October 28 Is Deadline to Submit 2014 Annual Meeting Abstracts

The deadline to submit abstracts for the 2014 Annual Meeting in Philadelphia is October 28, 2013. In addition to abstracts in a wide variety of neuroscience topics, specific abstracts are sought for the Integrated Neuroscience Sessions. These half-day sessions provide in-depth subspecialty concentration around a topic, using a combination of presentations such as invited lectures, data blitz sessions, and poster rounds. Integrated Neuroscience Session topics for 2014 include:
- Temporal Lobe Epilepsy and Febrile Seizures
- New Antithrombotic Agents for Stroke Prevention
- Clocks, Sleep, Brain Health and Disorders: Impact on Mechanism, Expression, and Treatment
- Recent Advances in Translational Research in Autism
- Revolution of Genetic Tools and the Impact on Neurology
- Emerging Therapeutic Advances in Multiple Sclerosis
- Clinical Decision Making After the Dust Settles on Clinical Trials
- Emerging Concepts in Headache Therapy
- The Global Burden of Neurological Disease
- Proteinopathy in Neurodegenerative Disease
- Concussion in Sports and the Military
- Peripheral Neuropathy

Abstract submitters should complete the online form, available in early September, at www.aan.com/view/AM14 for their work to be considered. For more information, contact science@aan.com or (612) 928-6112.

Seeking Applications for 2014 Awards

The AAN is now accepting applications for the prestigious 2014 AAN awards to be presented at the 66th AAN Annual Meeting in Philadelphia. Each year, the AAN honors some of the best research and achievements by neurologists and neuroscientists around the globe with prizes and other compensation, such as complimentary travel expenses and registration for the Annual Meeting.

AAN awards recognize scientists at all stages of their careers for a variety of activities. Apply for one—or encourage your colleagues to apply—today.

Scientific Awards (Application Deadline: October 30)

- Extended Neuroscience Award
- G. Milton Shy Award in Clinical Neurology
- Roland P. Mackay Award in Historical Aspects
- Saul R. Korey Award in Experimental Neurology

AAN Launches Campaign to Stop Proposed EEG Cuts by CMS

The AAN is launching a major campaign to prevent proposed reimbursement cuts by CMS to physicians who perform EEG services. Under the latest CMS proposed fee schedule, neurologists who practice in an office setting and bill globally for EEG services could be subject to drastic cuts if a Medicare policy calling for a cap on practice expense values is finalized. For more information, see article on page 4.

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**NEWS BRIEFS**

- The AAN’s public relations campaign for its updated sports concussion guideline has reached $1 million in free publicity value.
- The AAN convened a panel to develop quality measures for the treatment of headache. An important part of the measure development process is soliciting comments from the public; this comment period will open on August 27 and run for 30 days. Visit AAN.com for more information.
- A record 152 applications were received for open jobs through the Neurology Career Center in July, topping the previous monthly record of 135 set in April 2013 and a sharp increase compared to 39 applications in July 2012.
- Members interested in serving on AAN committees and subcommittees can review job descriptions and indicate their interest online at www.aan.com/membership/committees/apply-for-a-committee. The current term for committees concludes April 25, 2015. Should vacancies arise during the current term the president will review the committee interest list.
AAN’s Commitment to Providing High-quality Education for Its Members

Because September is traditionally “back to school” month, this is an opportune time to call your attention to some of the Academy’s great educational offerings. In addition, there are significant savings to AAN members, who can also receive CME, self-assessment, and performance improvement credits that will count toward Maintenance of Certification (MOC) milestones mandated by the American Board of Psychiatry and Neurology.

The Academy’s next notable education event is our Fall Conference which will be held October 25 to 27 in Las Vegas. This regional meeting is designed to provide a more intimate and compact experience for attendees who want to brush up on their clinical skills with the Neurology Update series or improve efficiencies in their offices using the Practice Management track. Along with additional programs on “Physician-led Advocacy,” “Continuum® Test Your Knowledge,” and “Dystonia Skills Workshop,” the AAN is also responding to member needs with a “Neuromuscular Disease Update” and a free informational session on MOC.

It was not that long ago when evidence-based guidelines were dismissed as “cookbook medicine,” but now evidence-based medicine is acknowledged as the best way to address common clinical issues and provide the best patient care.

In this regard, I have been pleased to learn that the AAN’s Evidence-based Medicine (EBM) Toolkit training seminar has been a great success with our members, from program directors to experienced practicing neurologists. The next EBM training experience will be offered September 27 to 28 at our Minneapolis headquarters.

The AAN continues to add to a strong list of digital products that bring quality education to your desktop, laptop, or smartphone. These include the new NeuroLearn Recurrent Ischemic Stroke Prevention course and the NeuroSAE in Clinical Neurophysiology. Additionally, I have been told that the NeuroSAE 6th Edition will be available at the end of this month. Finally, throughout the year, the Academy has been presenting a series of Practice Management Webinars covering a wide variety of practice issues, and we recently added several free quality improvement topics.

I have emphasized in previous columns how crucial it is to be engaged with health policy decision makers ranging from Congress and public and private payers to state legislatures and hospital administrators. The AAN’s Donald M. Palatucci Advocacy Leadership Forum has trained more than 300 members to be effective advocates for both neurology and people living with neurologic disease. The Academy is now accepting applications (through September 29) for the 2014 Palatucci Forum which will take place in San Diego. I’m a graduate of the 2012 advocacy class, and I can tell you that this is a remarkable, effective, and energizing experience that is clearly having an impact in helping neurologists advocate effectively for our profession and the best care for our patients. Because PALF also includes neurologists from countries around the world, we are having a positive international impact on neurologists and neurologic patient care, as well.

While the 2014 Annual Meeting is still months away, registration opens in November for those early birds who want to assure themselves of getting valuable discounts and the hotel accommodations they desire in Philadelphia. I hope you’ll join us for part or all of the meeting, to be held April 26 to May 3.

You can learn more about these opportunities at our newly redesigned website at AAN.com.

It’s good to remember that the AAN’s education programs are developed and led by neurologists like you. They know the issues that concern you and have the expert skills to assemble the information you need to help you become a better neurologist.

Timothy A. Pedley, MD, FAAN
President, AAN
Upcoming Webinars Discuss Quality Improvement, Meaningful Use Stage 2

The AAN will offer a free webinar to members seeking to better understand quality improvement. “Quality Improvement: Beginning Steps in the Right Direction,” will be presented by Anup Patel, MD, member of the AAN Quality Measurement and Reporting Subcommittee, on September 17, from 12:00 p.m. to 1:00 p.m. ET. The deadline for registration is September 16 and the webinar is free for AAN members and $99 for nonmembers. No CME credits are available for this webinar. Upon completion, participants should be able to:

• Understand the language of quality improvement based on the Institute for Healthcare Improvement model
• Identify the tools and methods for planning and implementing quality improvement projects
• Examine quality improvement methods using an example from neurology

“Meaningful Use Stage 2: Prepare Your Practice” will be presented by Allison L. Weathers, MD, member of the AAN Practice Management and Technology Subcommittee, on October 8, from 12:00 p.m. to 1:30 p.m. ET. Physicians will earn 1.5 AMA PRA Category 1 Credits™ per webinar and non-physicians who attend will receive a certificate of completion. Register by October 7 to learn how to:

• Understand the federal incentives that are available for the use of an EHR
• Describe the requirements that must be met to obtain the incentives
• Apply with CMS to receive the incentives
• Understand what is required of a neurologist to demonstrate meaningful use
• Calculate the consequences for physicians who do not purchase an EHR
• Properly utilize available AAN resources
• Recognize changes between Stage 1 and Stage 2 of the Medicare EHR Incentive Program

With the exception of the free webinar, the cost to participate in the 2013 webinars is $149 for the first and $50 for each additional webinar—more than 25 percent off the pricing for nonmembers. The bundling discount is applicable only when multiple webinars are purchased in the same transaction. Participants are charged per phone line, so additional staff can listen in with no extra cost. All registrants will have access to both the live and recorded options for the webinar(s) they purchase. Slides are included with all webinar purchases. Learn more about these webinars and register at www.aan.com/view/pmw13. Even if you have scheduling conflicts, registration gives you access to the recorded webinar if you miss the live event!

Chronic Care Coordination, Revision of Physician Cost Structure in 2014 MPFS Proposed Rule

Neurologists may be able to receive payment for the management of chronic care services, according to the 2014 Medicare Physician Fee Schedule (MPFS) proposed rule released in July by the Centers for Medicare & Medicaid Services (CMS). CMS is proposing to create two new G codes to establish payment for complex chronic care management services. These codes will describe the typical non-face-to-face care management work involved for beneficiaries with multiple chronic conditions that are not adequately reflected in existing E/M codes.

Neurologists who satisfy the reporting requirements may be able to report these codes. However, the AAN recognizes that the standards are stringent and could potentially exclude neurologists. For example, CMS is linking the reporting of these codes to the physician who performs the annual wellness visit for the beneficiary. These codes will be implemented in 2015 in order to allow CMS sufficient time to develop and obtain public input on the standards necessary to report these services. The AAN expects to continue working with CMS and other stakeholders in the development of these codes.

In addition, Medicare payments from the Sustainable Growth Rate (SGR) potentially can decrease by 24 percent in 2014. However, Congress has acted to avert the cuts since 2003 and the AAN is working with Congress on legislation to permanently eliminate the SGR. CMS estimates that allowed charges for neurologists will decrease by two percent, though this will vary depending on the services a practice provides. Part of the decrease comes from a dramatic reduction in the technical component for EEG codes. This is due to a provision calling for a cap on practice expense values to not exceed the hospital outpatient payment rate.

