

avert sequestration in March is grim. Congress has thus far proven incapable of agreeing on how to apply the remaining \$1.2 trillion of cuts mandated by the 2011 Budget Control Act, and Senate Minority Leader Mitch McConnell (R-KY) says additional revenue as an offset is off the table. It is hard to imagine how a deal can come together to avert se-

questration without revenue offsets or a complete repeal. And having delayed sequestration once, it is unlikely Congress would kick the can down the road again.

“ASN shares concerns about the growing national debt and supports responsible federal deficit reduction measures. But federal NDD programs like medical research are not the main

drivers of our nation’s debt and have already done a fair share for deficit reduction,” said ASN Research Advocacy Committee Chair John R. Sedor, MD. “I urge everyone to join ASN’s campaign in support of medical research and other NDD programs. Visit <http://www.asn-online.org/policy/> to learn how.” ●

U.S. Preventive Services Task Force Supports Kidney Disease Screening Research

By Ian H. de Boer, Grant Olan, and Uptal D. Patel, on behalf of the American Society of Nephrology Chronic Kidney Disease Advisory Group

In 2012, the Agency for Healthcare Research and Quality (AHRQ) comprehensively summarized the available evidence evaluating the risks and benefits of screening for chronic kidney disease (CKD) in the general population. Utilizing these data, the U.S. Preventive Services Task Force (USPSTF) determined that existing evidence was insufficient to balance the benefits and harms of routine screening for CKD in asymptomatic adults. Subsequently, the USPSTF identified screening for CKD as its top priority in a report to Congress on high-priority evidence gaps for clinical preventive services. USPSTF also identified screening for CKD in African Americans as the most important evidence gap related to specific populations.

ASN commended the USPSTF for its recommendation to Congress for further research on CKD screening to fill evidence gaps and also urged ongoing CKD screening among high-risk populations.

“The USPSTF recommendation shows the task force recognizes that CKD is a serious and growing public health threat,” said ASN CKD Advisory Group Chair Uptal D. Patel, MD. “More than 26 million Americans are estimated to have kidney disease today, and only 1 in 10 are aware they have the disease,” Patel said. “When identified by health professionals early, however, the progression of kidney disease to kidney failure can be slowed or halted, thus reducing the high morbidity and costs associated with dialysis and transplantation.”

The initial USPSTF determination specifically excluded people diagnosed with diabetes mellitus and hypertension. Diabetes and hypertension are the most common risk factors for CKD. The prevalence of CKD is approximately 27.5 percent among the 30.6 percent of adults 20 years of age or older in the United States with hypertension, and approximately 34.5 percent among the 10.6 percent of adults

Continued on page 14

Important Safety Information: (cont)

