Don’t Forget to Renew Your Membership for 2017

Keep Your Benefits Coming in the New Year!

The new year is just around the corner—and you don’t want to risk losing access to your valuable benefits to help you stay on top of your game in 2017. Make it your resolution to visit AAN.com/dues to renew your AAN membership so you can continue to have access to continuing education and training resources, industry news, and the latest research you won’t find anywhere else.

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- Practice reimbursement and management tools and resources to help you maximize your success
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- Member-only tools and resources on AAN.com, the leading online resource for neurologists across the world

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Abstracts Sought for 2017 Annual Meeting Emerging Science Program

Have you conducted major research since the October 24, 2016, AAN Annual Meeting abstract deadline? If so, we encourage you to submit your abstracts for the 2017 AAN Emerging Science program by February 9, 2017. Abstracts may be submitted online at AAN.com/view/17EmergingScience.

Continued on page 31

Register for Free Webinar: Decoding the 2017 Medicare Fee Schedule and MACRA Rule

The AAN is offering a free practice management webinar on the new 2017 Medicare Physician Fee Schedule recently published by the Centers for Medicare & Medicaid Services (CMS), as well as an update on changes in store for MACRA in the coming year.

Continued on page 14
Because treating relapsing MS is important...

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

**Important Safety Information**
TECFIDERA is contraindicated in patients with known hypersensitivity to dimethyl fumarate or any of the excipients of TECFIDERA. TECFIDERA can cause anaphylaxis and angioedema after the first dose or at any time during treatment. Patients experiencing signs and symptoms of anaphylaxis and angioedema (which have included difficulty breathing, urticaria, and swelling of the throat and tongue) should discontinue TECFIDERA and seek immediate medical care.

Progressive multifocal leukoencephalopathy (PML) has occurred in patients with MS treated with TECFIDERA. PML is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. A fatal case of PML occurred in a patient who received TECFIDERA in a clinical trial. PML has also occurred in the postmarketing setting in the presence of lymphopenia (<0.8 x 10⁹/L) persisting for more than 6 months. While the role of lymphopenia in these cases is uncertain, the majority of cases occurred in patients with lymphocyte counts <0.5 x 10⁹/L. The symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. At the first sign or symptom suggestive of PML, withhold TECFIDERA and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms. TECFIDERA may decrease lymphocyte counts; in clinical trials there was a mean decrease of ~30% in lymphocyte counts during the first year which then remained stable. Four weeks after stopping TECFIDERA, mean lymphocyte counts increased but not to baseline. Six percent of TECFIDERA patients and <1% of placebo patients had lymphocyte counts <0.5 x 10⁹/L. TECFIDERA has not been studied in patients with pre-existing low lymphocyte counts.

There was no increased incidence of serious infections observed in patients with lymphocyte counts <0.8 x 10⁹/L or ≤0.5 x 10⁹/L in controlled trials, although one patient in an extension study developed PML in the setting of prolonged lymphopenia (lymphocyte counts predominantly <0.5 x 10⁹/L for 3.5 years). In controlled and uncontrolled clinical trials, 2% of patients experienced lymphocyte counts <0.5 x 10⁹/L for at least six months. In these patients, the majority of lymphocyte counts remained <0.5 x 10⁹/L with continued therapy. A complete blood count including lymphocyte count should be obtained before initiating treatment, 6 months after starting, every 6 to 12 months thereafter and as clinically indicated. Consider treatment interruption if lymphocyte counts <0.5 x 10⁹/L persist for more than six months and follow lymphocyte counts until lymphopenia is resolved. Consider withholding treatment in patients with serious infections until resolved. Decisions about whether or not to restart TECFIDERA should be based on clinical circumstances.

TECFIDERA may cause flushing (e.g., warmth, redness, itching, and/or burning sensation). 40% of patients taking TECFIDERA reported flushing, which was mostly mild to moderate in severity. Three percent of patients discontinued TECFIDERA for flushing and <1% had serious flushing events that led to hospitalization. Taking TECFIDERA with food may reduce flushing. Alternatively, administration of non-enteric coated aspirin prior to dosing may reduce the incidence or severity of flushing. TECFIDERA may cause gastrointestinal (GI) events (e.g., nausea, vomiting, diarrhea, abdominal pain, and dyspepsia). Four percent of TECFIDERA patients and <1% of placebo patients discontinued due to GI events. The incidence of
IN THE 2-YEAR DEFINE* TRIAL†:

![Proportion of Patients Relapsed (PPR)](image)

Half as many patients relapsed

Defining PPR:
Percentage of patients who had one or more relapses over the course of the trial

Established tolerability and safety¹
TECFIDERA warnings and precautions include: Anaphylaxis and Angioedema, Progressive multifocal leukoencephalopathy, Lymphopenia, and Flushing

Important Safety Information (cont’d)
serious GI events was 1%. The most common adverse reactions associated with TECFIDERA versus placebo are flushing (40% vs 6%) and GI events: abdominal pain (% vs 10%), diarrhea (14% vs 11%), nausea (12% vs 9%).

Elevations in hepatic transaminases have been reported. A transient increase in mean eosinophil counts was seen during the first two months. 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 1-866-810-1462 or visiting www.TECFIDERApregnancyregistry.com.

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

* Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS, a 2-year, randomized, double-blind, placebo-controlled study in 1234 patients with relapsing-remitting multiple sclerosis (RRMS).²

¹ Included patients who had experienced at least 1 relapse over the year preceding the trial or had a brain magnetic resonance imaging (MRI) scan demonstrating at least 1 gadolinium-enhancing (Gd+) lesion within 6 weeks of randomization and had an Expanded Disability Status Scale (EDSS) score ranging from 0 to 5.³

² Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection that lasted for at least 24 hours and were accompanied by new objective neurologic findings.⁴

³ Based on number of prescriptions from IMS NPA™ Weekly Data (September 27, 2013 to June 3, 2016).


For more information, visit TECFIDERAHCP.COM

More than 200K patients treated globally—and growing³

TECFIDERA has been prescribed in the US more than any other oral therapy for RMS as of September 2013¹

5+ years of clinical and real-world experience¹³

Biogen

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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.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The starting dose for TECFIDERA is 120 mg twice a day orally. After 7 days, the dose should be increased to the maintenance dose of 240 mg twice a day orally. Temporary dose reductions to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose. Within 4 weeks, the recommended dose of 240 mg twice a day should be resumed. Discontinuation of TECFIDERA should be considered for patients unable to tolerate return to the maintenance dose. The incidence of flushing may be reduced by administration of TECFIDERA with food. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to TECFIDERA dosing may reduce the incidence or severity of flushing [see Clinical Pharmacology (12.3)].

TECFIDERA should be swallowed whole and intact. TECFIDERA should not be crushed or chewed and the capsule contents should not be sprinkled on food. TECFIDERA can be taken with or without food.

2.2 Blood Test Prior to Initiation of Therapy

Obtain a complete blood cell count (CBC) including lymphocyte count before initiation of therapy [see Warnings and Precautions (5.3)].

3 DOSAGE FORMS AND STRENGTHS

TECFIDERA is available as hard gelatin delayed-release capsules containing 120 mg or 240 mg of dimethyl fumarate. The 120 mg capsule has a green cap and white body, printed with “BG-12 120 mg” in black ink on the body. The 240 mg capsules have a green cap and a green body, printed with “BG-12 240 mg” in black ink on the body.

4 CONTRAINDICATIONS

TECFIDERA is contraindicated in patients with known hypersensitivity to dimethyl fumarate or to any of the excipients of TECFIDERA. Reactions have included anaphylaxis and angioedema [see Warnings and Precautions (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Angioedema

TECFIDERA can cause anaphylaxis and angioedema after the first dose or at any time during treatment. Signs and symptoms have included difficulty breathing, urticaria, and swelling of the throat and tongue. Patients should be instructed to discontinue TECFIDERA and seek immediate medical care should they experience signs and symptoms of anaphylaxis or angioedema.

5.2 Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has occurred in patients with MS treated with TECFIDERA. PML is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. A fatal case of PML occurred in a patient who received TECFIDERA for 4 years while enrolled in a clinical trial. During the clinical trial, the patient experienced prolonged lymphopenia (lymphocyte counts predominantly <0.5x10^9/L for 3.5 years) while taking TECFIDERA [see Warnings and Precautions (5.3)]. The patient had no other identified systemic medical conditions resulting in compromised immune system function and had not previously been treated with natalizumab, which has a known association with PML. The patient also was not taking any immunosuppressive or immunomodulatory medications concomitantly.

PML has also occurred in the postmarketing setting in the presence of lymphopenia (<0.8x10^9/L) persisting for more than 6 months. While the role of lymphopenia in these cases is uncertain, the majority of cases occurred in patients with lymphocyte counts <0.5x10^9/L. At the first sign or symptom suggestive of PML, withhold TECFIDERA and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

5.3 Lymphopenia

TECFIDERA may decrease lymphocyte counts. 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 <0.5x10^9/L (lower limit of normal 0.91x10^9/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 <0.8x10^9/L or ≤0.5x10^9/L in controlled trials, although one patient in an extension study developed PML in the setting of prolonged lymphopenia (lymphocyte counts predominantly <0.5x10^9/L for 3.5 years) [see Warnings and Precautions (5.2)]. In controlled and uncontrolled clinical trials, 2% of patients experienced lymphocyte counts <0.5x10^9/L for at least six months, and in this group the majority of lymphocyte counts remained ≤0.5x10^9/L with continued therapy. TECFIDERA has not been studied in patients with pre-existing low lymphocyte counts.

Obtain a CBC, including lymphocyte count, before initiating treatment with TECFIDERA, 6 months after starting treatment, and then every 6 to 12 months thereafter, and as clinically indicated. Consider interruption of TECFIDERA in patients with lymphocyte counts ≤0.5x10^9/L persisting for more than six months. Given the potential for delayed recovery of lymphocyte counts, continue to obtain lymphocyte counts until their recovery if TECFIDERA is discontinued or interrupted due to lymphopenia. Consider withholding treatment from patients with serious infections until resolution.

Decisions about whether or not to restart TECFIDERA should be individualized based on clinical circumstances.

5.4 Flushing

TECFIDERA may cause flushing (e.g., warmth, redness, itching, and/or burning sensation). In clinical trials, 43% 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. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to TECFIDERA dosing may reduce the incidence or severity of flushing [see Dosing and Administration (2.1) and Clinical Pharmacology (12.3)].

6 ADVERSE REACTIONS

The following important adverse reactions are described elsewhere in labeling: Anaphylaxis and Angioedema (5.1), Progressive multifocal leukoencephalopathy (5.2), Lymphopenia (5.3), Flushing (5.4) [see Warnings and Precautions].

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>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TECFIDERA N=769</th>
<th>Placebo N=771</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Flushing</td>
<td>40</td>
<td>6</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>Pruritus</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Rash</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Albumin urine present</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Erythema</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>2</td>
<td>&lt;1</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 limit 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 been followed for periods up to 4 years with an overall exposure of 4603 person-years. Approximately 1162 patients have received more than 2 years of treatment with TECFIDERA. 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 <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 limit 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.

8.2 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
Advises the patient to read the FDA-approved patient labeling (Patient Information)

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.

Informed 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)].

Anaphylaxis and Angioedema
Advises patients to discontinue TECFIDERA and seek medical care if they develop signs and symptoms of anaphylaxis or angioedema [see Warnings and Precautions (5.1)].

Progressive Multifocal Leukoencephalopathy
Inform patients that progressive multifocal leukoencephalopathy (PML) has occurred in patients who received TECFIDERA. Inform the patient that PML is characterized by a progression of deficits and usually leads to death or severe disability over weeks or months. Inform the patient of the importance of contacting their doctor if they develop any symptoms suggestive of PML. Inform the patient that typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. [see Warnings and Precautions (5.2)].

