FDA's Mycophenolate REMS Education Blueprint for Healthcare Providers Who Prescribe

Background

In September 2012, FDA approved the Mycophenolate Shared System Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of mycophenolate outweigh the risks. The Mycophenolate REMS covers the following products: CellCept® (mycophenolate mofetil), Myfortic® (mycophenolic acid), generic mycophenolate mofetil and generic mycophenolic acid.

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

1. Educating healthcare providers 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 miscarriage and birth defects.
   - The importance of pregnancy prevention and planning when taking mycophenolate.

As part of the Mycophenolate REMS, Mycophenolate Applicants must provide training for healthcare providers who prescribe mycophenolate.

The Agency believes there is an opportunity to expand the educational reach of the training by including alternate options for educating healthcare providers, such as continuing education. To facilitate the development of continuing education (CE) educational materials and activities as part of the Mycophenolate REMS, FDA has developed an FDA Blueprint for the Mycophenolate REMS, hereafter referred to as the Blueprint. The Blueprint contains a high-level outline of the core educational messages that must be included in the educational programs developed under the Mycophenolate REMS. The core messages are directed to healthcare providers who prescribe and/or participate in the treatment of patients taking mycophenolate products.

Accrediting bodies and CE providers will ensure that the CE activities developed comply with the standards for CE of the Accreditation Council for Continuing Medical Education, or another CE accrediting body, depending on the target audience's medical specialty or healthcare profession. FDA will make the *Blueprint*, approved as part of the Mycophenolate REMS, available on the REMS@FDA Website (www.fda.gov/REMS), where it will remain posted for use by CE providers as they develop the

CE materials and activities. A list of the REMS-compliant CE activities supported by unrestricted educational grants from the MRG to accredited CE providers should also be posted on the following website, (insert link when available) as that information becomes available.

Reasons why healthcare provider education is so important

Healthcare providers should be aware that there are increased risks of first trimester pregnancy loss and congenital malformations associated with exposure to mycophenolate products during pregnancy. Surveys have indicated that female patients taking mycophenolate products during reproductive age may NOT understand these risks. It is important to improve patient understanding of the risk and provide contraception counseling to reduce the number of unplanned pregnancies to women taking mycophenolate products.

Purpose of the Mycophenolate Healthcare Provider Educational Effort[1]

The Agency believes there is an opportunity to expand the educational reach of the training by including alternate options for educating healthcare providers, such as CE. REMS-based CE training can be effective in improving stakeholder participation in REMS programs both when training is voluntary for healthcare providers, such as in the Mycophenolate REMS.

Following completion of educational activities under the Mycophenolate REMS, healthcare providers should be knowledgeable about the following:

- The increased risks of first trimester pregnancy loss and congenital malformations associated with mycophenolate.
- Importance of educating females of reproductive potential about the increased risk of first trimester pregnancy loss and congenital malformations associated with exposure to mycophenolate during pregnancy.
- Importance of prescribers providing or facilitating patient education about pregnancy prevention and planning, including acceptable methods of contraception during mycophenolate treatment.
- When treating a pregnant patient or a patient who is considering pregnancy, consider alternative immunosuppressants with less potential for embryofetal toxicity.
- Importance of reporting to the Mycophenolate Pregnancy Registry any pregnancies that occur during mycophenolate treatment or within 6 weeks following discontinuation of treatment.
- Importance of encouraging pregnant patients to participate in the Mycophenolate Pregnancy Registry.

[1] U.S. Food and Drug Administration. REMS and Continuing Education for Health Care Providers — FDA Feasibility Report. November 2017. https://www.fda.gov/media/109104/download. Accessed April 30, 2019.

At a minimum, the following content should be included in the developed CE program:

Section 1: Product Information
Mycophenolate is an immunosuppressant available in two formulations: mycophenolate mofetil or mycophenolic acid.

Mycophenolate mofetil is approved for the indication of prophylaxis of organ rejection in recipients of allogeneic kidney, heart or liver transplants, in combination with other immunosuppressants. It is available as an oral capsule, oral tablet, oral suspension, or injection.