- **Embryofetal Toxicity:** *myfortic*[®] can cause fetal harm when administered to a pregnant female. Use of *myfortic*[®] during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations
- **Pregnancy Exposure Prevention and Planning:** FRP 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. (See additional important Pregnancy Testing, Contraception, and Pregnancy Planning information below)
- **Lymphoma and Other Malignancies:** Patients receiving immunosuppressive regimens involving combinations of drugs, including *myfortic*[®], as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin
- **Infections:** Oversuppression of the immune system can also increase susceptibility to infection, fatal infections, and sepsis
- **Polyomavirus Infections:** Immunosuppressed patients are at increased risk for opportunistic infections, including Polyomavirus infections. Polyomavirus infections in transplant patients may have serious and sometimes fatal outcomes. These include cases of JC virus-associated progressive multifocal leukoencephalopathy (PML) and Polyomavirus-associated nephropathy (PVAN), especially due to BK virus infections, which have been observed in patients receiving *myfortic*[®]. PVAN, especially due to BK virus infection, is associated with serious outcomes, including deteriorating renal function and renal graft loss. Patient monitoring may help detect patients at risk for PVAN
- Cases of PML have been reported in patients treated with MPA derivatives including MMF and mycophenolate sodium. PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies, and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms, and consultation with a neurologist should be considered as clinically indicated. Reduction in immunosuppression should be considered for patients who develop evidence of PML or PVAN. Physicians should also consider the risk that reduced immunosuppression represents to the graft
- **Blood Dyscrasias Including Pure Red Cell Aplasia:** Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA in combination with other immunosuppressive agents. In some cases, PRCA was found to be reversible with dose reduction or cessation of therapy with MPA derivatives. In transplant patients, however, reduced immunosuppression may place the graft at risk. Patients receiving *myfortic*[®] should be monitored for blood dyscrasias (eg, neutropenia or anemia). If blood dyscrasias occur (eg, neutropenia develops [ANC <1.3 x 10³/μL or anemia]), dosing with *myfortic*[®] should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately
- **Pregnancy Testing:** To prevent unplanned exposure during pregnancy, FRP should have a serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL immediately before starting *myfortic*[®]. 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
- **Contraception:** FRP taking *myfortic*[®] must receive contraceptive counseling and use acceptable contraception during the entire *myfortic*[®] therapy, and for 6 weeks after stopping *myfortic*[®], unless the patient chooses abstinence. Patients should be aware that *myfortic*[®] reduces blood levels of the hormones in the oral contraceptive pill, and could theoretically reduce its effectiveness. (Please see package insert for acceptable contraceptive methods for females)
- **Pregnancy Planning:** For patients who are considering pregnancy, consider alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of *myfortic*[®] should be discussed with the patient
- **Gastrointestinal Disorders:** Gastrointestinal bleeding (requiring hospitalization) has been reported in *de novo* renal transplant patients (1.0%) and maintenance patients (1.3%) treated with *myfortic*[®] (up to 12 months)
- **Patients with Renal Impairment:** Subjects with severe chronic renal impairment (GFR <25 mL/min/1.73 m²) may present higher plasma MPA and MPAG AUC relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG
- **Concomitant Medications:** Caution should be used with drugs that interfere with enterohepatic recirculation because of the potential to reduce efficacy
- **Hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) Deficiency:** *myfortic*[®] should be avoided in patients with HGPRT deficiency such as Lesch-Nyhan and Kelley-Seegmiller syndrome
- **Immunizations:** Use of live attenuated vaccines should be avoided
- The principal adverse reactions associated with the administration of *myfortic*[®] include constipation, nausea, and urinary tract infection in *de novo* patients and nausea, diarrhea, and nasopharyngitis in maintenance patients

Reference: 1. FDA approved drug products: mycophenolate mofetil. Drugs@FDA Web site. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=MYCOPHENOLATE%20MOFETIL>. Updated January 13, 2012. Accessed January 13, 2012.

Please see Brief Summary of Prescribing Information, including **Boxed WARNINGS**, on adjacent pages.



Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080 © 2012 Novartis 9/12 MYF-1163301



Policy Update

Task Force

Continued from page 13

20 years of age or older in the United States with diabetes. Clinical trials in these populations demonstrate that antihypertensive interventions reduce the risk of both CKD progression and cardiovascular complications.

For these reasons, ASN recommended to the USPSTF continued screening of patients with hypertension and diabetes for CKD. Existing guidelines from a number of professional organizations, including the American Diabetes Association, the National Kidney Foundation, and the Joint National Commission on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, also recommend screening these high-risk populations for CKD.

In addition to screening patients who have comorbid conditions that cause CKD, ASN's response to the USPSTF highlighted other patient characteristics that confer increased risk and may also warrant screening, including family history of kidney failure as a strong risk factor for kidney disease. The National Kidney Disease Education Program (NKDEP) at the National Institutes of Health has advocated for screening patients who have a family history of kidney disease.

Moreover, ASN noted that screening individuals with a family history of kidney disease may also help address disparities among racial and ethnic minority populations in the United States. African Americans and Native Americans are up to four times more likely than Caucasians to progress to kidney failure, while Hispanics are twice as likely. The elevated risk of developing CKD and kidney failure in these groups is not well explained by the higher prevalence of diabetes and hypertension. (African Americans, for example, are at disproportionate risk for developing focal segmental glomerulosclerosis and primary glomerulopathy, due in part to a high prevalence of high-risk polymorphisms in the *Apolipoprotein L1* gene.) However, recent findings indicate that CKD screening and treatment of African Americans may be more cost-effective than CKD screening and treatment of non-African Americans.