Lymphocyte Counts
Inform patients that TECFIDERA may decrease lymphocyte counts. A blood test should be obtained before they start therapy. Blood tests are also recommended after 6 months of treatment, every 6 to 12 months thereafter, and as clinically indicated [see Warnings and Precautions (5.3), Adverse Reactions (6.1)].

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. Advise patients experiencing flushing that taking TECFIDERA with food or taking a non-enteric coated aspirin prior to taking TECFIDERA may help. [see Adverse Reactions (6.1)].

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 1-866-810-1462 or visit www.TECFIDERApregnancyregistry.com for more information [see Use in Specific Populations (8.1)].
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### NEWS BRIEFS

**Neurology Now®** has been honored with the Clarion Award for its June/July 2106 article on actress Connie Shulman, who spent a year documenting a friend’s dementia to raise awareness of a fatal disease, and discovered new depths of friendship. The award was given by the Association of Women in Communications. *
Registry Success Is Good News for AAN Members

Here at the AAN, we’re not afraid to take on large projects. But the biggest task I’ve been aware of is our Axon Registry. And while I would love to take credit for the very successful recent conclusion of its pilot phase, I have to say I am merely the messenger of this good news. The kudos belong to my predecessor, Past President Timothy A. Pedley, MD, FAAN, who launched the registry in 2014; former President Bruce Sigsbee, MD, FAAN, and the members of the Registry Committee that he chairs; and our remarkable Academy staff.

I also need to thank the nearly 1,000 AAN member neurologists who volunteered their practices as test beds to actively engage in “real world” use of the registry. They effectively proved the concept and demonstrated the robust execution of this ambitious project. Furthermore, we reached one million patient records faster than any other registry that FIGMD, our vendor, has developed.

After Dr. Sigsbee made his recent report to the Board of Directors on conclusion of the pilot phase, the Board agreed it was successful and voted to begin to expand the program. Our new goal is to have 2,000 members participating in the registry in 2017, and 4,000 member participants by the end of 2018. We also will conduct a quality assessment on the beta data to ensure it meets certain quality reporting requirements. You can read more about this on page 9.

The AAN has made a significant investment of dollars and resources to create the Axon Registry. We are doing this for several reasons. First and foremost, the registry is focused on clinical quality improvement. The Centers for Medicare & Medicaid Services and other policy makers have taken a very positive view of specialty societies that demonstrate their commitment to improving the quality and value of care by creating clinical data registries. CMS considers collecting and analyzing quality data and interventions based on these data as essential to a high-value health care system as we all seek to improve quality and reduce costs.

Second, the registry enables AAN members across the US to use clinical data to improve care delivery and patient outcomes. You will be able to track your performance and really understand important aspects of your individual practice and compare each of these against your peers.

Third, the Axon Registry will enable you to save time and energy while complying with requirements and demonstrate quality care. It will help you:

- Meet the MOC Part IV PIP Clinical Module requirement
- Submit data that will be required under MACRA
- Submit data for PQRS and/or Meaningful Use

In most instances, the registry software will discreetly “pull” the necessary records from your EHR with little or no effort on your part. For larger clinics secured by firewalls that disallow third-party vendor access, it will be necessary to periodically “push” the required data to FIGMD. Still, this is a virtually effortless way to fulfill key reporting requirements.

Currently, the Axon Registry is a free benefit only to AAN members, and we anticipate it will be very popular with members based on our experience with the pilot cohorts. So I want to encourage you to look into participating in 2017 and enjoy the efficiencies the registry provides for the data reporting you need to do. Read the latest updates at AAN.com/view/Axon and watch the brief videos featuring Dr. Sigsbee’s explanation of the registry. You can ask questions by emailing registry@aan.com or submit your name to participate by going online at AAN.com/view/Axon.

Again, my thanks to all who have had a hand in the successful launch of the Axon Registry and I trust we can look forward to a glowing report from our future President Ralph L. Sacco, MD, MS, FAHA, FAAN, after the 2017 results are evaluated.

Terrence L. Cascino, MD, FAAN
President, American Academy of Neurology
tcascino@aan.com
Robert A. Gross, MD, PhD, FANA, FAAN

This is the latest in a series of profiles of members of the Board of Directors for the AAN and AAN Institute.

Robert A. Gross, MD, PhD, FANA, FAAN, is associate chair for academic affairs in neurology and founder and current director of the Academic Research Track at the University of Rochester Medical Center in New York. He was the 1988 recipient of the S. Weir Mitchell Award from the AAN, served as associate editor of Neurology® for eight years—two of which were as deputy editor—is the current editor-in-chief of the Neurology journals, and chairs the AAN Publications Committee.

What moved you to join the BOD?
The editor-in-chief of the Neurology journals has a seat on the board. When the previous editor stepped down, and I was appointed interim editor-in-chief, this was my first experience on the board. Previously, I had participated in AAN courses, reviewed abstracts, and interacted with various committees as part of my associate editor role. I realize this probably isn’t the usual response to this question! So, even though my route to sitting on the board was an unusual one, I would add that I have enjoyed the experience tremendously, and now strongly advocate for AAN service to my colleagues and those I mentor. The board is strategic, operates at a high level with important discussions, and strives to serve our members in numerous, substantive ways. And it pays benefits in other ways, as I have friends and colleagues with whom I now have the pleasure of working on a regular basis.

What experiences and viewpoints do you bring to this role?
I was trained as a basic scientist (though I no longer have a lab) and have participated in clinical research; I was active in educational efforts at my institution (formal medical school courses, director of one; directing a year-out program for mentored research for medical students); and of course my experience as an active clinician in our epilepsy center (for which I was director for several years). As the editor-in-chief of the Neurology journals, and the founding chair of the Publications Committee, I also bring an editorial and business perspective to the board. I have worked with AAN committees and sections in the past, which gave me an operational view of the Academy.

From your experiences as an AAN leader, what is one of the more common misperceptions members may have about the Academy?
I suspect that not all members are aware of the breadth and depth of Academy activities: advocacy, educational support, programs to benefit clinical activities and credentialing. And there are efforts on behalf of our patients: health fairs, educational materials (Neurology’s Patient Page and Neurology Now®). Most are aware of our publications, but possibly not the full range—a patient book series, for example, has been a successful and important program. This column is one way to help dispel misconceptions, but transparent communication is something we continually seek.

In your view, how does the AAN benefit the field of neurology most?
It’s difficult to single out one item, but if I must: our educational and publication efforts; the scope of activity at the Annual Meeting and in our various publications, including CME material, a weekly podcast, a newspaper (Neurology Today®)...it’s amazing. Combined with the efforts of the communications team that gets the word out about our various activities, these are important, successful efforts. Political advocacy must be on a par, though—as a relatively small specialty, these endeavors greatly help our profession. And (now fully violating these endeavors greatly help our profession. And (now fully violating the ‘most’ part of the question) our efforts internationally with neurologists and those in allied positions (trial coordinators, advanced practice providers) are important and continuing endeavors.

How should members evaluate the success of the AAN and the BOD in supporting their careers and neurology in general?
That should be an individual metric, I would think. What does the Academy do that helps you, directly or indirectly? And how responsive is the Academy if there are areas that need greater support? Recent examples that come to mind include the efforts on behalf of members in understanding burnout and, more important, how to remediate burnout. Ultimately, involvement in the AAN is the best way to effect change to address areas of need.

How do you deal with the challenges of balancing the demands of your work and personal life?
The answer to this question has varied throughout my career. But the real answer is that I have the support of my family for my work; and in turn, I always try to be there for family time. With my wife having retired, and my kids out of college and busy on their own, it’s a different balance than when I made time to attend football or lacrosse games! Now, there’s more time for winery tours, or a dinner at one of our favorite restaurants. Since journal work is never-ending, I rely on my associate editors to pick up for me when I take the time to unplug and travel for pleasure: I owe them a great debt for covering for my two-week trip to Italy with my wife last year! And the yearly international jazz festival here in Rochester, NY, is a great time to relax with friends and family and to hear great music. *
Axon Registry: Ensuring Data Quality

Administrative and clinical data generated through the routine delivery of health care are rich sources of information. The AAN’s Axon Registry™ extracts these data directly from the electronic health record (EHR) and data are used for quality improvement, quality-based payments, and maintenance of certification.

“The potential uses of these data are wide ranging and as the AAN implements the Axon Registry it is vital that users of the data are confident that the data in Axon Registry are sound,” said Bruce Sigsbee, MD, FAAN, chair of the AAN Registry Committee. “This means that the data elements are captured correctly from the EHR, the computer logic is accurate, and the quality measures are reliable and valid.”

AAN leaders agree analyses of the data will confirm the completeness and accuracy of the data in Axon Registry. To that end, the AAN Registry Committee has developed a multi-pronged data validation strategy based on the methods used by the National Committee for Quality Assurance, the Physician Consortium for Performance Improvement Foundation, and the National Quality Forum. These strategies include practice level validation, reviewing the measure logic, conducting chart audits, and measure testing.

Two of these types of validation are continuous and include reviewing the computer logic and practice level validation. The purpose of reviewing the measure logic is to confirm the registry vendor correctly identifies patients in—or excluded from—the numerator and denominator. In addition, when participants join the Axon Registry they participate in a series of telephone calls to ensure the data fields are accurately mapped in their EHR and are captured and extracted completely.

In 2017, the AAN will take additional steps to analyze the data for completeness, reliability, validity, and feasibility. First, a cross section of Axon Registry users will review a representative sample of their patient medical records and compare patient data and performance against the data displayed on the Axon Registry dashboard. Also, the AAN plans to hire an external party to test the scientific acceptability of quality measures. This will ensure the measures and their specifications are reliable and that the measures lead to valid conclusions about the quality of care provided.

Attention in health care providers’ performance will continue to expand and the Axon Registry helps neurology practices meet these data needs. These data are the foundation for value-based payments and certification and there could be numerous other potential uses of the data; a robust and scientifically sound database and clinical quality measures will be imperative.

For more information about the Axon Registry or to participate, visit AAN.com/practice/axon-registry. *

Magazines Highlight Migraine Awareness, Pressures on Emergency Departments

The AAN’s patient magazine Neurology Now® offers a portrait of Bellamy Young, the actress who portrays former First Lady Melody “Mellie” Grant in the ABC drama series “Scandal.” Young is devoted to numerous causes, but is a staunch advocate for migraine awareness, as she discusses in this issue’s cover story. Other articles highlight electronic health records, intimacy and neurology, and women and neurologic disease.

Neurology Now is a free benefit for AAN members and their patients. AAN members may elect to receive multiple copies to distribute to their patients, who also can subscribe for free. Visit NeurologyNow.com to learn more or access your AAN member profile to adjust the number of copies you receive.

Two papers and an accompanying editorial in this issue of Neurology® Clinical Practice discuss emergency department burden and access to outpatient clinics. In “Practice Current: Establishing worldwide connections,” Editor Luca Bartolini, MD, reviews the first year of this section that encourages data sharing to provide insights to practice approaches used around the world. There also is a timely review of Zika virus disease that provides updates on the latest reported neurologic complications, mechanisms of transmission, and testing.

Neurology: Clinical Practice, published six times a year, is available in print (for US members only), online, and for the iPad and Android. Visit Neurology.org/cp for more information. *
New 2017 Medicare Physician Fee Schedule Includes Neurology Successes

Last month, the Centers for Medicare & Medicaid Services (CMS) issued its final Medicare Physician Fee Schedule for 2017. The AAN is pleased to see CMS finalize several proposals enabling neurologists to have more opportunities to be reimbursed for the cognitive care provided to patients. These changes to the fee schedule reflect the AAN’s work in developing a proactive relationship with officials at CMS. In September, the AAN submitted comments to the agency and held numerous meetings with Medicare officials to explain the need for more appropriate reimbursement in the cognitive specialties. Below are key changes for neurology.

New Codes/Newly Covered Services

CMS now will reimburse for four new CPT codes and four existing, previously unpaid, codes.