Mycophenolic acid is approved for the indication of prophylaxis of organ rejection in adult patients receiving kidney transplants and in pediatric patients at least 5 years of age and older who are at least 6 months post kidney transplant and should be used in combination with cyclosporine and corticosteroids. It is available as a delayed release tablet containing enteric-coated mycophenolate sodium.

Section 2: Embryofetal toxicity
Mycophenolate can cause fetal harm when administered to a pregnant female. Exposure to mycophenolate products during pregnancy is associated with an increased risk of:

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

Risk summary of mycophenolate exposure in pregnancy

- Refer to individual product labeling, Section 8 Use in Special Populations for the most recent data on risk of pregnancy loss and congenital malformations.

Healthcare providers need to be aware of their responsibilities in the Mycophenolate REMS in order to encourage implementation of the Mycophenolate REMS. The training available to healthcare providers encourages them to document training in the Mycophenolate REMS and acknowledge that they:
1) train themselves or a staff member in contraceptive counseling and education of patients on acceptable use of their chosen contraceptive method(s);
and 2) develop a strong relationship and partner with an obstetrician/gynecologist or women's healthcare provider that can counsel their patients about contraception, prescribe the full range of available contraceptive methods, and provide fitting/insertion, demonstration, and/or instruction on acceptable uses.

Section 3: Management of Mycophenolate in Females of Reproductive Potential
Definitions:

- 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.

- Menopause should be clinically confirmed by a patient's healthcare practitioner. Some commonly used diagnostic criteria include:
    - 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy)
    - Post-surgical from a bilateral oophorectomy

Healthcare providers need to understand their role in managing mycophenolate in females of reproductive potential:

1. Educate females of reproductive potential using the Patient Counseling Materials (*Mycophenolate REMS Brochure: What You Need to Know About Mycophenolate*)
    a. Educate about the risks of mycophenolate exposure during pregnancy
    b. Provide contraception counseling including:
        i. Acceptable contraception methods
        ii. Duration of contraception
            1. During entire treatment with mycophenolate
            2. For 6 weeks after patients stop taking mycophenolate
        iii. Emergency contraception
    c. Provide pregnancy planning education including:
        i. Advise patients to let providers know if they are considering pregnancy
2. Check Pregnancy Status
    a. Determine if females of reproductive potential are pregnant:
        i. One pregnancy test with a sensitivity of at least 25 mIU/mL should be done immediately before starting mycophenolate
        ii. Another pregnancy test with the same sensitivity should be done 8 to 10 days later
        iii. Repeat pregnancy tests should be performed at routine follow-up visits
        iv. Results of all pregnancy tests should be discussed with the patient
            1. 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.
            2. The patient should be apprised of the potential hazard to the fetus.
            3. In certain situations, you and the patient may decide that the maternal benefits outweigh the risks to the fetus.
3. Reassess treatment options for patients who are considering to become pregnant
    a. Determine whether there are appropriate treatment options with less potential for embryofetal toxicity
    b. Refer patients for pre-conception counseling and high-risk obstetrical care as needed and coordinate care among the patient's established providers
4. Report any mycophenolate-exposed pregnancies

a. 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 the risks of mycophenolate exposure in utero.
b. Instruct patients to tell you if they get pregnant during treatment with mycophenolate or within 6 weeks following discontinuation of treatment.
c. If you learn that a patient is pregnant:
    i. Report the pregnancy to the Mycophenolate Pregnancy
        1. By phone: 1-800-617-8191
        2. Online: www.MycophenolatePregnancyRegistry.com; or
        3. By mail: Mycophenolate Pregnancy Registry, 200 Pinecrest Plaza, Morgantown, WV 26505-8065
    ii. Inform patients that you may report pregnancies to the Mycophenolate Pregnancy Registry. Provision of patient contact and medical information to the Mycophenolate Pregnancy Registry is covered by a HIPAA waiver.
        1. Encourage the patient to participate in the Mycophenolate Pregnancy Registry

Section 4. Additional Educational Resources

The Mycophenolate REMS website includes resources for education of healthcare providers and patients:

- Brochure for Healthcare Providers
- Patient Brochure: What You Need to Know About Mycophenolate