ASN also pointed out that NKDEP and the American Heart Association also recommend CKD screening for patients with a clinical diagnosis of cardiovascular disease, who are also at high risk of kidney disease. CKD is common among patients with cardiovascular disease and is a strong independent risk factor for cardiovascular events and death. As such, screening for CKD has been recommended for all adult patients with cardiovascular disease, including

those with coronary artery disease or congestive heart failure.

The thorough evaluation of CKD screening among asymptomatic adults without diabetes or hypertension completed by AHRQ and USPSTF raises important unanswered questions for public health. ASN recommends ongoing screening of high-risk groups

for CKD, both good for patients and good economic sense, and applauds the USPSTF recommendation to Congress for further research on CKD screening to fill evidence gaps. ●

Ian H. de Boer, MD, is affiliated with the division of nephrology at the Kidney Research Institute, University of

Washington, Seattle.

Grant Olan, is a policy associate with ASN. Uptal Patel, MD, is an associate professor of medicine and pediatrics, an investigator in the Health Services Research and Development Unit at the Durham Veterans Affairs Medical Center, and core faculty at the Duke Clinical Research Institute.

Myfortic® (mycophenolic acid*) delayed-release tablets *as mycophenolate sodium

Rx only

BRIEF SUMMARY: Please see package insert for full prescribing information.

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. (see WARNINGS and PRECAUTIONS)

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 Myfortic® (mycophenolic acid). Patients receiving Myfortic 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. (see WARNINGS and PRECAUTIONS)

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Myfortic® (mycophenolic acid) is contraindicated in patients with a hypersensitivity to mycophenolate sodium, mycophenolic acid, mycophenolate mofetil, or to any of its excipients.

WARNINGS (SEE BOXED WARNING)

EMBRYOFETAL TOXICITY

Myfortic can cause fetal harm when administered to a pregnant female. Use of Myfortic 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 (see PRECAUTIONS: Pregnancy).

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. For recommended pregnancy testing and contraception methods (see PRECAUTIONS: Pregnancy Exposure Prevention and Planning).

Lymphoma and Other Malignancies

Patients receiving immunosuppressive regimens involving combinations of drugs, including Myfortic® (mycophenolic acid), as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see ADVERSE REACTIONS). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

The rates for lymphoproliferative disease or lymphoma in Myfortic-treated patients were comparable to the mycophenolate mofetil group in the *de novo* and maintenance studies (see ADVERSE REACTIONS). As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Infections

Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis. Fatal infections can occur in patients receiving immunosuppressive therapy (see ADVERSE REACTIONS).

Polymavirus Infections

Patients receiving immunosuppressants, including Myfortic are at increased risk for opportunistic infections, including Polyomavirus infections. Polyomavirus infections in transplant patients may have serious, and sometimes, fatal outcomes. These include cases of JC virus associated progressive multifocal leukoencephalopathy (PML) and Polyomavirus associated nephropathy (PVAN) especially due to BK virus infection which have been observed in patients receiving Myfortic.

PVAN, especially due to BK virus infection, is associated with serious outcomes, including deteriorating renal function and renal graft loss (see ADVERSE REACTIONS). Patient monitoring may help detect patients at risk for PVAN.

Cases of PML, have been reported in patients treated with MPA derivatives which include mycophenolate mofetil (MMF) and mycophenolate sodium (see ADVERSE REACTIONS). PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Reduction in immunosuppression should be considered for patients who develop evidence of PML or PVAN. Physicians should also consider the risk that reduced immunosuppression represents to the functioning allograft.

Blood Dyscrasias Including Pure Red Cell Aplasia

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolic acid (MPA) derivatives in combination with other immunosuppressive agents. The mechanism for MPA derivatives induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppressive regimen is also unknown. In some cases PRCA was found to be reversible with dose reduction or cessation of therapy with MPA derivatives. In transplant patients, however, reduced immunosuppression may place the graft at risk. Changes to Myfortic therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimize the risk of graft rejection (see ADVERSE REACTIONS, Post-marketing Experience).