- Newly covered (previously unpaid) codes include prolonged E/M service codes 99358 and 99359, which capture the non-face-to-face work associated with patient care outside of an E/M visit. Previously, these service elements were “bundled” into E/M visit codes, which meant that additional work efforts by neurologists were not paid for outside of the E/M visit. Under the new policy, neurologists will be paid for this significant amount of time spent outside of the in-person office visit caring for the individual needs of their patients.

- Other previously unpaid codes include complex chronic care management service codes 99487 and 99489, which now will be reimbursed by CMS. The final rule also improves payment for visits that initiate chronic care management (CCM) services with the establishment of new code G0506.

- CMS recognizes the value neurologists play in the health care system, as the final rule specifies that Medicare will begin paying for cognitive and functional assessment and care planning services for patients with cognitive impairment, which will be reported with new code G0505.

- We are also pleased to see CMS finalize two new codes that describe initial and subsequent encounters for critical care consultations furnished via telehealth: G0508 and G0509. The new codes provide a mechanism to report an intensive telehealth consultation service for the critically ill patient under the circumstance when a qualified health care professional has in-person responsibility for the patient but the patient benefits from additional services from a distant-site consultant specially trained in providing critical care services.

To better understand the new codes and how to implement them into your practice, the AAN has developed a 2017 Coding Table which includes the full code description, proposed payment, required elements, and billing requirements. The table can be accessed at AAN.com/practice/medicare/medicare-payments.

Appropriate Use Criteria

In the final rule, CMS took another step toward new standards governing the use of advanced imaging services.

- The Protecting Access to Medicare Act establishes a program under the Medicare fee-for-service program to promote the use of appropriate use criteria (AUC) for advanced diagnostic imaging services. This policy requires physicians ordering certain imaging services for Medicare beneficiaries to consult with AUC applicable to the imaging modality.

- The agency plans to require physicians to consult clinical decision support technology before conducting certain advanced scans if they want to qualify for Medicare reimbursements.

- In the final rule, CMS set parameters for what exactly qualifies as a support tool and identified eight clinical areas where it will focus its initial oversight. Headache was listed as one of the eight areas.

- The final rule includes clinical decision support mechanism (CDSM) requirements and outlines the application process. Noting that a list of qualified CDSMs is not yet available and will not be available by January 1, 2017, CMS will not require ordering professionals to meet this requirement by that date. At the earliest, the first qualified CDSMs will be specified on June 30, 2017. CMS anticipates that providers may begin reporting as early as January 1, 2018.

- CMS finalized three exceptions to the AUC consultation and reporting requirements. One is for an applicable imaging service ordered for an individual with an emergency medical condition. A second is for applicable imaging services ordered for an inpatient and for which payment is made under Medicare Part A. The third is for an ordering professional who CMS determines, on a case-by-case basis and subject to annual renewal, that consultation with applicable AUC would result in a significant hardship, such as in the case of a professional practicing in a rural area without sufficient Internet access.
ACO/PQRS Change

CMS finalized its proposal to establish a secondary Physician Quality Reporting System (PQRS) reporting period for the 2017 PQRS payment adjustment for individual eligible professionals (EPs) or group practices who bill under the TIN of an ACO participant if the ACO failed to report on behalf of such individual EPs or group practices during the previously established reporting period for the 2017 PQRS payment adjustment.

- The secondary reporting period for the 2017 PQRS payment adjustment would coincide with the reporting period for the 2018 PQRS payment adjustment (January 1, 2016, through December 31, 2016).
- This option is limited to EPs and group practices that bill through the TIN of an ACO participant in an ACO that failed to satisfactorily report on behalf of its EPs and would not be available to EPs and group practices that failed to report for purposes of PQRS outside the Shared Savings Program.
- CMS specifies these affected EPs may utilize the secondary reporting period either as an individual EP or as a group practice using one of the registry, QCDR, direct EHR product, or EHR data submission vendor reporting options.

Global Surgical Services

Under the misvalued code initiative in the 2015 final rule, CMS finalized a policy to transform all 10- and 90-day global codes to 0-day global codes, beginning in 2018. Under this policy, CMS would have valued the surgery or procedure to include all services furnished on the day of surgery and paid separately for visits and services furnished after the day of the procedure. Although Congress ultimately intervened, CMS is now required to gather data on visits in the post-surgical period that could be used to accurately value these services.

- CMS is basing adjustments to Medicare global surgical pay on a sample of physicians and services, instead of making all practitioners submit claims data on pre- and post-operative visits as proposed by the agency this summer to the displeasure of providers and lawmakers.
- An appropriate valuation of the global surgical period will create more fairness in the Fee Schedule

“The final rule continues an evolving trend,” said Marc Raphaelson, MD, the AAN’s RUC Representative and member of the Coding Subcommittee. “CMS now recognizes and pays for some of our care between office visits with complex patients. CMS expects that specialists and primary care teams will find better ways to coordinate care for complex patients, to provide better provide better outcomes and more services at lower overall costs. We can meet these goals, but we will all have to work out new ways to share responsibilities with our referring primary care practices.”

You can learn more about how the provisions of the final Medicare Physician Fee Schedule affect neurology by visiting our website and by registering for our free webinar, “Decoding the 2017 Medicare Fee Schedule and MACRA Rule,” on December 13, from 12:00 to 1:00 p.m. ET. Register by December 12 at AAN.com/view/pmw16.

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AAN Lobbying Helps Ease Impact of MACRA Changes on Neurologists

In one of the biggest changes in the history of Medicare, the Centers for Medicare & Medicaid Services (CMS) announced in October its final rules on the 2017 implementation of MACRA—the Medicare Access and CHIP Reauthorization Act of 2015.

The AAN and other stakeholders pressed CMS to make MACRA easier on physicians, especially those in small, solo, and rural practices. Over the summer, the Academy submitted neurology-specific comments and met with CMS on the proposed rule.

In the final rule, CMS reaffirmed its plan to create a “Quality Payment Program” that replaces old reporting programs. This new program involves a two-track system for Medicare reimbursement: Merit-based Incentive Payment System (MIPS) and Advanced Alternative Payment Models (APMs). But CMS made several modifications to its previously proposed rule.

“The release of the final rule shows that our intensive work on behalf of our members to share their concerns and suggestions with CMS was successful,” said AAN President Terrence L. Cascino, MD, FAAN. “Neurologists using the MIPS reporting system will be able to select their own pace of reporting in the first year of this new payment program. The low-volume threshold should be a big help to smaller practices that see relatively few Medicare patients. And our early development of new Alternative Payment Models for headache and epilepsy have us on the right track for answering the needs of neurologists seeking to participate in this part of the program.”

Merit-based Incentive Payment System (MIPS)

The Merit-based Incentive Payment System (MIPS) consolidates components of the Physician Quality Reporting System (PQRS), the Value-based Payment Modifier (VM), and the Medicare Electronic Health Record (EHR) Incentive Program. The rule finalizes the 2017 MIPS performance period, which begins on January 1 and ends on December 31 for all measures and activities.

CMS will begin measuring performance for physicians and other clinicians through MIPS in 2017, with payments based on those measures beginning in 2019. However, CMS announced a modification to this timeline that makes four choices available for physicians to “pick their pace” of participation in the first MACRA performance period that begins on January 1, 2017. Neurologists may choose from any one of the four options to ensure that they do not receive a payment penalty in 2019 based on their 2017 data:

- **Full-year reporting:** this offers an opportunity to earn a moderate positive payment bonus
- **Partial-year reporting:** by submitting 90 days of 2017 data to Medicare, you may earn a neutral or small positive payment bonus
- **Test-option reporting:** through the submission of a minimal amount of 2017 data to Medicare, such as one quality measure or one improvement activity, you can avoid a payment penalty
- **APMs:** participating in an Advanced Alternative Payment Model (APM)

CMS states that eligible physicians who choose not to submit any 2017 data will receive a negative four-percent payment penalty. CMS also announced that it anticipates providing a similar transitional approach in 2018. Specific proposals will be announced in 2017.

The final rule defines how CMS will exclude eligible clinicians who do not exceed the low-volume threshold: those with $30,000 or less in Medicare Part B allowed charges or 100 or fewer Medicare patients as measured at the TIN/NPI level for individual reporting, the TIN level for group reporting, and the APM Entity level for reporting under the APM scoring standard.

CMS projects that nearly 25 percent of neurologists will be excluded in the first year, primarily because they fall below the low-volume threshold. Others will be excluded because they are newly enrolled Medicare providers or participants in Advanced APMs. Excluded clinicians under this low-volume threshold are not eligible to participate in MIPS.

The final rule further outlines the four MIPS performance categories, each comprising a different percentage of an overall performance score in the first year of implementation which determines how the provider is paid. The final rule lowers the required amount of measures that must be reported and also adjusts the weights for the quality and cost categories:

- **Quality – 60 percent of the score.** Most clinicians will need to report up to six measures from a range of options that accommodate differences among specialties and practices. This is required for a minimum of 90 days. If fewer than six measures apply to a clinician or group, then they will only be required to report on each measure that is applicable.

- **Advancing care information – 25 percent of the score.** In the final rule, CMS reduced the total number of required measures from 11 to five measures. All other measures are optional for reporting. However, clinicians can choose to report up to nine customizable measures for a minimum of 90 days for additional credit.
Clinical practice improvement activities – 15 percent of the score. This is intended to reward activities like care coordination, beneficiary engagement, and patient safety. CMS lowered the threshold requirements in the final rule, stating that most participants will need to attest to having completed four “medium-weighted” or two “high-weighted” activities for a minimum of 90 days to receive full credit. Groups with fewer than 15 participants, or those located in a rural or health professional shortage area, may attest to having completed up to only two “medium-weighted” or one “high-weighted” activity for a minimum of 90 days.

Cost – 0 percent of the score. Counted starting in 2018, the score will be based on Medicare claims, which means there are no reporting requirements for clinicians. This category will use episode-specific measures to account for differences among specialties. Additionally, CMS finalized a process for providing performance feedback to MIPS eligible clinicians. Initially, the agency will provide feedback on an annual basis. In the future, CMS desires to provide feedback on a more frequent basis, as well as providing feedback on the performance categories of improvement activities and advancing care information. The final rule included a targeted review process under MIPS wherein an eligible clinician may request the agency review the calculation and MIPS payment penalty.

The agency also is finalizing requirements for third-party data submission to MIPS with an aim to decrease the burden on individual clinicians. Qualified clinical data registries, like the AAN’s Axon Registry™, will have the ability to act as an intermediary on behalf of a neurologist under MIPS to submit data to CMS across the quality, improvement activities, and advancing care information performance categories.

“We are still waiting for CMS to fill in some details about APMs, but are pleased that CMS seems to be trying to make it easier for physicians to participate in APMs,” said Joel M. Kaufman, MD, FAAN, member of the Medical Economics and Management Committee. “This is important for smaller practices and a key message from the AAN to CMS. Our work-to-date at the AAN required that we make some assumptions as to the direction CMS might go regarding APMs, and it was nice to see that our aim was correct. We ask that neurologists keep tuned in the coming year as we present our APM models to PTAC and the CMS Innovation Center. More to come!”

Advanced Alternative Payment Models (APMs)

CMS continues to work on finding the appropriate levels of risk for Alternative Payment Models but did finalize a number of proposals to establish Advanced APMs. CMS intends to broaden opportunities for clinicians to participate in Advanced APMs by working to include some existing models as meeting the necessary criteria and working with the CMS Innovation Center to create new models, including those recommended by the Physician-focused Payment Models Technical Advisory Committee (PTAC).

The AAN has created two condition-based APMs for neurology that will be submitted to the PTAC. The initial APMs focus on two common disease areas, headache and epilepsy, and the AAN plans to develop more condition-based APMs. In the future, these models may qualify under the APM track of MACRA and allow neurologists to negotiate new arrangements with payers. Learn about the AAN-developed draft alternative payment models at AAN.com/practice/alternative-payment-models/neurology-specific-apms.