“We are very concerned about the reduction in EEG services,” said Orly Avitzur, MD, MBA, FAAN, chair of AAN’s Medical Economics and Management Committee. “While neurologists who report the professional component only will not be affected, practices that own their EEG equipment

Continued on page 14
Stroke Is Subject of New Neurology Now Books Series Title

Navigating the Complexities of Stroke, published by the AAN’s Neurology Now® Books and now available through The AAN Store® and all major booksellers, provides a practical, straightforward, and accessible guide for people with stroke, their families and caregivers, and medical professionals.

The book is written by Louis R. Caplan, MD, FAAN, one of the world’s foremost authorities on stroke. Caplan expands on his earlier 2006 AAN book Stroke as he examines the anatomy and function of the brain and how blood flows to it from the heart. Caplan then explores the processes behind ischemic and hemorrhagic strokes and the damage they inflict—in children and young adults as well as older individuals. Along with detailing stroke risk factors, symptoms, how strokes are evaluated, and treatment and rehabilitation, Caplan shares the stories of real-life stroke victims and the challenges they, their families, and their caregivers face during treatment and recovery. The book is written in a highly readable style and format, with key information called out and important terms bolded and defined to help ease understanding. A question-and-answer approach is taken with practical information that may not be addressed in patient-physician meetings. The book runs 288 pages, includes illustrations, and sells for $19.95 to the public and $16.95 to AAN members.

The new stroke publication joins three other patient education books in the Neurology Now Books series: Navigating Smell and Taste Disorders, by Ronald DeVere, MD, and Marjorie Calvert; Navigating Life with a Brain Tumor, by Lynne P. Taylor, MD, and Alyx B. Porter Umphrey, MD, with Diane Richard; and Navigating Life with Parkinson’s Disease, by Sotirios Parashos, MD, PhD, and Rose Wichman, PT, with Todd Melby. All books can be purchased by AAN members at a discount through The AAN Store at www.aan.com/aanstore, where more information is available about each volume. Patients and caregivers may purchase the books through The AAN Store, Oxford University Press, or any major bookseller.


Save 10% when you register for a full program track!

Choose from:
- Neurology Update
- Practice Management

Hotel registration deadline: September 23
Early registration deadline: October 1

Learn more and register now at www.AAN.com/view/2013fall
Get Ready to Land Your Next Job

The AAN’s popular Neurology Career Week, offered online October 7 to 11, is quickly approaching. To get the most out of this neurology-focused job fair, with more than 400 open neurology positions, make sure you create or update a Job Seeker profile between now and October 11 for a chance to win a $500 Visa gift card and other prizes. Then, take advantage of these great opportunities to improve your resume, get insightful tips on making the most of your career, and more.

• Be one of the first 100 members to register for a CV review and it’s FREE. Submit your curriculum vitae to careers@aan.com by September 30 to receive a professional review.
• Thirty-minute personal sessions with a professional career coach via Skype are available FREE to the first 50 members who sign up. Email careers@aan.com to reserve your session.
• Attend free webinars on how to use the AAN’s Neurology Career Center to its fullest and get an overview of the neurology market and types of private practice and research jobs now available.

Learn more about Neurology Career Week and additional Neurology Career Center resources for job seekers and employers at www.aan.com/careers.

Movement Disorders Examined in Latest Continuum Audio

From recognizing psychogenic movement disorders and parkinsonian syndromes to treating chorea and myoclonus, the September and October issues of Continuum® Audio, the AAN’s exclusive CME audio program, will provide practical information on the care of patients with movement disorders.

“The experts also will discuss the most up-to-date information regarding diagnostic criteria, treatment options, and other important issues in the areas of dystonia, cerebellar and afferent ataxias, tremor syndromes, and tic disorders,” said Guest Editor Daniel G. Lariviere, MD, JD, FAAN.

The four-part series includes:

Hour 1:
Parkinsonian Syndromes: Clinical Recognition and Treatment / Irene Litvan, MD, FAAN
Tremor Syndromes: Clinical Recognition, Classification, and Treatment / Mark J. Edwards, MD, PhD

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Share Your Knowledge: Clinical Practice Journal Seeks Authors

The AAN’s journal Neurology® Clinical Practice encourages AAN members to share their insights, expertise, and experiences that may benefit others in their subspecialty or the larger neurology field. Topics can cover a wide area, such as:

How are you employing drugs and devices in your field?
What ethical challenges do you face?
Do you have a case report that is illustrative of a clinical challenge?
What challenges have you faced or successes have you enjoyed in bringing greater efficiency to your practice?

“We think Neurology: Clinical Practice is the perfect venue for a wide variety of articles that are directly relevant to the practicing clinician,” said Editor John R. Corboy, MD, FAAN.

“We have been humbled by the high level of articles published so far, and look forward to an ever expanding variety of submissions in the future.”

If you are interested in delivering a high-quality, peer-reviewed message, visit Neurology.org/cp to see the range of topics that have been published and refer to the “Information for Authors” section for style and format information. Papers can be submitted online at submit.cp.neurology.org.
IN THE TREATMENT OF RELAPSING FORMS OF MS

DON’T LET MS DEFINE YOUR PATIENTS

WARNING: HEPATOTOXICITY AND RISK OF TERATOGENICITY

Hepatotoxicity - Severe liver injury including fatal liver failure has been reported in patients treated with leflunomide, which is indicated for rheumatoid arthritis. A similar risk would be expected for teriflunomide because recommended doses of teriflunomide and leflunomide result in a similar range of plasma concentrations of teriflunomide. Concomitant use of AUBAGIO with other potentially hepatotoxic drugs may increase the risk of severe liver injury. Obtain transaminase and bilirubin levels within 6 months before initiation of AUBAGIO therapy. Monitor ALT levels at least monthly for six months after starting AUBAGIO. If drug induced liver injury is suspected, discontinue AUBAGIO and start an accelerated elimination procedure with cholestyramine or charcoal. AUBAGIO is contraindicated in patients with severe hepatic impairment. Patients with pre-existing liver disease may be at increased risk of developing elevated serum transaminases when taking AUBAGIO.

Risk of Teratogenicity - Based on animal data, AUBAGIO may cause major birth defects if used during pregnancy. Pregnancy must be excluded before starting AUBAGIO. AUBAGIO is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during AUBAGIO treatment or prior to the completion of an accelerated elimination procedure after AUBAGIO treatment.

Please see additional Important Safety Information and Brief Summary of Full Prescribing Information on the following pages.
FOCUS ON EVERY DAY

AUBAGIO® (teriflunomide)—a once-daily oral therapy for relapsing forms of MS

EFFICACY

INDICATION
AUBAGIO® (teriflunomide) is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

IMPORTANT SAFETY INFORMATION

Hepatotoxicity—AUBAGIO is contraindicated in patients with severe hepatic impairment and in patients taking leflunomide. Severe liver injury, including fatal liver failure, has been reported in patients treated with leflunomide, which is indicated for rheumatoid arthritis. Teriflunomide is the principal active metabolite of leflunomide. A similar risk would be expected for teriflunomide because recommended doses of teriflunomide and leflunomide provide similar plasma concentrations of teriflunomide. Obtain transaminase and bilirubin levels within 6 months before starting AUBAGIO; monitor ALT levels at least monthly for 6 months after starting AUBAGIO. Patients with preexisting liver disease may be at increased risk of elevated serum transaminases when taking AUBAGIO. Patients with preexisting acute or chronic liver disease, or those with serum alanine aminotransferase (ALT) >2 times the upper limit of normal (ULN) before initiating treatment, should not normally be treated with AUBAGIO. In clinical trials, if ALT elevation was >3 times the ULN on 2 consecutive tests, AUBAGIO was discontinued and patients underwent accelerated elimination.

Consider additional monitoring if coadministering AUBAGIO with other potentially hepatotoxic drugs because of increased risk of severe liver injury; monitor patients who develop symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine). If drug-induced liver injury is suspected, discontinue use of AUBAGIO, start accelerated elimination, and monitor liver tests weekly until normalized.

Risk of Teratogenicity—AUBAGIO is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Based on animal data, AUBAGIO may cause major birth defects if used during pregnancy. Before starting therapy, pregnancy must be excluded, use of reliable contraception confirmed, and the patient fully counseled. Patients having delayed onset of menses or other reason to suspect pregnancy should immediately notify their physician and be apprised of the potential hazards to the fetus. If the patient is pregnant or wishes to become pregnant, treatment should be discontinued immediately, followed by accelerated elimination until plasma concentrations of <0.02 mcg/mL are verified. It is not known whether AUBAGIO passes into breast milk; patients should be counseled on whether they should take AUBAGIO or breastfeed—they should not do both at the same time. Women who become pregnant while taking AUBAGIO should enroll in the AUBAGIO Pregnancy Registry to monitor fetal outcomes, by calling 1-800-745-4447, option 2.

AUBAGIO is eliminated slowly from the plasma. Without accelerated elimination, reaching plasma concentrations of <0.02 mcg/mL takes an average of 8 months or, in some patients, up to 2 years. Accelerated elimination may cause disease activity to return in patients who were responding to AUBAGIO treatment.

AUBAGIO is detected in human semen. Men not wishing to father a child should use reliable contraception to minimize possible risk. Men wishing to father a child should discontinue AUBAGIO and undergo accelerated elimination until plasma concentrations of <0.02 mcg/mL are verified.

Additional Safety Information
Decreases in white blood cell counts, mainly of neutrophils and lymphocytes, and platelets have been reported in clinical studies of AUBAGIO. Obtain a complete blood cell count within 6 months before

Please see Brief Summary of Full Prescribing Information, including boxed WARNING.
ONCE-DAILY ORAL DOSING

starting treatment. Further monitoring should be based on symptoms suggestive of bone marrow suppression. AUBAGIO is not recommended for patients with severe immunodeficiency, bone marrow disease, or severe uncontrolled infections. Treatment in patients with infection(s), acute or chronic, should not be started until the infection(s) is resolved. Medications such as teriflunomide have immunosuppressive potential; patients may therefore be more susceptible to infections.

