MYCOPHENOLATE REMS
RISKS OF FIRST TRIMESTER PREGNANCY LOSS AND CONGENITAL MALFORMATIONS

IMPORTANT DRUG WARNING
Regarding Mycophenolate-Containing Products

Indications and Important Selected Safety Information About Mycophenolate-Containing Products

Indications:

CellCept® (mycophenolate mofetil) is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. CellCept should be used concomitantly with cyclosporine and corticosteroids.

Myfortic® (mycophenolic acid) is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids.

Mycophenolate mofetil is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. Mycophenolate mofetil should be used concomitantly with cyclosporine and corticosteroids.

Mycophenolic acid is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids.

CONTRAINDICATIONS:

- Allergic reactions to mycophenolate-containing products have been observed; therefore, mycophenolate-containing products are contraindicated in patients with a hypersensitivity to mycophenolate mofetil, mycophenolic acid or any component of the drug product.
- CellCept Intravenous is contraindicated in patients who are allergic to Polysorbate 80 (TWEEN).

WARNING: EMBRYOFETAL TOXICITY, MALIGNANCIES AND SERIOUS INFECTIONS

Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Females of reproductive potential (FRP) must be counseled regarding pregnancy prevention and planning.

Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma and other neoplasms. Only physicians experienced in immunosuppressive therapy and management of organ transplant recipients should prescribe mycophenolate-containing products. Patients receiving mycophenolate-containing products should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

WARNINGS:

Embryofetal Toxicity

- Mycophenolate-containing products can cause fetal harm when administered to a pregnant female. Use of mycophenolate-containing products during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney.

Pregnancy Exposure Prevention and Planning

- Females of reproductive potential must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention and planning.

Lymphoma and Malignancy

- Patients receiving immunosuppressive regimens involving combinations of drugs, including mycophenolate-containing products, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin.

Combination with Other Immunosuppressive Agents

- Mycophenolate mofetil has been administered in combination with the following agents in clinical trials: antithymocyte globulin, OKT3, cyclosporine, and corticosteroids.
- Mycophenolic acid has been administered in combination with the following agents in clinical trials: antithymocyte/lymphocyte immunoglobulin, muromonab-CD3, basiliximab, daclizumab, cyclosporine, and corticosteroids.
- The efficacy and safety of the use of mycophenolate-containing products, in combination with other immunosuppressive agents have not been determined.

Serious Infections

- Patients receiving immunosuppressants, including mycophenolate, are at increased risk of developing bacterial, fungal, protozoal and new or reactivated viral infections, including opportunistic infections. These infections may lead to serious, including fatal outcomes.

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Important Selected Safety Information About Mycophenolate-Containing Products (cont'd)

- Polyomavirus associated nephropathy (PVAN), JC virus associated progressive multifocal leukoencephalopathy (PML), cytomegalovirus (CMV) infections, reactivation of hepatitis B (HBV) or hepatitis C (HCV) have been reported.

Neutropenia

- Severe neutropenia [absolute neutrophil count (ANC) <0.5 x 10^3/µL] developed in up to 2.0% of renal, up to 2.8% of cardiac, and up to 3.6% of hepatic transplant patients receiving mycophenolate mofetil 3g daily.
- Patients receiving mycophenolate-containing products should be monitored for neutropenia.
- If neutropenia develops [absolute neutrophil count (ANC) <1.3 x 10^3/µL] or anemia occurs, dosing with mycophenolate-containing products should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately.

Pure Red Cell Aplasia

- Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolate-containing products in combination with other immunosuppressive agents. Patients receiving mycophenolate-containing products should be monitored for blood dyscrasias.

CAUTION: CELLCEPT INTRAVENOUS SOLUTION SHOULD NEVER BE ADMINISTERED BY RAPID OR BOLUS INTRAVENOUS INJECTION

PRECAUTIONS:

Pregnancy Exposure Prevention and Planning

- Females of reproductive potential* must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention and planning.
- Females of reproductive potential taking mycophenolate-containing products must receive contraceptive counseling and use acceptable contraception during entire therapy with mycophenolate-containing products and for 6 weeks after stopping therapy (see full Prescribing Information for acceptable contraception methods).
- Patients should be aware that mycophenolate-containing products reduce blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness.
- To prevent unplanned exposure during pregnancy, females of reproductive potential should have a serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL immediately before starting a mycophenolate-containing product.
- Another pregnancy test with the same sensitivity should be done 8 to 10 days later. Repeat pregnancy tests should be performed during routine follow-up visits.
- Results of all pregnancy tests should be discussed with the patient.
- In the event of a positive pregnancy test, females should be counseled with regard to whether the maternal benefits of mycophenolate treatment may outweigh the risks to the fetus in certain situations.
- For patients who are considering pregnancy, consider alternative immunosuppressants with less potential for embryofetal toxicity.

Pregnancy Category D

- Mycophenolate-containing products can cause fetal harm when administered to a pregnant female. If mycophenolate-containing products are used during pregnancy, or if the patient becomes pregnant while taking mycophenolate-containing products, the patient should be apprised of the potential hazard to the fetus. In certain situations, the patient and her healthcare practitioner may decide that the maternal benefits outweigh the risks to the fetus. Risks and benefits of mycophenolate-containing products should be discussed with the patient.

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Important Selected Safety Information About Mycophenolate-Containing Products (cont'd)

- For those females using mycophenolate-containing products at any time during pregnancy and those becoming pregnant within 6 weeks of discontinuing therapy, the healthcare practitioner should report the pregnancy to the **Mycophenolate Pregnancy Registry (1-800-617-8191)**. The healthcare practitioner should also strongly encourage the patient to enroll in the pregnancy registry.

Gastrointestinal Disorders

- Gastrointestinal bleeding (requiring hospitalization) has been reported in de novo renal transplant patients (1.0%) and maintenance patients (1.3%) treated with mycophenolic acid (up to 12 months); and in approximately 3% of renal, in 1.7% of cardiac and in 5.4% of hepatic transplant patients treated with mycophenolate mofetil 3g daily.
- Mycophenolate-containing products should be administered with caution in patients with active serious digestive system disease because mycophenolate-containing products have been associated with an increased incidence of digestive system adverse events.

Concomitant Medications

- It is recommended that mycophenolate-containing products not be administered concomitantly with azathioprine because of the potential to cause bone marrow suppression and inhibit purine metabolism.
- Caution should be used in the concomitant administration of mycophenolate-containing products with drugs that interfere with enterohepatic recirculation such as cholestyramine because of the potential to reduce the efficacy of mycophenolate-containing products.

Immunizations

- During treatment with mycophenolate-containing products, avoid the use of live attenuated vaccines and advise patients that vaccinations may be less effective.

Phenylketonurics

- Care should be taken if mycophenolate mofetil oral suspension is administered to patients with phenylketonuria. Complete blood counts should be performed weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year.

Nursing Mothers

- It is not known whether mycophenolate-containing products are excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from mycophenolate-containing products, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
- Patients should not breastfeed during mycophenolate-containing products therapy.

ADVERSE REACTIONS:

- The principal adverse reactions associated with the administration of mycophenolate mofetil include diarrhea, leukopenia, sepsis, vomiting, and there is evidence of a higher frequency of certain types of infections, eg, opportunistic infections. Phlebitis and thrombosis have been reported with intravenous administration.
- The principal adverse reactions associated with the administration of mycophenolic acid include constipation, nausea, and urinary tract infection in de novo patients and nausea, diarrhea, and nasopharyngitis in maintenance patients.

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

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