Free Webinar and Additional Resources

Check out AAN resources for additional information on MACRA at AAN.com/view/MACRA. The AAN will host a free practice management webinar, “Decoding the 2017 Medicare Fee Schedule and MACRA Rule,” on December 13, 2016, from 12:00 p.m. to 1:00 p.m. ET. Members are encouraged to review CMS’ new Quality Payment Program at https://qpp.cms.gov. CMS offers a fact sheet that provides details and infographics on this new program, and practices can identify organizations to help them with MACRA.
Register for Free Webinar: Decoding the 2017 Medicare Fee Schedule and MACRA Rule

Continued from cover

Decoding the 2017 Medicare Fee Schedule and MACRA Rule

December 13 • 12:00 p.m.–1:00 p.m. ET
Register by December 12
Directors: William S. Henderson, FACMPE, and Lyell K. Jones, MD, FAAN

This free webinar will help you:
- Understand payment changes in the Medicare Physician Fee Schedule effective January 1, 2017
- Review final MACRA reporting requirements for 2017
- Learn how to implement new procedure codes (CPT) effective January 1, 2017
- Identify opportunities and challenges for neurology practices in 2017 based on final regulations

Visit AAN.com/view/pmw16 for more information or to register.

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Available by December 1
- Neurology: School Aged Cognition in Children Exposed to Levetiracetam, Topiramate or Sodium Valproate
  Nathan B. Fountain, MD, and Rebecca Bromley, PhD
- Neurology: Progression of Brain Atrophy in PSP and CBS over Six Months and One Year
  John C. Morgan, MD, PhD, and Adam L. Boxer, MD, PhD
- Neurology: Efficacy and Safety of Deflazacort Versus Prednisone and Placebo for Duchenne Muscular Dystrophy
  Kelly Graham Gwathmey, MD, and Robert C. Griggs, MD
- Neurology: Emerging Temporal Trends in Tissue Plasminogen Activator Use: Results from the BASIC project
  Kevin M. Barrett, MD, MSc, and Lynda D. Lisabeth, PhD, MPH
- Neurology: Practice Advisory: The Utility of EEG Theta/Beta Power Ratio in ADHD Diagnosis
  Adam Lawrence Numis, MD, and David Gloss, MD
- Neurology: Clinical Practice: Incidence of Meningeal Enhancement on Brain MRI Secondary to Lumbar Puncture
  Jonathan Perk, MD, PhD, and Sarah Flanagan Wesley, MD, MPH
- Neurology: Clinical Practice: Alice in Wonderland Syndrome: A Systematic Review
  David A. Lapides, HS, and Jan Dirk Blom, MD, PhD
New Practice Management Webinar Series Launches in January

Gain valuable insight and tools to help navigate through the changes that lay ahead in the new health care landscape. These webinars feature:

- Convenient one-hour sessions, 12:00 p.m.–1:00 p.m. ET
- 1 AMA PRA Category 1 Credit™ per webinar for physicians
- Certificate of completion for non-physicians
- Presentation slides and access to webinar recording if you miss the live event
- $99 per webinar or subscribe to the complete 2017 webinar series for only $189

To register for a 2017 subscription for all 10 live webinars and access to recordings, simply start registering for a single webinar and the option to bundle will be presented. Registration for recorded webinars presented in 2016 must be made in a separate transaction.

Add These 2017 Webinars to Your Calendar

- January 18  How to Approach Advance Care Planning
- February 7  Successfully Participate in MACRA
- March 8  Getting What You Deserve—A Primer on Contracting
- March 28  Thriving in Small and Solo Neurology Practices
- May 2  Coding for Risk: How It Impacts Payment
- June 6  Break the Code, or It Will Break Your Practice: Coding for Neurodiagnostic Procedures
- August 1  A Guide to Teleneurology: Use It in Your Practice
- September 12  Open Your Heart, Open Your Notes: A Guide to Patient Engagement
- October 10  Using the EHR or Axon Registry to Drive Quality Improvement
- November 7  iNeurology: Best IT Practices

MACRA and MIPS Performance

Beginning July 1, 2017, according to the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA), the Department of Health and Human Services (HHS) will make available feedback on Merit-based Incentive Payment System (MIPS) performance, including feedback on data submitted through qualified clinical data registries such as the AAN’s Axon Registry™.

Starting July 1, 2018, HHS will include information on resource use by patients, including costs attributed to other providers.

Learn more about MACRA and MIPS at AAN.com/view/MACRA.

QRUR Is Your Crystal Ball to Foresee Future Medicare Payments

It’s hard to predict the future, much less prepare for it. But you have a better chance to do both if you access your Quality and Resource Use Report (QRUR) available from the Centers for Medicare & Medicaid Services (CMS). Currently, Medicare uses data from two years prior to make payment adjustments (e.g., 2015 data affects payments in 2017). That’s a strong reason to download your QRUR now.

Your QRUR informs you how your practice will fare under Medicare payment programs in future years. It tells you how you did in each evaluated area and alerts you to your composite score—and its subsequent effect on your payments in the Medicare program.

Consequently, you need to review your QRUR so you know how you are performing and how your 2017 payments may be impacted. CMS will have alerted you that your QRUR for the 2015 calendar year is available to download if you have added your email address to the required Enterprise Identity Management System (EIDM) account. If you have not provided CMS with your email, you will need to visit its website to access your QRUR.

The QRUR serves as the final summary report on quality and cost performance. It includes cost, claims-based outcome measures, and utilization data based on all services provided to a TIN’s attributed patients; and quality data is based on PQRS quality data submitted by the TIN. It reports your value-based modifier (VBM) to show how you will fare (if eligible) or how you would have fared (if not eligible) for that program year. It is used to adjust fee schedule payments to physicians based on that performance period.

Your QRUR will provide you with additional information regarding how CMS has assessed the cost and quality of care you have provided to certain patients. It also will help you understand how the VBM will affect your reimbursement. In practical terms, the QRUR report is a forecasting tool to benchmark progress and power your practice.

More information from CMS on how to obtain your QRUR can be found at http://go.cms.gov/1Q3ZBp5.

Learn more by viewing a short, animated video series designed to help you understand how to read your QRUR. Access the series at http://bit.ly/1P7kPDG.

Learn more by viewing a short, animated video series designed to help
Access Neurology Compensation and Productivity Report
Before Year End

Evaluate Factors that May Affect Your Income

If you want the latest information to compare your salary, benefits, and productivity to your subspecialty peers, you need to access the AAN’s 2016 Neurology Compensation and Productivity Report and customizable dashboard before December 31.

Access is free if you participated in this year’s Neurology Compensation and Productivity Survey. And if you did not participate in the survey, you still can purchase access to your report and the customizable dashboard for the discounted price only of $600 for AAN members (compared to $1,200 for nonmembers).

It’s important to understand how you and your practice compare to others across the country in order to identify areas where you can be more efficient and determine fair market value for your professional expertise.

But time is limited for this offer. Access or purchase your AAN 2016 Neurology Compensation and Productivity Report by December 31, 2016. For more information, visit AAN.com/view/2016NeuroReport.

Live Well
Taking Care of Your Patients Starts with Taking Care of You

Neurologists have one of the highest rates of burnout and lowest rates of work-life balance among medical specialties.

Find practical solutions to revitalize your well-being.

AAN.com/LiveWell
New Guideline Addresses Restless Legs Syndrome in Adults

The AAN’s latest practice guideline, “Treatment of Restless Legs Syndrome in Adults,” was published online on Neurology® on November 16, 2016, and in the December 13, 2016, print edition.

Restless legs syndrome (RLS) is a common neurologic disorder described as an urge to move the legs or arms, commonly in response to an uncomfortable and unusual feeling. There are multiple effective medication and non-medication treatments available that improve the core RLS symptoms as well as associated sleep disturbance. However, long-term effectiveness of the medication treatments is unknown.

The guideline states that in moderate to severe primary RLS, clinicians should consider prescribing medication to reduce RLS symptoms:

- There is strong evidence to support the use of pramipexole, rotigotine, and gabapentin encarabil (Level A)
- There is moderate evidence to support the use of ropinirole, pregabalin, and IV ferric carboxymaltose (Level B)
- There is weak evidence to support the use of levodopa (Level C)

Two complications of long-term treatment of RLS with dopaminergic medication may occur: augmentation and loss of efficacy. Augmentation is characterized by an overall worsening of RLS symptoms with earlier appearance during the day, increased intensity of symptoms, or spread of symptoms to the upper extremities.

“When addressing RLS, clinicians and patients must first determine whether symptoms require treatment, the setting in which this practice guideline is relevant,” said John W. Winkelman, MD, PhD, lead author of the guideline.

AAN Collaborates with Mexican Academy of Neurology on Guideline Translations

The AAN collaborated recently with the Mexican Academy of Neurology (MAN) to produce English-to-Spanish translations of a select number of the AAN’s clinical guidelines.

These new Spanish translations are offered through the AAN’s journal Neurology® and can be accessed at AAN.com/view/MultipleLanguage.

“The Mexican Academy of Neurology is doing remarkable things to strengthen its organization with the mission to provide cutting-edge scientific knowledge to meet the needs of members and improve the lives of patients living with neurologic disease,” said Cynthia Harden, MD, chair of the Guideline Development, Dissemination, and Implementation Subcommittee.

“Currently, several AAN guidelines are available in languages other than English, and we hope to expand this initiative between the Academy and the MAN in making additional AAN guidelines available in Spanish. We anticipate that clinician summaries and patient summaries will be translated and made available in the near future.”

AAN members who feel that a guideline or summary should be translated into an additional language may contact guidelines@aan.com. The AAN Guideline Development, Dissemination, and Implementation Subcommittee will review and prioritize any suggested topics at its quarterly meetings.
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 AAN.com/view/HillReport. Below are some recent highlights.

As the nation prepares for a new presidential administration and new session of Congress, President Cascino sent an email to US AAN members to personally assure them that as changes to health care policy are considered, the AAN will strongly advocate for the interests of neurology. Our primary goal remains to ensure your success.

At this point, it is expected that the Patient Protection and Affordable Care Act (ACA), passed in 2010, is likely to undergo significant reform. While we wait to learn the details, know that changes to the ACA are likely to impact the insurance marketplace, and consequently, your patients. Repeal of the ACA would not affect those enrolling for coverage for 2017.

Unlike the ACA, the Medicare Access and CHIP Reauthorization Act (MACRA) of 2015 was passed with wide bipartisan support. We do not believe MACRA will be significantly altered so as to affect your participation in 2017. You should continue to prepare to pick your pace of reporting—in the Merit-based Incentive Payment System or Advanced APM pathways. Learn more about MACRA on page 12 of this issue or at AAN.com/practice/MACRA, and register for a free webinar on December 13, “Decoding the 2017 Medicare Physician Fee Schedule and MACRA Rule.”

There are more questions than answers at this early stage. The AAN is looking out for the needs of your patients and our profession, and will continue to keep you informed and prepare you for whatever changes are ahead. 

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Carry the only card that helps support the American Academy of Neurology.

To apply for a credit card, visit AAN.com/view/CashRewards.

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*You will qualify for $100 bonus cash rewards if you use your new credit card account to make any combination of Purchase transactions totaling at least $500 (exclusive of any fees, returns and adjustments) that post to your account within 90 days of the account open date. Limit one (1) bonus cash rewards offer per new account. This one-time promotion is limited to new customers opening an account in response to this offer. Other advertised promotional bonus cash rewards offers can vary from this promotion and may not be substituted. Allow 8-12 weeks from qualifying for the bonus cash rewards to post to your rewards balance.

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Don’t let patients get lost in the noise of RMS

RMS = relapsing forms of multiple sclerosis.
QUIETING MS

Quietly*
for your patients with relapsing MS

*AUBAGIO is effective across key measures of disease activity: sustained disability progression (14 mg only), annualized relapse rate, and MRI activity. Overall discontinuation rates due to adverse events were 12.5% with AUBAGIO 14 mg, 11.2% with AUBAGIO 7 mg, and 7.5% with placebo, and treatment discontinuation rates due to common adverse events were ≤3.3% in the pooled clinical trials.1,2

MS=multiple sclerosis.