The risk of malignancy, particularly lymphoproliferative disorders, is increased with some immunosuppressive medications.

Vaccination with live vaccines is not recommended.

Tuberculosis has been observed in clinical studies of AUBAGIO. Before starting treatment, screen patients for latent tuberculosis infection with a tuberculin skin test.

Peripheral neuropathy, including polyneuropathy and mononeuropathy, has been reported with AUBAGIO. Age >60 years, concomitant neurotoxic medications, and diabetes may increase the risk. If peripheral neuropathy is suspected, consider discontinuing treatment and performing accelerated elimination.

Transient acute renal failure and treatment-emergent hyperkalemia, as well as increased renal uric acid clearance, have been reported with AUBAGIO. Monitor renal function and potassium if symptoms of acute renal failure or hyperkalemia appear.

Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported rarely in rheumatoid arthritis patients receiving leflunomide, with a similar risk expected for teriflunomide; therefore, stop treatment and use accelerated elimination if a severe skin reaction develops.

Increased blood pressure has occurred with AUBAGIO. Hypertension was reported in 4% of patients taking AUBAGIO vs 2% on placebo. Measure blood pressure at treatment initiation and manage appropriately during treatment.

Interstitial lung disease and worsened preexisting interstitial lung disease have been reported with leflunomide, with a similar risk expected with teriflunomide.

Teriflunomide is an inhibitor of CYP2C8 and may be a weak inducer of CYP1A2. Monitor patients when teriflunomide is coadministered with drugs metabolized by these pathways.

A 25% decrease in peak international normalized ratio (INR) was observed when teriflunomide was coadministered with warfarin vs warfarin alone. Close INR follow-up and monitoring are recommended.

The type or dose of oral contraceptives used in combination with teriflunomide should be considered because of increased ethinylestradiol and levonorgestrel levels following repeated doses of teriflunomide.

The most frequent adverse reactions (≥10% and ≥2% greater than placebo) with AUBAGIO 7 mg and 14 mg and placebo, respectively, were ALT increased (12% and 14% vs 7%), alopecia (10% and 13% vs 3%), diarrhea (15% and 18% vs 9%), influenza (9% and 12% vs 10%), nausea (9% and 14% vs 7%), and paresthesia (9% and 10% vs 8%).

The safety and effectiveness of AUBAGIO have not been established in pediatric patients and in patients aged >65 years.

AUBAGIO is available in 14 mg and 7 mg tablets.
FOCUS ON EVERY DAY

AUBAGIO® (teriflunomide)—a once-daily oral therapy for relapsing forms of MS

Efficacy demonstrated in the 2-year pivotal trial1,2*

- Statistically significant reductions with AUBAGIO 14 mg in annualized relapse rate (ARR), risk of sustained disability progression,† and MRI total lesion volume‡
  - The 7 mg dose of AUBAGIO achieved statistically significant reductions in ARR and MRI total lesion volume but not in sustained disability progression

Safety profile informed by >1300 patient-years of exposure in Phase II and TEMSO Phase III trials3

- The most frequent adverse reactions (incidence ≥10% and ≥2% greater than placebo) with AUBAGIO 14 mg, AUBAGIO 7 mg, and placebo, respectively, were alanine aminotransferase (ALT) increases (14%, 12%, and 7%), alopecia (13%, 10%, and 3%), diarrhea (18%, 15%, and 9%), influenza (12%, 9%, and 10%), nausea (14%, 9%, and 7%), and paresthesia (10%, 9%, and 8%)2
- Similar proportions of patients in the AUBAGIO 14 mg and 7 mg and placebo groups had serious adverse events (AEs) (15.9%, 14.1%, and 12.8%, respectively)1
- Overall discontinuation rate due to AEs was 10.9% with AUBAGIO 14 mg, 9.8% with AUBAGIO 7 mg, and 8.1% with placebo1

Once-daily oral dosing2

- Once-daily tablet can be taken any place, any time, with or without food

*In a double-blind, placebo-controlled Teriflunomide Multiple Sclerosis Oral (TEMSO) study, 1088 patients with relapsing forms of MS were randomized to receive AUBAGIO 14 mg (n=359) or 7 mg (n=366) or placebo (n=363) for 108 weeks.†

†Sustained disability progression was defined as at least a 1-point increase from baseline Expanded Disability Status Scale (EDSS) score ≥5.5 (or at least a 0.5-point increase for those with a baseline EDSS score ≥5.5) sustained for at least 12 weeks.

‡Defined as the total volume of all abnormal brain tissue; calculated as the sum of the total volume of the T2 lesion component and the T1 hypointense lesion component (prespecified end point).

AUBAGIO is contraindicated in patients with severe hepatic impairment, in pregnant women, in women of childbearing potential who are not using reliable contraception, and in patients currently taking leflunomide.

Please see brief summary of Full Prescribing Information, including boxed WARNING regarding hepatotoxicity and use in pregnancy.

WARNINGS: HEPATOTOXICITY AND RISK OF TERATOGENICITY

Hepatotoxicity
Severe liver injury including fatal liver failure has been reported in patients treated with leflunomide, which is indicated for rheumatoid arthritis. A similar risk would be expected for teriflunomide because recommended doses of teriflunomide and leflunomide result in a similar range of plasma concentrations of teriflunomide. Concomitant use of AUBAGIO with other potentially hepatotoxic drugs may increase the risk of severe liver injury. Obtain transaminase and bilirubin levels within 6 months before initiation of AUBAGIO therapy. Monitor ALT levels at least monthly for six months after starting AUBAGIO [see Warnings and Precautions (5.1)]. If drug induced liver injury is suspected, discontinue AUBAGIO and start an accelerated elimination procedure with cholestyramine or charcoal [see Warnings and Precautions (5.3)]. AUBAGIO is contraindicated in patients with severe hepatic impairment [see Contraindications (4.1)]. Patients with pre-existing liver disease may be at increased risk of developing elevated serum transaminases when taking AUBAGIO.

Risk of Teratogenicity
Based on animal data, AUBAGIO may cause major birth defects if used during pregnancy. Pregnant women must be advised that AUBAGIO is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during AUBAGIO treatment or prior to the completion of an accelerated elimination procedure after AUBAGIO treatment [see Contraindications (4.2), Warnings and Precautions (5.2), and Use in Specific Populations (8.1)].

1. INDICATIONS AND USAGE
AUBAGIO® is indicated for the treatment of patients with relapsing forms of multiple sclerosis [see Clinical Studies (14) in the full prescribing information].

2. DOSAGE AND ADMINISTRATION
The recommended dose of AUBAGIO is 7 mg or 14 mg orally once daily. AUBAGIO can be taken with or without food.

Monitoring to assess safety
- Obtain transaminase and bilirubin levels within 6 months before initiation of AUBAGIO therapy. Monitor ALT levels at least monthly for six months after starting AUBAGIO [see Warnings and Precautions (5.1)].
- Obtain a complete blood cell count (CBC) within 6 months before the initiation of treatment with AUBAGIO. Further monitoring should be based on signs and symptoms of infection [see Warnings and Precautions (5.4)].
- Prior to initiating AUBAGIO, screen patients for latent tuberculosis infection with a tuberculin skin test [see Warnings and Precautions (5.4)].
- Check blood pressure before start of AUBAGIO treatment and periodically thereafter [see Warnings and Precautions (5.9)].

4. CONTRAINDICATIONS
4.1. Severe Hepatic Impairment
Patients with severe hepatic impairment [see Warnings and Precautions (5.1)].

4.2. Patients Who are Pregnant or Women of Childbearing Potential Not Using Reliable Contraception
AUBAGIO may cause fetal harm when administered to a pregnant woman. In animal studies, teriflunomide has been shown to be selectively teratogenic and embryocidal in multiple species when administered during pregnancy at doses less than those used clinically. Nonclinical studies indicate further that the intended pharmacologic action of the drug is involved in the mechanism of developmental toxicity [see Use in Specific Populations (8.1)]. AUBAGIO is contraindicated in women who are pregnant or women of child bearing potential not using reliable contraception. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. If pregnancy does occur during treatment, the drug should be immediately discontinued and an accelerated elimination procedure should be initiated [see Warnings and Precautions (5.3)]. Under these conditions, the patient should be referred to an obstetrician/gynecologist, preferably experienced in reproductive toxicity, for further evaluation and counseling. [see Warnings and Precautions and Use in Specific Populations (5.2, 8.1)].

4.3. Current treatment with leflunomide
AUBAGIO is not administered to patients with leflunomide. AUBAGIO is contraindicated in patients with severe hepatic impairment [see Contraindications (4.1)]. In placebo-controlled trials, ALT greater than three times the ULN occurred in 14/429 (3%) and 21/415 (5%) of patients on teriflunomide 7 mg and 14 mg, respectively, and 17/421 (4%) of patients on placebo, during the treatment period. These elevations occurred mostly within the first year of treatment. Half of the cases returned to normal without drug discontinuation. In clinical trials, ALT elevation was greater than three times the ULN on two consecutive tests. AUBAGIO was discontinued and patients underwent an accelerated elimination procedure [see Warnings and Precautions (5.3)]. Of the patients who underwent discontinuation and accelerated elimination in controlled trials, half returned to normal or near normal values within 2 months of therapy.

One patient in the controlled trials developed ALT 32 times the ULN and jaundice 5 months after initiation of AUBAGIO 14 mg treatment. The patient was hospitalized for 5 weeks and recovered after plasmapheresis and cholestyramine accelerated elimination procedure. Teriflunomide-induced liver injury in this patient could not be ruled out.

Obtain serum transaminase and bilirubin levels within 6 months before initiation of AUBAGIO therapy. Monitor ALT levels at least monthly for six months after starting AUBAGIO. Consider additional monitoring when AUBAGIO is given with other potentially hepatotoxic drugs. Consider discontinuing AUBAGIO if serum transaminase increase (greater than three times the ULN) is continued or if severe hepatic injury occurs. In patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. If liver injury is suspected to be AUBAGIO-induced, discontinue teriflunomide and start an accelerated elimination procedure [see Warnings and Precautions (5.3)] and monitor liver tests weekly until normalized. If teriflunomide-induced liver injury is unlikely because some other probable cause has been found, resumption of teriflunomide therapy may be considered.