Patients receiving Myfortic should be monitored for blood dyscrasias (e.g. neutropenia or anemia (see PRECAUTIONS, Laboratory Tests)). The development of neutropenia may be related to Myfortic itself, concomitant medications, viral infections, or some combination of these events. If blood dyscrasias occur (e.g. neutropenia (ANC <1.3x10⁹/µL or anemia)), dosing with Myfortic should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see DOSAGE AND ADMINISTRATION in the full prescribing information).

Patients receiving Myfortic should be instructed to immediately report any evidence of infection, unexpected bruising, bleeding, or any other manifestation of bone marrow suppression.

Concomitant Use

Myfortic 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 Myfortic in combination with other immunosuppression agents have not been determined.

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 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) or 2) postsurgical from a bilateral oophorectomy.

Pregnancy Testing

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 Myfortic. 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.

Contraception

Females of reproductive potential taking Myfortic must receive contraceptive counseling and use acceptable contraception (see Table 4 for Acceptable Contraception Methods). Patients must use acceptable birth control during entire Myfortic therapy, and for 6 weeks after stopping Myfortic, unless the patient chooses abstinence (she chooses to avoid heterosexual intercourse completely).

Patients should be aware that Myfortic reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness (see PRECAUTIONS: Information for Patients and PRECAUTIONS: Drug Interactions: Oral Contraceptives).

Table 4 Acceptable Contraception Methods for Females of Reproductive Potential

Pick from the following birth control options:

Option 1		
Methods to Use Alone	Intrauterine devices (IUDs) Tubal sterilization Patient's partner had a vasectomy	
OR		
Option 2	Hormone Methods choose 1	Barrier Methods choose 1
Choose One Hormone Method AND One Barrier Method	Estrogen and Progesterone Oral Contraceptive Pill Transdermal patch Vaginal ring AND Progesterone-only Injection Implant	Diaphragm with spermicide Cervical cap with spermicide Contraceptive sponge Male condom Female condom
OR		
Option 3	Barrier Methods choose 1	Barrier Methods choose 1
Choose One Barrier Method from each column (must choose two methods)	Diaphragm with spermicide Cervical cap with spermicide Contraceptive sponge	AND Male condom Female condom

Pregnancy Planning

For patients who are considering pregnancy, consider alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of Myfortic should be discussed with the patient.

Gastrointestinal Disorders

Gastrointestinal bleeding (requiring hospitalization) has been reported in *de novo* renal transplant patients (1.0%) and maintenance patients (1.3%) treated with Myfortic® (mycophenolic acid) (up to 12 months). Intestinal perforations, gastrointestinal hemorrhage, gastric ulcers and duodenal ulcers have rarely been observed. Most patients receiving Myfortic were also receiving other drugs known to be associated with these complications. Patients with active peptic ulcer disease were excluded from enrollment in studies with Myfortic. Because MPA derivatives have been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, Myfortic should be administered with caution in patients with active serious digestive system disease (see ADVERSE REACTIONS).

Patients with Renal Impairment

Subjects with severe chronic renal impairment (GFR <25 mL/min/1.73 m²) may present higher plasma MPA and MPAG AUCs relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG.

In the *de novo* study, 18.3% of Myfortic patients versus 16.7% in the mycophenolate mofetil group experienced delayed graft function (DGF). Although patients with DGF experienced a higher incidence of certain adverse events (anemia, leukopenia, and hyperkalemia) than patients without DGF, these events in DGF patients were not more frequent in patients receiving Myfortic compared to mycophenolate mofetil. No dose adjustment is recommended for these patients; however, such patients should be carefully observed (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in the full prescribing information).

Concomitant Medications

In view of the significant reduction in the AUC of MPA by cholestyramine when administered with mycophenolate mofetil, caution should be used in the concomitant administration of Myfortic with drugs that interfere with enterohepatic recirculation because of the potential to reduce the efficacy (see PRECAUTIONS, Drug Interactions).

Patients with HGPRT Deficiency

On theoretical grounds, because Myfortic is an IMPDH inhibitor, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Immunizations

During treatment with Myfortic, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective (see PRECAUTIONS, Drug Interactions, Live Vaccines).