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

IMPORTANT SAFETY INFORMATION

WARNING: HEPATOTOXICITY AND RISK OF TERATOGENICITY

- 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. AUBAGIO is contraindicated in patients with severe hepatic impairment and in patients taking leflunomide.

- 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 6 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.

- 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.

CONTRAINDICATIONS

- AUBAGIO is contraindicated in patients with severe hepatic impairment, in pregnant women, in women of childbearing potential who are not using reliable contraception, in patients with a history of hypersensitivity to teriflunomide, its inactive ingredients, leflunomide, or who are currently taking leflunomide.

WARNINGS AND PRECAUTIONS

- Hepatotoxicity: Patients with pre-existing acute or chronic liver disease, or those with serum 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, patients discontinued AUBAGIO and underwent accelerated elimination. Consider additional monitoring if co-administering AUBAGIO with other potentially hepatotoxic drugs; monitor patients who develop symptoms suggestive of hepatic dysfunction (eg, unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine).

- Use in Women of Childbearing Potential: Before starting therapy, use of reliable contraception must be confirmed, and the patient counseled on risks to the fetus. Patients with delayed onset of menses or other reason to suspect pregnancy should immediately see their physician for pregnancy testing. Patients who become pregnant or wish to become pregnant should discontinue treatment, followed by accelerated elimination until plasma concentrations of <0.02 mcg/mL are verified, a level expected to pose minimal risk to the fetus. Women who become pregnant while taking AUBAGIO may enroll in the AUBAGIO pregnancy registry by calling 1-800-745-4447, option 2.
AUBAGIO® (teriflunomide) was proven again and again to reduce key measures of disease activity: sustained disability progression (14 mg only), annualized relapse rate, and MRI activity

- AUBAGIO 14 mg is the only oral RMS therapy with 2 pivotal Phase III trials that show a significant reduction in the risk of sustained disability accumulation
  - AUBAGIO 7 mg did not demonstrate a significant reduction in risk of sustained disability progression in either trial
- 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
- AUBAGIO has demonstrated a consistent safety profile across 4 separate trials in 2047 patients
- One daily tablet that can be taken with or without food
- Health care professionals should run certain tests before prescribing AUBAGIO and should monitor patient liver enzyme levels monthly for the first 6 months

**TEMSO:** A double-blind, placebo-controlled trial in patients with relapsing forms of MS (N=1088). Patients were randomized to receive AUBAGIO 14 mg (n=359), AUBAGIO 7 mg (n=366), or placebo (n=363) daily for 108 weeks.1
**TOWER:** A double-blind, placebo-controlled trial in patients with relapsing forms of MS (N=1169). Patients were randomized to receive AUBAGIO 14 mg (n=372), AUBAGIO 7 mg (n=380), or placebo (n=389) daily with results for up to 40 months of treatment.1,5
**TOPIC:** A double-blind, placebo-controlled trial in patients with relapsing forms of MS (N=618). Patients were randomized to receive AUBAGIO 14 mg (n=216), AUBAGIO 7 mg (n=205), or placebo (n=197) once daily for 108 weeks. Patients had a first clinical event consistent with acute demyelination occurring within 90 days of randomization with 2 or more T2 lesions at least 3 mm in diameter characteristic of MS.1,4

**Study 4:** A double-blind, placebo-controlled trial in patients with relapsing forms of MS (N=179). Patients were randomized to receive AUBAGIO 14 mg (n=57), AUBAGIO 7 mg (n=61), or placebo (n=61) daily once for 36 weeks.1

**Procedure for Accelerated Elimination of Teriflunomide:** Teriflunomide is eliminated slowly from the plasma—it takes an average of 8 months, or up to 2 years, to reach plasma concentrations <0.02 mcg/mL. Elimination may be accelerated by administration of cholestyramine or charcoal, but this may cause disease activity to return in patients who were responding to AUBAGIO.

- **Bone Marrow Effects/Immunosuppression Potential/Infections:** Decreases in white blood cell counts, mainly of neutrophils and lymphocytes, and platelets have been reported with AUBAGIO. Thrombocytopenia, including rare cases with platelet counts less than 50,000/mm³, have been reported in the postmarketing setting. Obtain a complete blood cell count within 6 months before starting treatment, with further monitoring based on signs and symptoms of bone marrow suppression. AUBAGIO is not recommended for patients with severe immunodeficiency, bone marrow disease, or severe uncontrolled infections. Tuberculosis (TB) has been observed in clinical studies of AUBAGIO. Before starting treatment, screen patients for latent TB infection with a tuberculin test. Treatment in patients with serious or chronic infections should not be started until the infection(s) is resolved. Administration of live vaccines is not recommended. The risk of malignancy, particularly lymphoproliferative disorders, or infection may be increased with the use of some medications with immunosuppressive potential, including teriflunomide.

- **Hypersensitivity and Serious Skin Reactions:** AUBAGIO can cause anaphylaxis and severe allergic reactions. Signs and symptoms have included dyspnea, urticaria, and angioedema including lips, eyes, throat, and tongue. Cases of serious skin reactions, including Stevens-Johnson syndrome and a fatal case of toxic epidermal necrolysis, have been reported with AUBAGIO. Very rare cases of Drug Reaction with Eosinophilia and Systemic Symptoms have also been reported with leflunomide. If a severe skin reaction develops with AUBAGIO, stop treatment and begin accelerated elimination. In such cases, patients should not be re-exposed to teriflunomide.

- **Peripheral Neuropathy:** 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.

- **Increased Blood Pressure:** Systolic and diastolic pressure increases and hypertension have occurred with AUBAGIO. Measure blood pressure at treatment initiation and manage any elevations during treatment.

- **Respiratory Effects:** Interstitial lung disease (ILD), including acute interstitial pneumonitis, has been reported with AUBAGIO. ILD may be fatal and may occur acutely at any time during therapy with a variable clinical presentation. If discontinuation of the drug is necessary, consider initiation of an accelerated elimination procedure.

**Adverse Reactions:** The most frequent adverse reactions (≥10% and ≥2% greater than placebo) with AUBAGIO 7 mg and 14 mg and placebo, respectively, were headache (18% and 16% vs 15%), ALT increased (13% and 15% vs 9%), diarrhea (13% and 14% vs 8%), alopecia (10% and 13% vs 5%), and nausea (8% and 11% vs 7%).

- **Drug Interactions:** Monitor patients when teriflunomide is coadministered with warfarin, or with drugs metabolized by CYP1A2, CYP2C8, substrates of OAT3 transporters, substrates of BCRP, or OATP1B1/1B3 transporters.

**Use in Specific Populations:** AUBAGIO is detected in human semen. To minimize any possible fetal risk, men not wishing to father a child and their female partners should use reliable contraception. Men wishing to father a child should discontinue therapy and undergo accelerated elimination, with verification of plasma concentrations <0.02 mcg/mL. Nursing mothers should not use AUBAGIO.

Please see Brief Summary of Full Prescribing Information, including boxed WARNING regarding hepatotoxicity and use in pregnancy, on the following pages.
PERSONAL SUPPORT FROM THE START

AUBAGIO® (teriflunomide) and MS One to One® may help your patients manage their RMS

- Getting started: the AUBAGIO Start form is both a prescription for AUBAGIO and enrollment for support offered by MS One to One

For more information, visit www.AubagioHCP.com or call 1-855-MSOne2One (1-855-676-6326).

AUBAGIO is effective across key measures of disease activity: sustained disability progression (14 mg only), annualized relapse rate, and MRI activity. Overall discontinuation rates due to adverse events were 12.5% with AUBAGIO 14 mg, 11.2% with AUBAGIO 7 mg, and 7.5% with placebo, and treatment discontinuation rates due to common adverse events were ≤3.3% in the pooled clinical trials.¹²

Please see Important Safety Information on previous pages and Brief Summary of Full Prescribing Information, including boxed WARNING regarding hepatotoxicity and use in pregnancy, on the following pages.


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AUBAGIO® (teriflunomide) tablets, for oral use  

**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 [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)]. 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 [see Contraindications (4), Warnings and Precautions (5.3), 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.

2 **DOSE AND ADMINISTRATION**

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

- 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 or blood test for mycobacterium tuberculosis infection [see Warnings and Precautions (5.4)].
- Check blood pressure before start of AUBAGIO treatment and periodically thereafter [see Warnings and Precautions (5.7)].

4 **CONTRAINDICATIONS**

AUBAGIO is contraindicated in:

- Patients with severe hepatic impairment [see Warnings and Precautions (5.1)].
- Pregnant women or women of childbearing potential not using reliable contraception. AUBAGIO may cause fetal harm [see Warnings and Precautions (5.2 and 5.3) and Use in Specific Populations (8.1)].
- Patients with a history of a hypersensitivity reaction to teriflunomide, leflunomide, or any of the inactive ingredients in AUBAGIO. Reactions have included anaphylaxis, angioedema, and serious skin reactions [see Warnings and Precautions (5.3)].
- Co-administration with leflunomide [see Clinical Pharmacology (12.3 in the full prescribing information)].

5 **WARNINGS AND PRECAUTIONS**

5.1 Hepatotoxicity

Severe liver injury including fatal liver failure and dysfunction has been reported in some 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. Patients with pre-existing liver disease may be at increased risk of developing elevated serum transaminases when taking AUBAGIO. Patients with pre-existing acute or chronic liver disease, or those with serum alanine aminotransferase (ALT) greater than two times the upper limit of normal (ULN) before initiating treatment, should not normally be treated with AUBAGIO. AUBAGIO is contraindicated in patients with severe hepatic impairment [see Contraindications (4)].

In placebo-controlled trials, ALT greater than three times the ULN occurred in 61/1045 (5.8%) and 62/1002 (6.2%) of patients receiving AUBAGIO 7 mg and 14 mg, respectively, and 38/997 (3.8%) of patients receiving 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, if 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. 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. AUBAGIO-induced liver injury in this patient could not be ruled out.

Obtain serum transaminase and bilirubin levels within 6 months before initiation of 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. AUBAGIO-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 confirmed. Monitor serum transaminase and bilirubin on AUBAGIO therapy, particularly in patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, and/or jaundice and/or dark urine. If liver injury is suspected to be AUBAGIO-induced, discontinue AUBAGIO and start an accelerated elimination procedure [see Warnings and Precautions (5.3)] and monitor liver tests weekly until normalized. If AUBAGIO-induced liver injury is unlikely because of any other possible cause has been found, resumption of AUBAGIO 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)].

Women of childbearing potential must not be started on AUBAGIO until pregnancy is excluded and it has been confirmed that they are using reliable contraception. Before starting 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 possibility of pregnancy, pregnancy must be avoided during AUBAGIO therapy or prior to the completion of an accelerated elimination procedure after AUBAGIO treatment. 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 verification of teriflunomide plasma concentrations less than 0.02 mg/L (0.02 mcg/mL). Human plasma concentrations of teriflunomide less than 0.02 mg/L (0.02 mcg/mL) are expected to have minimal risk [see Contraindications (4), 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 mg/L, although because of individual variations in drug clearance it may take up to 2 years. An accelerated elimination procedure may decrease the risk to the fetus from 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 either 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 concentration.

Use of the accelerated elimination procedure may potentially result in return of disease activity if the patient had been responsive to AUBAGIO treatment.