5.2. Use in Women of Childbearing Potential
There are no adequate and well-controlled studies evaluating AUBAGIO in pregnant women. However, based on animal studies, teriflunomide may increase the risk of teratogenic effects or fetal death when administered to a pregnant woman [see Contraindications (4.2)]. Women of childbearing potential must not be started on AUBAGIO until pregnancy is excluded and a negative pregnancy test has been confirmed that the woman is not pregnant. Before the initiation of treatment with AUBAGIO, patients must be fully counseled on the potential for serious risk to the fetus. The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must notify the physician immediately for pregnancy testing and, if positive, the physician and patient must discuss the risk to the fetus. It is possible that rapidly lowering the plasma concentration of teriflunomide by instituting an accelerated elimination procedure may decrease the risk to the fetus from AUBAGIO [see Warnings and Precautions (5.3)].

Upon discontinuing AUBAGIO, it is recommended that all women of childbearing potential undergo an accelerated elimination procedure. Women receiving AUBAGIO treatment who wish to become pregnant must discontinue AUBAGIO and undergo an accelerated elimination procedure, which includes verififcation of teriflunomide plasma concentrations less than 0.02 mcg/mL (0.02 mcg/mL). Human plasma concentrations of teriflunomide less than 0.02 mcg/mL (0.02 mcg/mL) are expected to have minimal risk. [see Contraindications (4.2), Warnings and Precautions (5.3) and Use in Specific Populations (8.1)].

5.3. Procedure for Accelerated Elimination of Teriflunomide
Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, it takes on average 8 months to reach plasma concentrations less than 0.02 mcg/mL, although because of individual variations in drug clearance it may take as long as 2 years. An accelerated elimination procedure could be used at any time after discontinuation of AUBAGIO. Elimination can be accelerated by either of the following procedures:
- Administration of cholestyramine 8 g every 8 hours for 11 days. If cholestyramine 8 g three times a day is not well tolerated, cholestyramine 4 g three times a day can be used.
- Administration of 50 g oral activated charcoal powder every 12 hours for 11 days. If elimination procedure is poorly tolerated, treatment days do not need to be consecutive unless there is a need to lower teriflunomide plasma concentration rapidly.

At the end of 11 days, both regimens successfully accelerated teriflunomide elimination, leading to more than 98% decrease in teriflunomide plasma concentrations. Use of the accelerated elimination procedure may provide a result in return of disease activity if the patient had been responding to AUBAGIO treatment.

5.4. Bone Marrow Effects/Immunosuppression Potential/Infections
White Blood Cell (WBC) count decrease
A mean decrease in white blood cell (WBC) count of approximately 15% (mainly neutrophils and lymphocytes) and in platelet count of approximately 10% was observed in placebo-controlled trials with 7 mg and 14 mg of AUBAGIO. The decrease in mean WBC count occurred during the first 6 weeks and WBC count remained low during treatment. In placebo-controlled studies, neutrophil count <1.5x10^9/L was observed in 10% and 16% of patients on AUBAGIO 7 mg and 14 mg, respectively, compared with 3% of patients on placebo; lymphocyte count <0.8x10^9/L was observed in 7% and 10% of patients on AUBAGIO 7 mg and 14 mg, respectively, compared with 5% of patients on placebo. No cases of serious pancytopenia were reported in premarketing clinical trials of AUBAGIO but rare cases of pancytopenia, agranulocytosis, and thrombocytopenia have been reported in the literature. In the absence of evidence to the contrary, the drug patient should be considered to have an increased risk for teriflunomide [see Clinical Pharmacology (12.3) in the full prescribing information]. Obtain a complete blood cell count (CBC) within 6 months before the initiation of treatment with AUBAGIO. Further monitoring should be based on signs and symptoms suggestive of bone marrow suppression.

Risk of Infection / Tuberculosis Screening
Patients with active acute or chronic infections should not start treatment until the infection(s) is resolved. If a patient develops a serious infection consider suspending treatment with AUBAGIO and using an accelerated elimination procedure to obtain the benefits and risks prior to resumption of therapy. Instruct patients receiving AUBAGIO to report symptoms of infections to a physician. AUBAGIO is not recommended for patients with severe immunodeficiency, bone marrow disease, or severe, uncontrolled infections. Medications like teriflunomide that have immuno-suppression potential may cause patients to be more susceptible to infections, including opportunistic infections.

In placebo-controlled studies of AUBAGIO, no overall increase in the risk of serious infections was observed with teriflunomide 7 mg (1.4%) or 14 mg (2.2%) compared to placebo (2.1%).
However, one fatal case of klesbiella pneumonia sepsis occurred in a patient taking teriflunomide 14 mg for 1.7 years. Fatal infections have been reported in the post-marketing setting, in patients receiving leflunomide, especially *Pneumocystis jiroveci* pneumonia and aspergillosis. Most of the reports were confounded by concomitant immunosuppressant therapy and/or comorbid illness, which, in addition to rheumatoid disease, may predispose patients to infection. In clinical studies with AUBAGIO, *cytomegalovirus* reactivation has been observed. In clinical studies with AUBAGIO, cases of tuberculosis have been observed. Prior to initiating AUBAGIO, screen patients for latent tuberculosis infection with a tuberculin skin test. AUBAGIO has not been studied in patients with a positive tuberculin screen, and the safety of AUBAGIO in individuals with latent tuberculosis infection is unknown. For patients testing positive in tuberculosis screening, treat by standard medical practice prior to therapy with AUBAGIO.

Vaccination

No clinical data are available on the efficacy and safety of vaccinations in patients taking AUBAGIO. Vaccination with live vaccines is, however, not recommended. The long half-life of AUBAGIO should be considered when contemplating administration of a live vaccine after stopping AUBAGIO.

Malignancy

The risk of malignancy, particularly lymphoproliferative disorders, is increased with the use of some immunosuppressive medications. There is a potential for immunosuppression with teriflunomide. No apparent increase in the incidence of malignancies and lymphoproliferative disorders was reported in the AUBAGIO clinical trials, but larger and longer-term studies would be needed to determine whether there is an increased risk of malignancy of lymphoproliferative disorders with AUBAGIO.

5.5 Peripheral Neuropathy

In placebo-controlled trials, treatment-emergent peripheral neuropathy, including both polyneuropathy and mononeuropathy (*e.g.*, carpal tunnel syndrome), was reported more frequently in patients taking AUBAGIO than in patients taking placebo. In one 108-week placebo-controlled study in 1086 patients with multiple sclerosis, the incidence of peripheral neuropathy confirmed by nerve conduction studies was 1.2% (4 patients) and 1.9% (6 patients) on 7 mg and 14 mg, respectively, compared with 0% on placebo. Treatment was discontinued in 2 patients with polyneuropathy, one on each dose, one of them recovered following treatment discontinuation. The other cases of peripheral neuropathy did not resolve with continued treatment. There have also been reports of peripheral neuropathy in patients receiving leflunomide. Age older than 60 years, concomitant neurotoxic medications, and diabetes may increase the risk for peripheral neuropathy. If a patient taking AUBAGIO develops symptoms consistent with peripheral neuropathy, such as bilateral numbness or tingling of hands or feet, consider discontinuing AUBAGIO therapy and performing an accelerated elimination procedure [see Warnings and Precautions (5.3)].

5.6 Acute Renal Failure

In placebo-controlled trials, 10 of 844 (1.2%) of AUBAGIO-treated subjects had transient acute renal failure, with a creatinine measurement increased by 100% or more of their baseline serum creatinine value, compared to 0 of 421 placebo-treated subjects. Seven of the 10 subjects had a nadir creatinine clearance less than 30 cc/min. In each of the 10 subjects, the serum creatinine level was normal on the next reported measurement (6–48 days from the increase in creatinine) with continued teriflunomide use. These increased creatinine measurements occurred between 12 weeks and 2 years after first dose of teriflunomide. Of the 6 subjects with available serum potassium measurements, 3 (50%) had hyperkalemia (measurements of 6.7, >7.3, and >7.3 mEq/L). No associated symptoms were documented.

5.7 Skin Reactions

Rash cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients with rheumatoid arthritis receiving leflunomide. A similar risk would be expected for teriflunomide [see Clinical Pharmacology (12.3) in the full prescribing information]. If a patient taking AUBAGIO develops any of these conditions, stop AUBAGIO therapy and perform an accelerated elimination procedure [see Warnings and Precautions (5.3)].

5.8 Blood Pressure Increase

In placebo-controlled studies, mean change from baseline in systolic blood pressure was 2.9 mmHg and 2.7 mmHg for AUBAGIO 7 mg and 14 mg, respectively, and -1.3 mmHg for placebo. The change from baseline in diastolic blood pressure was 1.4 mmHg and 1.3 mmHg for AUBAGIO 7 mg and 14 mg, respectively, and -0.9 mmHg for placebo. Hypertension was reported as an adverse reaction in 4% of patients treated with 7 mg or 14 mg of AUBAGIO, compared with 2% on placebo. Check blood pressure before start of AUBAGIO treatment and periodically thereafter. Elevated blood pressure should be appropriately managed during treatment with AUBAGIO.

5.10 Respiratory Effects

Interstitial lung disease and worsening of pre-existing interstitial lung disease have been reported with leflunomide. A similar risk would be expected with teriflunomide [see Clinical Pharmacology (12.3) in the full prescribing information]. Interstitial lung disease may be fatal. Interstitial lung disease may occur acutely at any time during therapy and have a variable clinical presentation. New onset or worsening pulmonary symptoms, such as cough and dyspnea, with or without associated fever, may be a reason for discontinuation of the therapy and for further investigation as appropriate. If discontinuation of the drug is necessary, consider initiation of an accelerated elimination procedure [see Warnings and Precautions (5.3)].

