy

*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.
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As a healthcare provider, you need to complete the following five steps to help ensure the implementation of Mycophenolate REMS with females of reproductive potential:

1 DOCUMENT YOUR REMS TRAINING

- Become familiar with the increased risks of embryofetal toxicity associated with mycophenolate and the requirements of the Mycophenolate REMS
- Consider enrolling in an accredited CME/CE activity to further understand your role in the treatment of patients taking mycophenolate products. A full list of CME/CE providers can be found at MycophenolateREMS.com
- Complete and submit the online *Prescriber Training Confirmation Form* to document that you understand, and will comply with the Mycophenolate REMS requirements. Submit your form by:
  - Visiting MycophenolateREMS.com
  - Calling 1-800-617-8191, Faxing a hard copy to 1-800-617-5768, or emailing a copy to support@mycophenolateREMS.com
  - Contacting the Mycophenolate REMS Coordinating Center at 1-800-617-8191 for the mailing address

2 EDUCATE FEMALES OF REPRODUCTIVE POTENTIAL

- Educate females about the increased risks of mycophenolate exposure during pregnancy
- Provide females of reproductive potential with a *Patient Information Brochure: What You Need To Know About Mycophenolate* and review it with them.
- Provide pregnancy planning education
- 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
    - Emergency contraception

ACCEPTABLE BIRTH CONTROL OPTIONS

Guide your patients to choose from the following birth control options for use during treatment with mycophenolate:

Option 1 | Use Method Alone

- Pick one item from (A)
  - Most effective: Less than 1 pregnancy per 100 women in one year

A


Intrauterine Device (IUD)

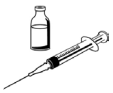

Tubal Sterilization


Vasectomy

Option 2 | Use Hormone & Barrier

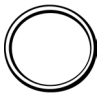
- Pick one item from (B) **and** one item from (C1) or (C2) shown below
  - 4-7 pregnancies per 100 women in one year

B


Progesterone Only Injection


Birth Control Pill


Birth Control (Progesterone) Patch


Vaginal Ring


Progesterone Only Implant

Option 3 | Use Two Barriers

- Pick one item from (C1) **and** one from (C2)
  - Least effective: 13 or more pregnancies per 100 women in one year

C

1


Female Condom


Male Condom

2


Female Diaphragm with Spermicide


Female Birth Control Sponge


Cervical Cap with Spermicide

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.
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3 CHECK PREGNANCY STATUS

- 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 increased 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 increased risks to the fetus.

4 REASSESS TREATMENT OPTIONS FOR PATIENTS WHO ARE CONSIDERING BECOMING PREGNANT

- Determine whether there are appropriate treatment options with less potential for embryofetal toxicity.
- Refer patients for pre-conception counselfing and high-risk obstetrical care as needed and coordinate care among the patient's established providers.

5 REPORT MYCOPHENOLATE-EXPOSED PREGNANCIES

- 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 Registry by:
  - Visiting **www.MycophenolateREMS.com**
  - Calling 1-800-617-8191
  - Contacting the Mycophenolate REMS Coordinating Center at 800-617-8191 for the mailing address
- Inform your patient 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 a HIPAA waiver.

ADDITIONAL RESOURCES

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

- Patient Information Brochure
- Prescriber Training Confirmation Form
- Center Training Confirmation Form
- Medication Guides
- Mycophenolate Pregnancy Registry Frequently Asked Questions (FAQs) for Patients
- Contraception: plannedparenthood.org
- Birth Defects: CDC.gov
- Birth Control: FDA.gov

For additional resources and more information about the Mycophenolate REMS, please visit **www.MycophenolateREMS.com** or call the Mycophenolate REMS at **1-800-617-8191.**

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