5.4 Bone Marrow Effects/Immunosuppression Potential/Infections

Bone Marrow Effects

A decrease in white blood cell count (WBC) 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 compared to baseline. The decrease in mean WBC count occurred during the first 6 weeks and was a count normal low during treatment. In placebo-controlled studies, neutrophil count <1.5×10^9/L was observed in 12% and 16% of patients receiving AUBAGIO 7 mg and 14 mg, respectively, compared with 7% of patients receiving placebo; lymphocyte count <0.8×10^9/L was observed in 10% and 12% of patients receiving AUBAGIO 7 mg and 14 mg, respectively, compared with 6% of patients receiving placebo. No cases of pancytopenia or agranulocytosis were reported in premarketing clinical trials of AUBAGIO but rare cases of pancytopenia and agranulocytosis have been reported in the postmarketing setting with leflunomide. A similar risk would be expected for AUBAGIO [see Clinical Pharmacology (12.3 in the full prescribing information)].
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 is resolved and no patient development. Infection consider suspending treatment with AUBAGIO and using an accelerated elimination procedure. Reassess 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 AUBAGIO that have immunosuppression 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 AUBAGIO 7 mg (2.2%) or 14 mg (2.7%) compared to placebo (2.2%). However, one fatal case of klebsiella pneumonia sepsis occurred in a patient taking AUBAGIO 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 hepatitis 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 or with a blood test for mycobacterium tuberculosis infection. AUBAGIO has not been studied in patients with a positive tuberculin screen, and the safety of AUBAGIO in patients with latent tuberculosis infection is unknown. For patients testing positive in tuberculin screening, treat by standard medical practice prior to therapy with AUBAGIO.

Vaccination

No clinical data are available on the efficacy and safety of live vaccinations in patients taking AUBAGIO. Vaccination with live vaccines is 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 AUBAGIO. 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 or lymphoproliferative disorders with AUBAGIO.

5.5 Hypersensitivity and Serious Skin Reactions

AUBAGIO can cause anaphylaxis and severe allergic reactions (see Contraindications (4)). Signs and symptoms have included dyspnea, urticaria, and angioedema including lips, eyes, throat, and tongue. Cases of serious skin reactions, including cases of Stevens-Johnson syndrome (SJS) and a fatal case of toxic epidermal necrolysis (TEN), have been reported with AUBAGIO.

In patients treated with leflunomide, the parent compound, very rare cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported. Inform patients of the signs and symptoms of anaphylaxis and angioedema and signs and symptoms that may signal a serious skin reaction. Inform patients that a fever associated with signs of other organ system involvement (e.g., rash, lymphadenopathy, or hepatic dysfunction) may be drug-related. Instruct patients to discontinue AUBAGIO and seek immediate medical care should these signs and symptoms occur. Discontinue AUBAGIO, unless the reactions are drug-related, and begin an accelerated elimination procedure immediately (see Warnings and Precautions (5.3)). In such cases, patients should not be re-exposed to teriflunomide (see Contraindications (4)).

5.6 Peripheral Neuropathy

In placebo-controlled studies, peripheral neuropathy, including both polymyelopathy and mononeuropathy (e.g., carpal tunnel syndrome), occurred more frequently in patients taking AUBAGIO than in patients taking placebo. The incidence of peripheral neuropathy confirmed by nerve conduction studies was 1.4% (13 patients) and 1.9% (17 patients) of patients receiving 7 mg and 14 mg of AUBAGIO, respectively, compared with 0.4% receiving placebo (4 patients). Treatment was discontinued in 0.7% (8 patients) with confirmed peripheral neuropathy (3 patients respectively, compared with 0.4% receiving placebo (4 patients). Treatment was discontinued in 0.7% (8 patients) with confirmed peripheral neuropathy (3 patients receiving AUBAGIO 7 mg and 5 patients receiving AUBAGIO 14 mg). Five of them recovered following treatment discontinuation. Not all cases of peripheral neuropathy resolved with continued treatment. Peripheral neuropathy also occurred 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)).

5.7 Increased Blood Pressure

In placebo-controlled studies, the mean change from baseline to the end of study in systolic blood pressure was +2.3 mmHg and +2.7 mmHg for AUBAGIO 7 mg and 14 mg, respectively, compared with +0.6 mmHg for placebo. The change from baseline in diastolic blood pressure was +1.4 mmHg and +1.9 mmHg for AUBAGIO 7 mg and 14 mg, respectively, and -0.3 mmHg for placebo. Hypertension was an adverse reaction in 3.1% and 4.3% of patients treated with 7 mg or 14 mg of AUBAGIO compared with 1.8% for placebo. Check blood pressure before start of AUBAGIO treatment and periodically thereafter. Elevated blood pressure should be appropriately managed during treatment with AUBAGIO.

5.8 Respiratory Effects

Interstitial lung disease, including acute interstitial pneumonitis, has been reported with AUBAGIO in the postmarketing setting. Interstitial lung disease and worsening of pre-existing interstitial lung disease have also been reported during treatment with teriflunomide. Interstitial lung disease may be fatal and may occur acutely at any time during therapy with 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 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)).

5.9 Concomitant Use with Immunosuppressive or Immunomodulating Therapies

Co-administration with antineoplastic, or immunosuppressive therapies used for treatment of multiple sclerosis has not been evaluated. Safety studies in which AUBAGIO 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)).

ADVERSE REACTIONS

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

• Hepatotoxicity (see Contraindications (4) and Warnings and Precautions (5.1))
• Bone Marrow Effects/Immunosuppression Potential/Infections (see Warnings and Precautions (5.4))
• Hypersensitivity and Serious Skin Reactions (see Contraindications (4) and Warnings and Precautions (5.5))
• Peripheral Neuropathy (see Warnings and Precautions (5.6))
• Increased Blood Pressure (see Warnings and Precautions (5.7))
• Respiratory Effects (see Warnings and Precautions (5.8))

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the 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.

A total of 2047 patients receiving AUBAGIO (7 mg or 14 mg once daily) constituted the safety population in the pooled analysis of placebo controlled studies in patients with relapsing forms of multiple sclerosis; of these, 71% were female. The average age was 37 years.

Table 1 lists adverse reactions in placebo-controlled trials with rates that were at least 2% for AUBAGIO patients and also at least 2% above the rate in placebo patients. The most common were headache, an increase in ALT, diarrhea, alopecia, and nausea. The adverse reaction most commonly associated with discontinuation was an increase in ALT (3.3%, 2.6%, and 2.3% of all patients in the AUBAGIO 7 mg, AUBAGIO 14 mg, and placebo treatment arms, respectively).

Table 1. Adverse Reactions in Pooled Placebo-Controlled Studies in Therapies

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>AUBAGIO 7 mg (N=1045)</th>
<th>AUBAGIO 14 mg (N=1002)</th>
<th>Placebo (N=997)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>16%</td>
<td>16%</td>
<td>15%</td>
</tr>
<tr>
<td>Increase in Alanine</td>
<td>13%</td>
<td>15%</td>
<td>9%</td>
</tr>
<tr>
<td>Aminotransferase</td>
<td>13%</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13%</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>10%</td>
<td>13%</td>
<td>5%</td>
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<tr>
<td>Nausea</td>
<td>8%</td>
<td>11%</td>
<td>7%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>8%</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8%</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3%</td>
<td>4%</td>
<td>2%</td>
</tr>
</tbody>
</table>

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 AUBAGIO and cardiovascular death has not been established.

Acute Renal Failure

In placebo-controlled studies, creatinine values increased more than 100% over baseline in 11 to 15% of patients in the AUBAGIO group and 10 to 20% of patients in the placebo group. The increase in creatinine above baseline was not clearly related to the use of AUBAGIO.
patients in the 14 mg AUBAGIO group versus 4.997 (0.4%) patients in the placebo group. These elevations were transient. Some elevations were accompanied by hyperkalemia. AUBAGIO may cause acute uric acid nephropathy with transient acute renal failure because AUBAGIO increases renal uric acid clearance.

Hypophosphatemia

In clinical trials, 78% of AUBAGIO-treated patients had hypophosphatemia with serum phosphorus levels of at least 0.6 mmol/L, compared to 7% of placebo-treated patients; 4% of AUBAGIO-treated patients had hypophosphatemia with serum phosphorus levels at least 0.3 mmol/L but less than 0.6 mmol/L, compared to 0.8% of placebo-treated patients. No patient in any treatment group had a serum phosphorus below 0.3 mmol/L.

6.2 Post Marketing Experience

The following adverse reactions have been identified during post approval use of AUBAGIO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

• Hyperglycemia
• Hirsutism
• Jaundice, some of which were severe, such as anaphylaxis and angioedema [see Warnings and Precautions (5.5)]
• Severe skin reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome [see Warnings and Precautions (5.5)]
• Thrombocytopenia [see Warnings and Precautions (5.8)]
• Intestinal lung disease [see Warnings and Precautions (5.8)]
• Pancreatitis

7 Drug Interactions

Effect of AUBAGIO on CYP2C8 substrates

Teriflunomide is an inhibitor of CYP2C8 in vivo. In patients taking AUBAGIO, exposure of drugs metabolized by CYP2C8 (e.g., paclitaxel, pioglitazone, repaglinide, rosiglitazone) may be increased. Monitor these patients and adjust the dose of the concomitant drug(s) metabolized by CYP2C8 as required [see Clinical Pharmacology (12.3 in the full prescribing information)].

Effect of AUBAGIO on warfarin

Coadministration of AUBAGIO with warfarin requires close monitoring of the international normalized ratio (INR) because AUBAGIO may decrease peak INR by approximately 25%.

Effect of AUBAGIO on oral contraceptives

AUBAGIO may increase the systemic exposures of ethinylestradiol and levonorgestrel. Consideration should be given to the type or dose of contraceptives used in combination with AUBAGIO [see Clinical Pharmacology (12.3 in the full prescribing information)].

Effect of AUBAGIO on CYP1A2 substrates

Teriflunomide may be a weak inducer of CYP1A2 in vivo. In patients taking AUBAGIO, exposure of drugs metabolized by CYP1A2 (e.g., alloxan, duloxetine, theophylline, tizanidine) may be reduced. Monitor these patients and adjust the dose of the concomitant drug(s) metabolized by CYP1A2 as required [see Clinical Pharmacology (12.3 in the full prescribing information)].

Effect of AUBAGIO on BCRP and organic anion transporting polypeptide B1 and B3

[OATP1B1/1B3] substrates

Teriflunomide inhibits the activity of BCRP and OATP1B1/1B3 in vivo. For a patient taking AUBAGIO, the dose of rosuvastatin should not exceed 10 mg once daily. For other substrates of BCRP (e.g., mitoxantrone) and drugs in the OATP family (e.g., methotrexate, rifampin), especially HMG-CoA reductase inhibitors (e.g., atorvastatin, simvastatin), consider reducing the dose of these drugs and monitor patients closely for signs and symptoms of increased exposures to the drugs while patients are taking AUBAGIO [see Clinical Pharmacology (12.3 in the full prescribing information)].

8 Use in Specific Populations

8.1 Pregnancy

Pregnancy Category X [see Contraindications (4) and Warnings and Precautions (5.2)]

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 dosing 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).

Administration of teriflunomide (oral doses of 1, 3.5, or 12 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 malformation (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, embryofoetal and teratogenic effects were observed in pregnant rat and rabbit at or below clinically relevant plasma leflunomide exposures (AUC), in published reproduction studies in pregnant mice, leflunomide was embryolethal and increased the incidence of malformations (craniofacial, axial skeletal, heart and great vessel). 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.

Use in Males

AUBAGIO is detected in human semen. Animal studies to specifically evaluate the risk of male-mediated fetal toxicity have not been conducted. To minimize any possible risk, men not wishing to father a child and their female partners should use reliable contraception. Men wishing to father a child should discontinue use of AUBAGIO and undergo an accelerated elimination procedure to decrease the plasma concentration of teriflunomide to less than 0.02 mg/L (0.02 mcg/mL) [see Warnings and Precautions (5.3)].

Pregnancy Registry

Although AUBAGIO is contraindicated in pregnancy, a pregnancy registry has been established to monitor fetal outcomes of pregnant women exposed to AUBAGIO. Physicians are encouraged to enroll pregnant women in the AUBAGIO pregnancy registry, or pregnant women may enroll themselves, by calling 1-800-745-4447, option 2.