5.11 Concomitant Use with Immunosuppressive or Immunomodulating Therapies

Co-administration with antimetabolites, or immunosuppressive therapies used for treatment of multiple sclerosis has not been evaluated. Safety studies in which teriflunomide was concomitantly administered with other immune modulating therapies for up to one year (interferon beta, glatiramer acetate) did not reveal any specific safety concerns. The long term safety of these combinations in the treatment of multiple sclerosis has not been established. In any situation in which the decision is made to switch from AUBAGIO to another agent with a known potential for hematologic suppression, it would be prudent to monitor for hematologic toxicity, because there will be overlap of systemic exposure to both compounds. Use of an accelerated elimination procedure may decrease this risk, but may also potentially result in return of disease activity if the patient had been responding to AUBAGIO treatment [see Warnings and Precautions (5.3)].

6. ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the prescribing information:

- Hepatotoxicity [see Contraindications (4.1) and Warnings and Precautions (5.1)]
- Bone Marrow Effects [see Immunosuppression Potential Infections [see Warnings and Precautions (5.4).]
- Peripheral Neuropathy [see Warnings and Precautions (5.5)]
- Acute Renal Failure [see Warnings and Precautions (5.6)]
- Hyperkalemia [see Warnings and Precautions (5.7)]
- Serious Skin Reactions [see Warnings and Precautions (5.8)]
- Blood Pressure Effects [see Warnings and Precautions (5.9)]
- Respiratory Effects [see Warnings and Precautions (5.10)]

The most frequent adverse reactions reported during clinical studies of AUBAGIO were 1% or greater than placebo and greater than 20% but less than 100% of patients. The following table lists the adverse reactions and their incidences during clinical studies.

Table 1 Adverse Reactions in Study 1 (occurring in ≥2% of patients, and reported for teriflunomide 7 mg or 14 mg at ≥2% higher rate than for placebo)

<table>
<thead>
<tr>
<th>PRIMARY SYSTEM ORGAN CLASS</th>
<th>Teriflunomide (N=368)</th>
<th>Placebo (N=360)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Term (%)</td>
<td>14 mg (N=359)</td>
<td>7 mg (N=368)</td>
</tr>
</tbody>
</table>

**INFECTIONS AND INFESTATIONS**

- Influenza: 12% 9% 10%
- Upper respiratory tract infection: 9% 9% 7%
- Bronchitis: 8% 5% 6%

**SPECIAL SENSITIVITY**

- Urticaria: 6% 4% 4%
- Cystitis: 4% 2% 1%
- Gastroenteritis viral: 4% 2% 1%
- Oral herpes: 4% 2% 2%

**BLOOD AND LYMPHATIC SYSTEM DISORDERS**

- Neutropenia: 4% 2% 0.3%
- Leukopenia: 1% 2% 0.3%

**IMMUNE SYSTEM DISORDERS**

- Seasonal allergy: 3% 2% 1%

**PSYCHIATRIC DISORDERS**

- Anxiety: 4% 3% 2%

**NERVOUS SYSTEM DISORDERS**

- Headache: 19% 22% 18%
- Parasthesia: 10% 9% 8%
- Scoiatia: 3% 1% 1%
- Buring sensation: 3% 2% 1%
- Carpal tunnel syndrome: 3% 1% 0.3%

**EYE DISORDERS**

- Vision blurred: 3% 3% 1%
- Conjunctivitis: 1% 3% 1%

**CARDIAC DISORDERS**

- Palpitations: 2% 3% 1%
There was an increase in mean repaglinide Cmax and AUC0–24 (1.33- and 1.41-fold, respectively) following repeated doses of teriflunomide and a single dose of 0.25 mg repaglinide, suggesting a relationship between teriflunomide and CYP1A2 substrates.

In clinical trials, 18% of teriflunomide-treated subjects had mild hypophosphatemia (<0.6 mmol/L), compared to 1% of placebo-treated subjects. No subject in either treatment group had a serum phosphorus level less than that in humans at the maximum recommended human dose (MRHD).

A relationship between teriflunomide and cardiovascular death has not been established. In a post-marketing surveillance database, 2600 patients exposed to AUBAGIO in the premarketing database. These cardiovascular deaths were reported among approximately 10 patients exposed to teriflunomide (oral doses of 1, 3, or 10 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in high incidences of fetal malformation (primarily craniofacial, and axial and appendicular skeletal defects) and embryofetal death at doses associated with minimal maternal toxicity. Maternal plasma exposure at the no-effect dose (1.0 mg/kg/day) for embryofetal developmental toxicity in rabbits was less than that in humans at the MRHD. In studies in which teriflunomide (oral doses of 0.05, 0.1, 0.3, 0.6, or 1.0 mg/kg/day) was administered to rats during gestation and lactation, decreased growth, eye and skin abnormalities, and high incidences of malformations (limb defects) and postnatal death were observed in the offspring at doses not associated with maternal toxicity. Maternal plasma exposure at the no-effect dose for pre- and postnatal developmental toxicity in rats (0.10 mg/kg/day) was less than that in humans at the MRHD.

In animal reproduction studies of leflunomide, embryolethality and teratogenic effects were observed in pregnant rat and rabbit at or below clinically relevant plasma teriflunomide exposures (AUC). In published reproduction studies in pregnant mice, leflunomide was embryolethral and increased the incidence of malformations (craniofacial, axial skeletal, heart and great vessels). Supplementation with exogenous uridine reduced the teratogenic effects in pregnant mice, suggesting that the mode of action (inhibition of mitochondrial enzyme dihydroorotate dehydrogenase) is the same for therapeutic efficacy and developmental toxicity. At recommended doses in humans, teriflunomide and leflunomide result in a similar range of plasma concentrations of teriflunomide.

Administration of teriflunomide (oral doses of 1, 3, or 10 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in high incidences of fetal malformation (primarily craniofacial, and axial and appendicular skeletal defects) and embryofetal death at doses associated with minimal maternal toxicity. Maternal plasma exposure at the no-effect dose (1.0 mg/kg/day) for embryofetal developmental toxicity in rabbits was less than that in humans at the MRHD. In studies in which teriflunomide (oral doses of 0.05, 0.1, 0.3, 0.6, or 1.0 mg/kg/day) was administered to rats during gestation and lactation, decreased growth, eye and skin abnormalities, and high incidences of malformations (limb defects) and postnatal death were observed in the offspring at doses not associated with maternal toxicity. Maternal plasma exposure at the no-effect dose for pre- and postnatal developmental toxicity in rats (0.10 mg/kg/day) was less than that in humans at the MRHD.

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Cardiovascular deaths

Four cardiovascular deaths, including three sudden deaths, and one myocardial infarction in a patient with a history of hyperlipidemia and hypertension were reported among approximately 2600 patients exposed to AUBAGIO in the premarketing database. These cardiovascular deaths occurred during uncontrolled extension studies, one to nine years after initiation of treatment. A relationship between teriflunomide and cardiovascular death has not been established.

In clinical trials, 18% of teriflunomide-treated subjects had mild hypophosphatemia (≤0.6 mmol/L and < lower limit of normal), compared to 9% of placebo-treated subjects; 5% of teriflunomide-treated subjects had moderate hypophosphatemia (≥0.3 mmol/L and <0.6 mmol/L), compared to 1% of placebo-treated subjects. No subject in either treatment group had a serum phosphorus level less than that in humans at the MRHD.

7. DRUG INTERACTIONS

Effect of teriflunomide on CYP2C8 substrates

There was an increase in mean repaglinide Cmax and AUC (1.7- and 2.4-fold, respectively), following repeated doses of teriflunomide and a single dose of 0.25 mg repaglinide, suggesting that teriflunomide is an inhibitor of CYP2C8 in vivo. The magnitude of interaction could be higher at the recommended repaglinide dose. Therefore, monitoring patients with concomitant use of drugs metabolized by CYP2C8, such as repaglinide, pioglitazone, or rosiglitazone is recommended as they may have higher exposure.

Effect of teriflunomide on warfarin

A 25% decrease in peak international normalized ratio (INR) was observed when teriflunomide was coadministered with teriflunomide, close INR follow-up and monitoring is recommended.

Effect of teriflunomide on CYP3A4 substrates

There was an increase in mean ethinylestradiol Cmax and AUC (1.58- and 2.4-fold, respectively) and levonorgestrel Cmax and AUC (1.35- and 1.41-fold, respectively) following repeated doses of teriflunomide. Consideration should be given to the type or dose of oral contraceptives used in combination with teriflunomide.

Effect of teriflunomide on CYP1A2 substrates

Repeated doses of teriflunomide decreased mean Cmax and AUC of caffeine (CYP1A2 substrate) by 18% and 55% respectively, suggesting that teriflunomide may be in vivo a weak inducer of CYP1A2. Therefore, patients should be monitored when teriflunomide is coadministered with drugs metabolized by CYP1A2 (such as duloxetine, allosthenon, thopoxyltine, and tizanidine), as the efficacy of such drugs could be reduced.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [see Contraindications (4.2) and Warnings and Precautions (5.3)]

When teriflunomide (oral doses of 1, 3, or 10 mg/kg/day) was administered to pregnant rats throughout the period of organogenesis, high incidences of fetal malformation (primarily craniofacial, and axial and appendicular skeletal defects) and embryofetal death were observed at doses not associated with maternal toxicity. Adverse effects on embryofetal development were observed following doses at various stages throughout organogenesis. Maternal plasma exposure at the no-effect level (1.0 mg/kg/day) for embryofetal developmental toxicity in rats was less than that in humans at the maximum recommended human dose (MRHD, 14 mg/day).