8.3 Nursing Mothers

Teriflunomide was detected in rat milk following a single oral dose of teriflunomide. It is not known whether this drug is excrated in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from AUBAGIO a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of AUBAGIO did not include patients over 65 years old.

8.6 Hepatic Impairment

No dosage adjustment is necessary for patients with mild and moderate hepatic impairment. The pharmacokinetics of teriflunomide in severe hepatic impairment have not been evaluated. AUBAGIO is contraindicated in patients with severe hepatic impairment [see Contraindications (4) and Warnings and Precautions (5.1), and Clinical Pharmacology (12.3 in the full prescribing information)].

8.7 Renal Impairment

No dosage adjustment is necessary for patients with mild, moderate, and severe renal impairment [see Clinical Pharmacology (12.3 in the full prescribing information)].

10 OVERDOSAGE

There is no experience regarding teriflunomide overdose or intoxication in humans. Teriflunomide 70 mg daily up to 14 days was well tolerated by healthy subjects. In the event of clinically significant overdose or toxicity, cholestyramine or activated charcoal is recommended to accelerate elimination [see Warnings and Precautions (5.3)].

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
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June 2016

TER-BPL-SA-JUN16
“A Career-changing Experience”

Newer AAN members or those who are unaware of the power of grassroots advocacy may be curious about the dynamics of the Palatucci Advocacy Leadership Forum (PALF), what happens at the event, and how it impacts participants. AAN Board of Directors member Nicholas E. Johnson, MD, chair of the Academy’s Government Relations Committee and past PALF graduate and advisor, interviewed Glynnis Zieman, MD, a graduate of the 2016 class, to get her perspectives about the weekend program and how it has affected her professionally and personally.

What were your concerns about attending PALF and were they addressed by the experience?

I was, honestly, quite intimidated before attending PALF because I knew my experiences in the forum would take me out of my comfort zone. I’ve worked in a variety of settings in the past, but had never been exposed to media and interview training. I quickly learned, however, that I was not alone in my inexperience, and I was surprised at how easily the advisors and staff guided us through the process.

What was the most important thing you learned about advocacy?

We all entered PALF with a specific advocacy agenda, but little idea how to consolidate our ideas. I loved the training we received in forming action plans, as this helped me organize my thoughts and create an achievable, pointed goal in my area of interest. Advocacy requires creating partnerships, organization, and persistence and action plans are a wonderful tool to integrate these factors.

What was the most surprising thing you learned about yourself?

I came to PALF with extensive knowledge about my specific advocacy issue and was very comfortable talking about my passion of treating traumatic brain injury in domestic violence victims. What surprised me, however, was how difficult it was for me to succinctly communicate the issue and my message. I was more comfortable in front of the camera than I expected, but it took some work to articulate my advocacy issue in an effective and efficient manner.

How did you apply your newly learned skills in your action plan or daily work?

When I arrived at PALF, I had a broad goal for my advocacy issue, but I quickly learned my vision needed to be narrowed down in order to effectively carry out my plans. Although it took some time for me to focus my efforts into a specific plan, this exercise changed the way I address my goals. I have not only made progress on the action plan I completed at PALF, but have created other action plans for different projects, and the media training I received has helped me communicate my work to colleagues, media, and the public.

Have you been able to use these skills in your personal life?

Absolutely! I applied for PALF knowing the skills I’d gain during the training would be helpful for my career, but I didn’t realize how useful these would be for everyday life scenarios. The communication skills, planning, and organization I learned during my weekend at PALF have helped me navigate major life events like buying a home and organizing medical care for a family member.

What would you tell a colleague who might have an interest in applying for PALF?

Regardless of your specialty or your interest in working with the media, PALF is a career-changing experience. Everyone can benefit from the action planning, and the media and legislative training provided at the forum—especially if you have a particular interest in outreach and community involvement. PALF changed who I am as a physician and I will forever be grateful I was given this opportunity. *
Change Your Career,
Change Your Life—
In Just One Weekend

The AAN is accepting applications for the 2017 Palatucci Advocacy Leadership Forum, held from May 18 through 21, 2017, at the Hyatt Regency Hill Country Resort & Spa in San Antonio, TX. The application deadline is January 9, 2017.

The AAN established this award-winning leadership program in 2003 to provide effective advocacy training unavailable elsewhere, because neurologists are the best advocates for our profession and our patients. The skills you develop during this unforgettable weekend can enhance your career and revitalize your passion for neurology.

The Palatucci Advocacy Leadership Forum teaches neurologists how to:

- Build and maintain relationships with reporters; great advocates are great contacts for media
- Develop media communication skills; learn the three “Cs” of Confidence, Control, and Credibility to successfully present in front of the camera and develop written editorials
- Turn your needs and those of your patients into action plans; push for change, describe what change looks like, and take a strong position
- Represent your patients and profession with state and federal representatives; be a good storyteller with stories that create personal connections

Whether you are just starting out in your career or looking to reinvigorate your work life, it’s your turn to participate in this unique four-day forum that will change your career—and your life!

Learn more and apply at AAN.com/view/2017PALF.
AAN members can soon get help preparing for their American Board of Psychiatry and Neurology (ABPN) recertification examination in clinical neurology, and earn up to 15 self-assessment CME credits, anytime and anywhere with the AAN’s convenient new online Neurology MOC Prep Course.

“While the AAN does not mandate MOC, it is continually working on new ways to support members across their professional lives, including providing tools and resources to help members successfully meet the ABPN’s MOC requirements,” said Ralph F. Józefowicz, MD, FAAN, who served on the work group that created the new online program. “Since 2015, a live MOC Preparation Course has taken place at the Breakthroughs in Neurology Conference—and has proven very popular—and another live course was offered for the first time at this year’s Annual Meeting in Vancouver. We surveyed members on a preferred format for this type of course, and we heard clearly that an easy-to-access online option was important.”

**How it works:**
- Read syllabi on the most heavily weighted topics on the ABPN Content Outline
- Listen to condensed audio interviews from syllabi authors
- Complete the self-assessment exam

**Features:**
- All new materials written by neurologists for neurologists
- Based on the ABPN content outline for the cognitive expertise component (Part 3) of MOC
- Syllabi cover new and updated science and therapies
- Audio interviews allow for on-the-go listening
- 100 multiple-choice questions help you determine your strengths and areas for improvement
- Exam feedback by subspecialty areas and suggestions for further reading
- Performance results compared to other neurologists
- Convenient online format—take on your own time, at your own pace

Added Józefowicz, “I believe this new online course exemplifies the AAN’s commitment to hearing—and helping—its members with regard to their concerns with MOC.”

In addition to the new online MOC Preparation Course, the AAN offers a suite of online CME and MOC programs—free with membership—designed to help members meet their MOC requirements. Learn more at AAN.com/view/MOC.

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**Live Neurology MOC Prep Course to Take Place at January Breakthroughs in Neurology Conference**

Ericka P. Simpson, MD, will lead a Maintenance of Certification Preparation Course from 8:00 a.m. to 5:00 p.m. on Sunday, January 15, 2017, during the Breakthroughs in Neurology conference. The course will offer 11.25 CME credits.

Register at AAN.com/view/breakthroughs.
Muscle and Neuromuscular Junction Disorders Reviewed in Latest Continuum

Muscle and neuromuscular junction disorders such as inclusion body myositis, myasthenia gravis, and hyperCKemia are reviewed in the latest issue of Continuum: Lifelong Learning in Neurology®. Participants can earn up to 14 hours of AMA PRA Category 1 Credit™ (12 of which apply to MOC Self-Assessment credit).

“Greater understanding of the genetic myopathies has led to changes in diagnostic strategies and is paving the way for potential treatments,” said Hannah R. Briemberg, MD, FRCPC, of the University of British Columbia in Vancouver and guest editor of the issue. “The articles in this issue provide a practical approach to diagnosing and managing both the more common acquired myopathies and myasthenic syndromes as well as the less common, but likely also less recognized, hereditary muscle diseases.”

Articles include:

- The Role of Electrodiagnostic Testing, Imaging, and Muscle Biopsy in the Investigation of Muscle Disease
  Laura K. Rosow, MD, and Anthony A. Amato, MD, FAAN

- Approach to the Patient with HyperCKemia
  Shannon L. Venance, MD, PhD, FRCPC

- Toxic and Endocrine Myopathies
  Hans D. Katzberg, MD, and Charles Kassardjian, MD

- Metabolic Myopathies
  Mark A. Tarnopolsky, MD, PhD

- Autoimmune Myopathies
  Andrew L. Mammen, MD, PhD

- Inclusion Body Myositis
  Steven A. Greenberg, MD

- The Dystrophic and Nondystrophic Myotonias
  Valeria A. Sansone, MD

- Facioscapulohumeral Muscular Dystrophy
  Jeffrey M. Statland, MD, and Rabi Tawil, MD, FAAN

- An Overview of Congenital Myopathies
  Jean K. Mah, MD, MSc, FRCP, and Jeffrey T. Joseph, MD, PhD

- The Limb-Girdle Muscular Dystrophies and the Dystrophinopathies
  Stanley Jones P. Iyadurai, MSc, PhD, and John T. Kissel, MD, FAAN

- Myasthenia Gravis and Lambert-Eaton Myasthenic Syndrome
  Michael W. Nicolle, MD

- Genetic Testing of Presymptomatic Individuals at Risk for Progressive Myopathy
  Zachary Simmons, MD, FAAN

- Registry Participation in Neuromuscular Disease
  Anant M. Shenoy, MD

- Coding in Muscle Disease
  Lyell K. Jones, Jr, MD, FAAN, and John P. Ney, MD, MPH

Continuum® is published six times per year. Subscribe to Continuum by contacting Wolters Kluwer at (800) 361-0633, (301) 223-2300 (international), or LWW.com/continuum. Junior members who are transitioning to Active or Associate memberships can receive a 50-percent discount on the already low member rate for Continuum subscriptions.
More than 700 attendees—a record number—gathered at The Cosmopolitan of Las Vegas the weekend of October 14 through 16 for the Fall Conference, the AAN’s largest regional program. A record 40+ exhibitors were also in attendance. Participants raved, with 92 percent ranking the overall experience as above average to excellent.

The conference’s curriculum, networking opportunities, and exhibits continue to grow, providing a truly unique, year-end destination for acquiring the latest clinical advances in neurology from experts in the field while earning up to 15.75 CME credits. For the first time, the Fall Conference implemented an all-inclusive registration rate that offered attendees access to most of the education programs throughout the three days. Attendees praised the value and convenience of the new registration format, which allowed them to maximize their time and training budgets, eliminating their need to select courses in advance and giving them the freedom and flexibility to move between sessions as they wished.

Other exciting changes included those to the popular Neurology Update and Practice Management programs, which were divided into 12 90-minute sessions that provided additional flexibility for building tailored schedules based on programs of most interest.

Rounding out the conference’s well-received new additions were an Update in Stroke session, which was offered in two 90-minute courses; an AAN Leadership University course covering Challenges of Leadership in Private Practice; and a comprehensive Headache Skills Workshop.

“I feel like a stronger clinician because of the knowledge gained at this conference.”

“Excellent conference—would highly recommend it to all my colleagues!”

“I thought it was a great experience. The presentations were diverse and well-rounded with good speakers. Thanks for a good educational experience. I would do it again.”

“AAN FALL CONFERENCE
Las Vegas, 2016"
AAN Leaders Share Insights at Mexican Academy of Neurology Annual Meeting

Cancun, Mexico, was the setting for the recent 40th Annual Pan American Congress of Neurology hosted by the Mexican Academy of Neurology (MAN), and invited speakers included AAN President Terrence L. Cascino, MD, FAAN; Past President Timothy A. Pedley, MD, FAAN; and Executive Director/CEO Catherine M. Rydell.