Table 1 Adverse Reactions in Study 1 (occurring in ≥ 2% of patients, and reported for teriflunomide 7 mg or 14 mg at ≥ 2% higher rate than for placebo) (continued)

<table>
<thead>
<tr>
<th>PRIMARY SYSTEM ORGAN CLASS</th>
<th>Preferred Term (%)</th>
<th>Teriflunomide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>VASCULAR DISORDERS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>GASTROINTESTINAL DISORDERS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>18%</td>
<td>15%</td>
<td>9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>14%</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>6%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Toothache</td>
<td>4%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>1%</td>
<td>2%</td>
<td>0.3%</td>
</tr>
<tr>
<td>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>13%</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>Acne</td>
<td>3%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>4%</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>INVESTIGATIONS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>14%</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>Gamma-glutamyltransferase</td>
<td>3%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>3%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>2%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>2%</td>
<td>3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>1%</td>
<td>3%</td>
<td>0%</td>
</tr>
</tbody>
</table>

No dosage adjustment is necessary for patients with mild, moderate, and severe renal impairment [see Clinical Pharmacology (12.3) in the full prescribing information].
Chronic Care Coordination, Revision of Physician Cost Structure in 2014 MPFS Proposed Rule
Continued from page 4

and report the global (i.e., both the professional component and practice expense) will see cuts of approximately 50 percent. This is another devastating blow to private practice neurology, struggling to survive after the most recent EMG/NCS cuts,” she said. “It is frustrating that CMS has proposed yet another policy that hits a core neurology service. We need to ensure that neurologic care is properly valued and protected so that we can continue to provide care to our patients.”

Physician Value-based Payment Modifier (Value Modifier)
The value-based payment modifier, which penalizes or rewards physicians based on quality and cost metrics, will affect more physicians in the coming years. While only neurologists in group practices of 100 or more eligible professionals (EPs) will be subject to the value-based payment modifier in 2015, the modifier will apply to all physicians by 2017.

CMS is proposing to align the 2014 PQRS performance period with the 2016 value-based modifier. In addition, for the 2016 value-based modifier CMS proposes:

- To lower the group size threshold to groups of physicians with 10 or more EPs
- To increase the maximum penalty from one percent to two percent
- To include the Medicare Spending per Beneficiary measure in the cost composite
- To refine the cost measure benchmarking methodology to account for a physician’s specialty

For more information on the value based-modifier, visit www.aan.com/practice/medicare/medicare-payments.

Physician Quality Reporting System (PQRS)
Physicians successfully participating in the PQRS will receive a 0.5-percent bonus on all Medicare payments for 2014. 2014 is the last year physicians will be eligible for a bonus as it will transition to a -1.5-percent penalty in 2015. However, physicians who meet the criteria for the 2014 PQRS incentive will automatically avoid the penalty in 2016.

Neurologists’ participation in PQRS is becoming increasingly important, which only underscores the need for neurology-specific measures. CMS proposes the following measure sets for PQRS in 2014:

- Dementia
- Parkinson’s disease
- Sleep apnea
- Stroke rehabilitation

Epilepsy measures can also be reported as individual measures. “Our dementia and Parkinson’s disease measures address topic areas not otherwise covered in the PQRS measure set that affect millions of Medicare beneficiaries,” said Eric Cheng, MD, MS, FAAN, vice-chair of the AAN’s Quality Measurement and Reporting Subcommittee.

“It is far better for neurologists to be evaluated by measures specific to neurologic conditions instead of the generic measures that are used to evaluate primary care providers.”

With respect to PQRS reporting, CMS is proposing to increase the number of measures that have to be reported from three to nine. CMS also proposes to change the registry reporting threshold to 50 percent.

Electronic Health Record (EHR) Incentive Program
For 2014, CMS is proposing that physicians be able to report clinical quality measures through qualified clinical data registries. However, this option can only be used by physicians who are beyond their first year of demonstrating meaningful use.

The AAN submitted comments on the proposals, and CMS will review and respond to all comments in a final rule to be issued around November 1, 2013.
Movement Disorders Examined in Latest Continuum Audio
Continued from page 6

Hour 2:
Dystonia / Francesca Morgante, MD, PhD
Chorea: Differential Diagnosis and Treatment / Ruth H. Walker, MB, ChB, PhD, FAAN
Gait Disorders: Classification, Clinical Evaluation, Pathophysiology, and Treatment / Alfonso Fasano, MD, PhD

Hour 3:
Cerebellar and Afferent Ataxias / Massimo Pandolfo, MD
Myoclonus: Clinical Features, Pathophysiology, and Treatment / Alberto J. Espay, MD, MSc, FAAN

Hour 4:
Tic Disorders / Jonathan W. Mink, MD, PhD, FAAN
Psychogenic Movement Disorders: Phenomenology, Diagnosis, Pathophysiology, and Treatment / Alberto J. Espay, MD, MSc, FAAN

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Capitol Hill Report

Capitol Hill Report presents regular updates on legislative and regulatory actions and how the Academy ensures that the voice of neurology is heard on Capitol Hill. It is emailed to US members twice monthly and is posted at www.aan.com/go/advocacy/hillreport. Below are some recent highlights.

SGR Bill Hearing Highlights Cognitive Care
Before departing for the annual August recess, the US House Energy & Commerce Committee passed the Medicare Access and Patient Improvement Act (HR 2810) on a 51-0 vote. The bill repeals the flawed Sustainable Growth Rate (SGR) formula that threatens to drastically cut Medicare payments to physicians and creates a pathway to new physician payment plans. Although the bill provides a 0.5-percent increase in Medicare physician payments for each of the next five years, it doesn’t keep up with medical inflation or recognize the payment gap between E/M physicians and those who primarily bill procedural codes. The AAN vigorously advocated for a payment differential between E/M and procedures. This was not accepted. The bill goes to the House Ways & Means Committee, which is responsible for finding the “pay-fors”—spending cuts necessary to cover the costs of the bill, which is expected to be in the range of $175 to $225 billion over 10 years. Democrats and Republicans have agreed on the policy, but figuring out how to pay for it is another question that could easily derail the whole bill.

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AAN Publishes New Guideline on Treating Tardive Syndromes

A new guideline from the AAN finds that certain drugs may help treat tardive dyskinesia and other tardive syndromes. However, more and better studies are needed.

“Evidence-based Guideline: Treatment of Tardive Syndromes” was published in *Neurology* on July 30, 2013.

Drugs that may help treat symptoms of tardive syndromes include clonazepam, ginkgo biloba (studied only in inpatients with schizophrenia), tetrabenazine, and amantadine (short-term only).

“Tardive syndromes, including tardive dyskinesia, can occur with long-term use of many of the available antipsychotic medications, including second-generation antipsychotic drugs,” said Roongroj Bhidayasiri, MD, FRCP, guideline lead author. “However, the published literature suggests that some agents may have efficacy while the efficacy of others (diltiazem, galantamine, and eicosapentaenoic acid) was not supported by the available evidence. Some of these agents are likely to be useful in the clinic but just need more study. Moreover, we were surprised at how little hard evidence there is behind some of our common treatments or some ‘common sense’ approaches, like discontinuation of antipsychotics.”

The movements develop from long-term use of antipsychotic drugs. People who take these drugs should work closely with their doctors to learn about and prevent tardive syndromes. Because of their heterogeneity of clinical presentation and severity, tardive syndromes tend to be under-recognized. It is important to identify a tardive syndrome early. Doing so can help with decision making about managing treatment. Having a tardive syndrome can affect functioning and quality of life. It is important to weigh the benefit of a specific antipsychotic drug against the risk of developing a tardive syndrome.

Read the guideline and access PDF summaries for clinicians and patients, a slide presentation, and a clinical example at [www.aan.com/Guidelines](http://www.aan.com/Guidelines). For more information, contact Julie Cox at jcox@aan.com or (612) 928-6069.

Congress Looks at Guidelines as Medicare Incentive

Recognizing the AAN’s leadership and expertise in developing and publishing evidence-based guidelines, the Senate Finance Committee recently invited AAN staff to meet with committee staff members in Washington, DC, to discuss the role guidelines play in patient care. The meeting, also attended by the American College of Radiology, Society of Thoracic Surgeons, American Medical Association, American College of Cardiology, American College of Physicians, and the American Society of Clinical Oncology, explored how clinical guidelines, guidance statements, and/or appropriateness criteria can be used by Medicare to incent physicians to practice, as appropriate, according to published evidence. The Academy informed the Senate committee staff of the process used by the AAN, based on evidence with expert consensus, to develop guideline recommendations. The AAN advised that not all guidelines can be generalized to all types of patients, however, and it is appropriate, at times, to not practice by the guidelines because of the specific clinical situation.

Open Access Available to *Neurology* Authors

The AAN’s medical journal *Neurology* has joined the open access movement. *Neurology* is now offering a hybrid open access option to authors whose articles have been accepted for publication. With this choice, articles are made freely available online immediately upon publication. These articles are subject to the journal’s standard peer review process.

Authors who want to submit their papers for open access sign a license giving the publisher the right to publish the article, create derivatives, and sell reprints. The authors retain the copyright and anyone can use the article for non-commercial purposes with proper attribution. An article processing charge of $3,000 per article is being levied in 2013.

Authors who are required to publish via open access by funders (such as Research Council UK or Wellcome-Trust) must sign a license giving the publisher the right to publish the article. The authors retain copyright but anyone may reuse the article and create derivatives, even for commercial purposes, with proper attribution. A process charge of $3,800 per article is being levied in 2013. If the authors do not have funds to pay the article processing charge, they retain copyright, but cannot republish for commercial purposes and their articles are deposited into PubMed Central after an embargo period of at least 12 months.

Visit [Neurology.org](http://Neurology.org) for more information.
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Continued from Cover

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• Alliance Awards: S. Weir Mitchell Award

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• Dreifuss-Penry Epilepsy Award
• Harold Wolff-John Graham Award: An Award for Headache/Facial Pain Research
• Jon Stolk Award in Movement Disorders for Young Investigators
• Michael S. Pessin Stroke Leadership Prize
• Wayne A. Hening Sleep Award for Young Investigators
• Norman Geschwind Prize in Behavioral Neurology
• International Scholarship Award

Senior Authors
• Potamkin Prize for Research in Pick’s, Alzheimer’s, and Related Diseases
• Neuroendocrine Research Award
• John Dystel Prize for Multiple Sclerosis Research
• Sleep Science Award

• Sheila Essey Award: An Award for ALS Research
• Mitchell B. Max Award for Neuropathic Pain
• Movement Disorders Research Award
• Lawrence C. McHenry Award: An Award for the History of Neurology

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Other Awards and Fellowships
• AAN Award for Creative Expression of Human Values in Neurology
• A.B. Baker Award for Lifetime Achievement in Neurologic Education
• Association of Indian Neurologists in America (AINA) Lifetime Achievement Award
• H. Richard Tyler Award
• Kenneth M. Viste, Jr., MD, Patient Advocate of the Year Award (Deadline: November 3, 2013)
• Minority Scholars Program
• Patient Safety Award

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Deadline: October 30, 2013
Research Training Fellowship Applications Due October 1

In an effort to address the critical need for neurology research and recruit and train some of the best and brightest young investigators of today, the American Brain Foundation is accepting applications for several 2014 research fellowships in neurology. Fellowships provide residents and fellows with salary and tuition stipends, allowing them protected time to complete clinical research projects and take the next step toward a career in neurologic research. Apply online at www.aan.com/view/fellowships most application deadlines by October 1, 2013. For more information, contact Kristin Roehl at kroehl@aan.com or (612) 928-6082.

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- Clinician-Scientist Development Three-Year Award in Parkinson’s Disease
- Two-Year Clinical Research Training Fellowship in the Neurological Application of Neurotoxins
- Susan S. Spencer Two-Year Clinical Research Training Fellowship in Epilepsy
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Francis Runs with His Support for the Foundation

AAN member Gordon S. Francis, MD, FAAN, is not just a multiple sclerosis expert and head of the Neuroinflammation Therapeutic Area for Novartis, he’s also a seasoned runner. A runner who is as passionate about the sport he loves as he is about the future of neurology—a future filled with cures for neurologic diseases. To this end, Francis is a strong supporter of the American Brain Foundation and its determined vision to “cure brain diseases.” He understands that in order to achieve this vision, there needs to be more research into the cause, treatment, and prevention of brain disorders, and he knows that with the current limited funding, individual donations to the American Brain Foundation are critical.

Each spring, the Run/Walk for Brain Research event is held during the AAN Annual Meeting, and this year in San Diego provided a unique opportunity for Francis. For its 20th anniversary, the run was back on its original course in San Diego. Francis knew he wanted to participate, but he also wanted to use the occasion to spur others to participate, as well, so he offered a special incentive. “Prior to going to the meeting, I told our meeting organizer that I would make a donation for each Novartis participant already signed up for the race and if any runner beat my 1993 time [as verified by the finish line photo from that race], the donation would double,” said Francis. “I believe strongly in the cause and I wanted to find a fun, friendly, slightly competitive way to incentivize other runners to participate and ensure additional dollars would go to CNS research.”

Following the race, Francis donated $1,500 to the Foundation (matched by Novartis for a total of $3,000) as his 1993 time was beaten by two Novartis runners, including the fastest woman in the race. “I’ve been an avid runner for 25 years, and I didn’t expect there to be such stiff competition, let alone an Olympic trainee in our group!” he said. “Perhaps the thought of the challenge bringing more money to this important cause gave the runners an adrenaline boost, resulting in not only great race times by some, but also a win for the Foundation.”

Added Francis, “The concept of the challenge was fun, and I would encourage other members to consider creative means by which to incentivize others to donate as well.”

To make a donation to the American Brain Foundation, to get involved with fundraising activities, or to make a planned gift, contact info@americanbrainfoundation.org or (866) 770-7570.
American Brain Foundation Establishes “Brain Pavers” Fundraising Program

In an effort to become the world’s leader in raising money to cure brain disease, the American Brain Foundation has established a special third-party fundraising program. The Brain Pavers program is designed to make it easy—and fun—for anyone to engage family, friends, coworkers, and others who share philanthropic interests and want to support the Foundation’s important mission.

Brain Pavers are encouraged to host fundraising events, such as run/walks, bake sales, music festivals, and more. The program also encourages tribute or memorial gifts designed to honor loved ones.

“Working with the American Brain Foundation to raise money for research into cures for brain disease was not only rewarding, but it was easy!” said Leonel Ibarra, Jr., a Brain Paver who ran the San Diego Rock ‘n’ Roll Half Marathon last June, raising over $3,100 for the Foundation in memory of his mother, Maria Dolores Ibarra, who passed away in February from a brain disease. Her son, a San Diego area resident, first heard about the American Brain Foundation when he attended the popular Brain Health Fair during the 2013 Annual Meeting in San Diego. After the Brain Health Fair, Ibarra contacted the Foundation to express his interest in raising money for brain disease research in honor of his mother.

“I was already planning on running in the half marathon and wanted to add a fundraising element in honor of my mom,” he said. “The Foundation made the whole process so convenient. It was a great experience from beginning to end, and I know that my mom would be so proud of both of my efforts.

More than 40 volunteers—including an AAN physician member and a Corporate Roundtable member, as well as Academy and Foundation staff and families—represented the American Brain Foundation by “Paving the Way to a Cure for Brain Diseases” at the popular Aquatennial Torchlight Parade in downtown Minneapolis on July 17. The “Brain Pavers” got 50,000 people along the parade route thinking about their brains!

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For more information about the American Brain Foundation programs, contact info@americanbrainfoundation.org.

Marching for Cures in Minneapolis

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For secure online giving options, visit www.CureBrainDisease.org. For more information about the American Brain Foundation programs, contact info@ americanbrainfoundation.org.
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Application Deadline: Emerging Leaders Forum
www.aan.com/apps/leadership

SEPTEMBER 10
Webinar: 2013 Correct Coding for Diagnostic Sleep Testing
(Register by September 9)
www.aan.com/view/pmwebinar

SEPTEMBER 27–28
Evidence-based Medicine Toolkit Training
(Register by September 15)
AAN Headquarters, Minneapolis
www.aan.com/education/ebm

SEPTEMBER 29
Application Deadline: Donald M. Palatucci Advocacy Leadership Forum
www.aan.com/view/2014palf

OCTOBER 1
AAN Fall Conference
Early Registration Deadline
www.aan.com/view/2013fall

Application Deadline: Research Training Fellowships
www.aan.com/view/Fellowships

OCTOBER 7–11
AAN Neurology Career Week
www.aan.com/careers

OCTOBER 8
Webinar: Meaningful Use Stage 2: Prepare Your Practice
(Register by October 7)
www.aan.com/view/pmwebinar

OCTOBER 25–27
AAN Fall Conference
Las Vegas, NV
www.aan.com/view/2013fall

OCTOBER 28
Submission Deadline: 2014 Annual Meeting Abstracts
www.aan.com/view/am14

OCTOBER 29
Webinar: Protecting Your Reputation as a High Quality Physician
/Register by October 28)
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OCTOBER 30
Application Deadline: 2014 AAN Awards
www.aan.com/view/14awards

NOVEMBER 3
Application Deadline: Kenneth M. Viste, Jr., MD, Patient Advocate of the Year Award
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NOVEMBER 5
Webinar: Communication Strategies that Help Patients Understand
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Stroke Director Opportunity – PA. St. Luke’s University Health Network is seeking an BC/BE Neurologist for our Joint Commission Accredited Primary Stroke Program. Program is progressive and moving toward a Comprehensive Stroke Center. State-of-the-art diagnostic tools including low dose CT scanners, MRI with functional capabilities, ICANL accredited vascular lab, full service interventional radiology and neurointerventional capabilities and a Hybrid OR. 24/7 neurology and neurosurgery capability, established program for rapid evaluation and treatment of stroke patients. 2013 Get with the Guidelines Stroke Gold Plus Performance Achievement Award. 2 year MGMTA comparative salary guarantee with an attractive RVU based income. St Luke’s Neurology group is a part of the University Neuroscience team that has numerous subspecialty including centers for movement disorder, headache, neuro-rehabilitation, stroke including interventional, sleep, MS, neuropsychology, and functional neurosurgery. In addition, we offer: attractive compensation/benefit package, relocation assistance, malpractice coverage, CME allowance. Email drea.rosko@sluhn.org

Neurologist for Rockwall, Texas. Texas Neurology is North Texas’ largest physician-owned comprehensive neurology and epilepsy center and is expanding to Rockwall, Texas. This is an exciting and unique opportunity for a BC/BE neurologist to develop a satellite location in this prosperous and expanding suburb just east of Dallas, while being affiliated with the premier neurology group in the DFW area. Salary includes $20k per year guarantee with the potential for incentive compensation and a competitive benefits package. If you are interested in applying or learning more about this opportunity, please contact David A. Evans decoa@texasneurology.com or (214) 827-3610 ext. 224.

Neurologist. Seeking a BC/BE Neurologist to join our growing and successful private practice with five locations throughout Southern California. We specialize in spine, general orthopedics, and pain management. Ideal candidate will have a strong interest in general neurology services and in practicing in an outpatient-focused, multi-specialty group. We believe that patients benefit from a conservative, multi-disciplinary approach to treatment. Our focus is on addressing total patient care by guiding our patients through the process of diagnosis, treatment, and recovery. Applicant must possess an MD degree from an accredited medical school, and be eligible to obtain a California medical license. Very generous incentive and bonus package offered. Email lilly@spineandorthocenter.com

Pain Neurologist. Applications are invited for a full-time clinical faculty position in the Department of Neurology at the University of Wisconsin Hospital and Clinics. Four (4) days per week in outpatient clinical activities dedicated to pain neurology and general or other subspecialty in the Department’s neurology and community outreach clinics. Clinical duties would include attending on the inpatient and consultation services, clinical teaching activities, and participation in community medical education. The majority of effort would be devoted to pain neurology but subspecialty interest can be accommodated depending on demand for service and subspecialty background of the applicant. Candidates must be board certified or board eligible in neurology and committed to contributing in an active academic department through clinical and teaching activities. Please send curriculum vitae and the names of at least three references to Thomas Sutula, MD, PhD, Neurology Department Chair at applications@neurology.wisc.edu. Unless confidentiality is requested in writing, information regarding the applicants must be released upon request. The University of Wisconsin is an Affirmative Action/Equal Opportunity Employer.

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Ad copy for the November 2013 print edition of AANews must be submitted by October 1, 2013. The same deadline applies to changes/cancellations.

The American Academy of Neurology reserves the right to decline, withdraw, or edit advertisements at its discretion. Every care is taken to avoid mistakes, but the responsibility for clerical or printer errors does not exceed the cost of the ad.
TECFIDERA™ (dimethyl fumarate) delayed-release capsules, for oral use
Brief Summary of Full Prescribing Information

1 INDICATIONS AND USAGE
TECFIDERA is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Lymphopenia
TECFIDERA may decrease lymphocyte counts [see Adverse Reactions (6.1)]. In the MS placebo controlled trials, mean lymphocyte counts decreased by approximately 30% during the first year of treatment with TECFIDERA and then remained stable. Four weeks after stopping TECFIDERA, mean lymphocyte counts increased but did not return to baseline. Six percent (6%) of TECFIDERA patients and <1% of placebo patients experienced lymphocyte counts <0.5x10⁹/L (lower limit of normal 0.91x10⁹/L). The incidence of infections (60% vs 58%) and serious infections (2% vs 2%) was similar in patients treated with TECFIDERA or placebo, respectively. There was no increased incidence of serious infections observed in patients with lymphocyte counts <0.8x10⁹/L or 0.5x10⁹/L.

Before initiating treatment with TECFIDERA, a recent CBC (i.e., within 6 months) should be available. A CBC is recommended annually, and as clinically indicated. Withholding treatment should be considered in patients with serious infections until the infection(s) is resolved. TECFIDERA has not been studied in patients with pre-existing low lymphocyte counts.

5.2 Flushing
TECFIDERA may cause flushing (e.g., warmth, redness, itching, and/or burning sensation). In clinical trials, 40% of TECFIDERA treated patients experienced flushing. Flushing symptoms generally began soon after initiating TECFIDERA and usually improved or resolved over time. In the majority of patients who experienced flushing, it was mild or moderate in severity. Three percent (3%) of patients discontinued TECFIDERA for flushing and <1% had serious flushing symptoms that were not life-threatening but led to hospitalization. Administration of TECFIDERA with food may reduce the incidence of flushing.

6 ADVERSE REACTIONS
The following important adverse reactions are described elsewhere in labeling: Lymphopenia, Flushing [see Warnings and Precautions (5.1, 5.2)].

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most common adverse reactions (incidence ≥10% and ≥2% more than placebo) for TECFIDERA were flushing, abdominal pain, diarrhea, and nausea.

Adverse Reactions in Placebo-Controlled Trials
In the two well-controlled studies demonstrating effectiveness, 1529 patients received TECFIDERA with an overall exposure of 2244 person-years [see Clinical Studies (14)]. The adverse reactions presented in the table below are based on safety information from 769 patients treated with TECFIDERA 240 mg twice a day and 771 placebo-treated patients.

Table 1: Adverse Reactions in Study 1 and 2 reported for TECFIDERA 240 mg BID at ≥ 2% higher incidence than placebo

<table>
<thead>
<tr>
<th></th>
<th>TECFIDERA N=769</th>
<th>Placebo N=771</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Rash</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Erythema</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin urine present</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Gastrointestinal
TECFIDERA caused GI events (e.g., nausea, vomiting, diarrhea, abdominal pain, and dyspepsia). The incidence of GI events was higher early in the course of treatment (primarily in month 1) and usually decreased over time in patients treated with TECFIDERA compared with placebo. Four percent (4%) of patients treated with TECFIDERA and less than 1% of placebo patients discontinued due to gastrointestinal events. The incidence of serious GI events was 1% in patients treated with TECFIDERA.

Hepatic Transaminases
An increased incidence of elevations of hepatic transaminases in patients treated with TECFIDERA was seen primarily during the first six months of treatment and most patients with elevations had levels < 3 times the upper limits of normal (ULN). Elevations of alanine aminotransferase and aspartate aminotransferase to ≥ 3 times the ULN occurred in a small number of patients treated with both TECFIDERA and placebo and were balanced between groups. There were no elevations in transaminases ≥ 3 times the ULN with concomitant elevations in total bilirubin > 2 times the ULN. Discontinuations due to elevated hepatic transaminases were < 1% and were similar in patients treated with TECFIDERA or placebo.

Eosinophilia
A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.
Adverse Reactions in Placebo-Controlled and Uncontrolled Studies

In placebo-controlled and uncontrolled clinical studies, a total of 2513 patients have received TECFIDERA and have been followed for periods up to 4 years with an overall exposure of 4603 person-years. Approximately 1162 patients have received TECFIDERA for 2 years or more. The adverse reaction profile of TECFIDERA in the uncontrolled clinical studies was consistent with the experience in the placebo-controlled clinical trials.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. In animals, adverse effects on offspring survival, growth, sexual maturation, and neurobehavioral function were observed when dimethyl fumarate (DMF) was administered during pregnancy and lactation at clinically relevant doses. TECFIDERA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In rats administered DMF orally (25, 100, 250 mg/kg/day) throughout organogenesis, embryofetal toxicity (reduced fetal body weight and delayed ossification) were observed at the highest dose tested. This dose also produced evidence of maternal toxicity (reduced body weight). Plasma exposure (AUC) for monomethyl fumarate (MMF), the major circulating metabolite, at the no-effect dose is approximately three times that in humans at the recommended dose (RHD) of 480 mg/day. In rabbits administered DMF orally (25, 75, and 150 mg/kg/day) throughout organogenesis, embryolethality and decreased maternal body weight were observed at the highest dose tested. The plasma AUC for MMF at the no-effect dose is approximately 5 times that in humans at the RHD.

Oral administration of DMF (25, 100, and 250 mg/kg/day) to rats throughout organogenesis and lactation resulted in increased lethality, persistent reductions in body weight, delayed sexual maturation (male and female pups), and reduced testicular weight at the highest dose tested. Neurobehavioral impairment was observed at all doses. A no-effect dose for developmental toxicity was not identified. The lowest dose tested was associated with plasma AUC for MMF lower than that in humans at the RHD.

Pregnancy Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to TECFIDERA during pregnancy. Encourage patients to enroll by calling 1-800-456-2255.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TECFIDERA is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of TECFIDERA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

17.1 Dosage

Inform patients that they will be provided two strengths of TECFIDERA when starting treatment: 120 mg capsules for the 7 day starter dose and 240 mg capsules for the maintenance dose, both to be taken twice daily. Inform patients to swallow TECFIDERA capsules whole and intact. Inform patients to not crush, chew, or sprinkle capsule contents on food. Inform patients that TECFIDERA can be taken with or without food [see Dosage and Administration (2.1)].

17.2 Flushing and Gastrointestinal (GI) Reactions

Flushing and GI reactions (abdominal pain, diarrhea, and nausea) are the most common reactions, especially at the initiation of therapy, and may decrease over time. Advise patients to contact their healthcare provider if they experience persistent and/or severe flushing or GI reactions, as taking TECFIDERA with food may help [see Adverse Reactions (6.1)].

17.3 Pregnancy and Pregnancy Registry

Instruct patients that if they are pregnant or plan to become pregnant while taking TECFIDERA they should inform their physician.

Encourage patients to enroll in the TECFIDERA Pregnancy Registry if they become pregnant while taking TECFIDERA. Advise patients to call 1-800-456-2255 for more information [see Use in Specific Populations (8.1)].

17.4 Lymphocyte Counts

Inform patients that TECFIDERA may decrease lymphocyte counts. A recent blood test (i.e., within 6 months) should be available before they start therapy to identify patients with pre-existing low lymphocyte counts. Blood tests are also recommended annually, and as clinically indicated [see Warnings and Precautions (5.1), Adverse Reactions (6.1)].

41347-02

Manufactured by: Biogen Idec Inc. Cambridge, MA 02142

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03/2013
Biogen Idec Announces the Approval of Tecfidera
(dimethyl fumarate) delayed-release capsules 240 mg

For more information, please visit Tecfidera.com

Indication
Tecfidera™ (dimethyl fumarate) is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

Important Safety Information
Tecfidera may cause lymphopenia. A complete blood count is recommended within 6 months before initiating treatment, annually, and as clinically indicated. Consider withholding treatment in patients with serious infections. Tecfidera has not been studied in patients with pre-existing low lymphocyte counts.

Tecfidera may cause flushing (eg, warmth, redness, itching, and/or burning sensation). Tecfidera may cause gastrointestinal (GI) events (eg, nausea, vomiting, diarrhea, abdominal pain, and dyspepsia). The most common adverse reactions associated with Tecfidera are flushing, abdominal pain, diarrhea, and nausea.

Elevations in hepatic transaminases were primarily seen during the first 6 months of treatment with Tecfidera. A transient increase in mean eosinophil counts was seen during the first 2 months of treatment with Tecfidera.

Tecfidera may cause fetal harm. There are no adequate and well-controlled studies in pregnant women. Tecfidera should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Encourage patients who become pregnant while taking Tecfidera to enroll in the Tecfidera pregnancy registry by calling 1-800-456-2255.

For additional important safety information, please see Brief Summary of full Prescribing Information on adjacent pages.