“Even though the participation of AAN academics in the reunions of the MAN has been constant during its 40 years of existence, these had been more with an individual, infrequent, and isolated character,” said hosts Minerva López Ruiz, MD, president of MAN, and Ildefonso Rodriguez-Leyva, MD, Scientific Program Coordinator. “It wasn’t until 2013 when this participation became stronger (with over 50 speakers) and a new phase of the relationship started, becoming more institutional rather than that of individual characters. Ever since collaborative agreements have been established, one of the most evident examples of this is the agreement that permitted the translation to Spanish, through the MAN, of more than 13 clinic practice guidelines of the AAN.” (See article on these translations on page 23.)

Cascino spoke to attendees about the AAN’s recent successes, future priorities, international strategy, and relationship with Pan American countries. “Our international strategy is to enhance relationships with international societies. We are working together to discuss common problems and look for solutions. Collaborating with the MAN and the newly formed Pan-American Federation of Neurological Societies is a great example of developing a working relationship with close neighbors.”

The evolution of department chair leadership was the topic of Pedley’s talk. His message was that “Neurology department chairs are critical to the development of strong neurology departments, which includes mutually supportive relationships among the department, medical school, and hospital. Neurology chairs also have an important role to play in promoting the AAN and the importance of active membership for faculty members.”

Rydell highlighted the growth of the Academy. She discussed association leadership and the roles and responsibilities of volunteer leaders and professional staff. “It was a pleasure to attend the recent Mexican Academy of Neurology annual congress to further enhance our relationship with our colleagues to the south,” she said after the event. “Sharing the evolution of the AAN from an administrative and operational perspective was well-received by MAN leadership who are committed to fostering meaningful growth for their organization.”

Said López Ruiz and Rodriguez-Leyva, “As part of the MAN, we are convinced that our mutual relationship of collaborative work and the professional affinity will be of mutual benefit. The MAN aspires to enrich the services that are offered by Mexican neurologists, taking as reference the different processes that have been applied by the most successful neurological society. Furthermore, the AAN provides the MAN with an ‘entrance’ to broadcast and grow these programs that allow an access not only to the neuroscience in Mexico but also in Latin America. In the MAN, we are very grateful for the presence and the support given by the AAN, and reaffirm the commitment to continue working together for our collaborative projects to keep growing and diversifying in the pursuit of our common goals and the strengthening of our institutions.”

Abstracts Sought for 2017 Annual Meeting Emerging Science Program

Work should be of major scientific importance, with key aspects of the research having been conducted after the October 24 deadline, warranting expedited presentation and publication. Case studies are not eligible for submission. The fee for abstract submission is $100 for AAN member first authors and $200 for nonmember first authors. Junior and Student members may submit abstracts at no charge.

For more information, contact science@aan.com or (612) 928-6088.
Reminder: December 10 Application Deadline for 2017 Diversity Leadership Program

The December 10 application deadline is quickly approaching for the prestigious 2017 AAN Diversity Leadership Program. Up to 10 participants will be selected to engage with AAN leadership and staff to develop their own leadership skills. The purpose of the program is to cultivate high-potential members from diverse and underrepresented ethnic backgrounds who will be lifetime, engaged contributors to the Academy.

Space is limited and applications are required. Visit AAN.com/view/DiversityLeadershipProgram for eligibility requirements and to apply before the December 10 deadline.

“If the AAN is going to achieve its mission of promoting highest quality patient-centered neurologic care, it must, as an organization, understand the needs of the patients and communities served by its members.”

—José G. Merino, MD, MPhil, FAAN, chair of the AAN Leadership Development Committee

“I am extremely honored to have been selected to participate in the 2016 Diversity Leadership Program. As a mid-career neurologist specializing in cerebrovascular disease, the impact of this program has superseded my expectation. Through this program, I was made aware of the wonderful mission and vision statements set forth by the Academy leadership. More importantly, these laudable statements were personified when my colleagues and I were able to interact directly with the leadership and experience firsthand all of the words. Additionally, the group and personalized leadership development sessions that took place over the approximate 18-20 weeks helped me to better understand the strengths and weakness of my own leadership style, better equipping me with the tools needed to be more effective at what I do. I would strongly encourage eligible neurologists at all career stages to consider applying for the most meaningful program.”

—Richard T. Benson, MD, PhD, 2016 Diversity Leadership Program participant
Discover the Annual Meeting Everyone’s Talking About!

“I LOVE the new format.”

“There is energy at this meeting I haven’t seen in many years.”

“The one registration fee with freedom to move about was an AMAZING improvement to the meeting.”

“These changes enabled me to tailor my learning and get the most out of the conference to benefit my patients!”

“The clientele are changing and the AAN meeting has changed to meet the demands.”

What will you say?
Register now at AAN.com/view/AM17

Early registration discounts end March 30.
Hotel registration ends March 8.
Susan Schneider Williams’ Neurology Editorial Attracts Extensive Media Coverage

Susan Schneider Williams, the widow of beloved actor Robin Williams, chronicled her husband’s mental and physical struggles during the last few years of his life in an emotional editorial in Neurology® that attracted extensive media coverage. Schneider Williams is committed to educating physicians and caregivers about Lewy body disease and how it slowly and tragically altered every aspect of her husband’s life.

More than 650 articles garnering nearly two billion media impressions were published about the editorial, in major media outlets such as the New York Times, Washington Post, Chicago Tribune, TIME, USA Today, Associated Press, FOX News, ABC News, and the "Today" show. The news also drew attention from Hollywood and celebrity publications that do not normally cover the latest news from the Neurology journal, such as “Entertainment Tonight,” “Hollywood Reporter,” “TMZ,” People, Us Weekly, Vanity Fair, and Rolling Stone.

Schneider Williams also recorded an interview with Ted M. Burns, MD, for the September 27 Neurology podcast, which drew more than 60,000 downloads in four weeks, which is 20,000 more than an average podcast for Neurology.

About a month after the editorial was published, Schneider Williams was a special guest at a fundraising event in Minneapolis, MN, for the American Brain Foundation, which garnered additional local media coverage and, including an anonymous matching grant, raised nearly $80,000 for brain research. Schneider Williams has joined the American Brain Foundation Board of Directors.

“My goal is to turn Robin’s suffering into something meaningful,” she said. “Hopefully, from sharing his experience, our experience, I can help raise awareness and increase funding for brain disease research.” She added, “Working with the American Brain Foundation and their incredible community of medical professionals has given me hope that with more research, a cure is possible.”

Ben Utecht—Super Bowl champion, concussion sufferer, advocate, author, and singer—gave a moving performance at the event, which was held at the new U.S. Bank stadium, home of the Minnesota Vikings.

Susan Schneider Williams inspired the crowd of nearly 300 people at the American Brain Foundation Standing Strong event to support research into brain disease.
Your donations help us fund the best and the brightest scientific minds in the crucial research to cure brain disease. Join us today and make your gift when you renew your 2017 AAN membership dues.

Want to learn more? Visit AmericanBrainFoundation.org/Cure to learn about the researchers pictured above.
Neurology Position with Central Maine Medical Center - Maine: Central Maine Medical Group is seeking a BE/BC neurologist to join an established adult neurology practice primarily associated with Central Maine Medical Center. A focused interest in stroke, muscle disease, headache/migraine, epilepsy, or movement disorder would be a welcome addition, but is not required. Our diagnostic capabilities include: 1.5 T MRI, CT angiography, EMG, Evoked Potentials, EEG, and 24-72 Hour Ambulatory EEG. We also have an active Teleurology service that is affiliated with Massachusetts General Hospital, Central Maine Medical Center is the flagship hospital of Central Maine Healthcare. The medical center has 260 inpatient beds and offers a broad range of services that include, among many, neurosurgery, a Level II trauma center, cardiovascular medicine, vascular and cardiac surgery, and medical and radiation oncology. The Central Maine Medical Group comprises of approximately 350 providers, approximately half of which are in primary care. The group delivers care across almost 2500 square miles at numerous outpatient sites and four hospitals. A competitive salary and attractive benefits package are enhanced by the scenic beauty and abundant outdoor adventure found in Maine. Interested candidates, please send CV to Gina Mallozzi, Central Maine Medical Center, 300 Main Street, Lewiston, ME 04240. Fax: (207) 796-5696, email: MallozziGi@cmhc.org, or call: (800) 445-7431. Not a J1 Opportunity.

Neurology-Physician Scientist for Section Chief with Carilion Clinic and Virginia Tech - Carilion Clinic, along with the Virginia Tech Carilion Research Institute (VTCRI), seeks a highly regarded physician-scientist to lead the Section of Neurology into the next phase of academic and clinical development. Carilion Clinic headquartered in Roanoke, Virginia is the largest not-for-profit integrated health system in western Virginia serving one million people with 7 hospitals and 680+ physicians in over 70+ specialties. Practice and Research highlights include: oversee the continued maturation of the Neurology program through faculty development and recruitment, improve access, and extend the scope of services; lead a team of eight Neurologists while collaborating with nine Neurosurgeons; ACGME Neurology Residency in its second year; develop research programs with VTCSOM and VTCRI, with a cadre of NIH funded scientists; VTCRI has state-of-the-art facilities in functional brain imaging multiple research dedicated MIRs, molecular biology cores, high field cryo-electron microscopy, electrophysiology, computational and high capacity data analysis/storage, human cognitive/behavioral assessment facilities, and a vivarium; start-up packages, laboratory facilities and support are highly competitive. Roanoke is one of the best kept secrets. Quality of life in the Blue Ridge Mountains is high and the cost of living is low. The area offers a four season playground for mountain and lake recreation, as well as a rich array of arts, humanities, and cultural experiences. Preferred candidates will be MD/PhD with BC in Neurology by the American Board of Psychiatry and Neurology and have a track record of high impact research productivity and ongoing NIH research grant funding. Please forward curriculum vitae with cover letter to Thomas M. Kerkering, MD, Carilion Clinic tmkerkering@carilionclinic.org

Fellowship in Neuroimaging: Winchester Neurological Consultants, Inc., in conjunction with Virginia Commonwealth University and Winchester Medical Center, is offering a clinical Neuroimaging Fellowship for SC/BE neurology graduates that can be completed in one or two years. Located approximately an hour from Washington, DC, our United Council of Neurologic Subspecialties fully accredited fellowship offers extensive training in the performance and interpretation of diagnostic inpatient and outpatient MRI, CT, Doppler, TCD, and myelography--utilizing four state of the art MRI scanners and four multi-slice CT units. Responsibilities include supervision and interpretation of imaging, assisting with acute stroke protocols, and direct patient care. Availability: immediate. Research interests are encouraged. Salary is $60,000.00 per year plus benefits. CV’s should be emailed to gstele@winchesterneurolological.com

Interventional Neurologist: Must have research experience in the contribution of vascular, hormonal, and oxidative stress factors to sub-clinical and clinical outcomes of common diseases of old age, such as vascular brain disease. Focus on data analysis, study design and neuroepidemiology, utilize and work with large epidemiologic studies. Engage in clinical research in the field of interventional neuroradiology and endovascular neurosurgery. Take part in a large randomized multi-center clinical trial in acute stroke. Must have experience performing acute and elective interventional procedures for treatment of vascular disorders of the brain and spinal cord, specifically strokes, cerebral aneurysms, arteriovenous malformations, arteriovenous fistulas, tumors, and carotid artery disease. Be able to provide full weekend and weekend coverage for all acute neuro-interventional emergencies and be responsible for the adequate management of all tertiary stroke referrals to hospitals. Have extensive prior experience in the field of interventional neuroradiology, endovascular neurosurgery, stroke, and critical care neurology. Email dlightsch@neurosurgerynj.com

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NOW APPROVED AND AVAILABLE FOR RELAPSING FORMS OF MS

Zinbryta™
(daclizumab)
150 mg Subcutaneous Injection

ZINBRYTA is a once-monthly, self-administered subcutaneous injection indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (MS).¹

In all controlled and uncontrolled trials performed in patients with relapsing MS, 2,236 patients received ZINBRYTA for a total of 5,214 person-years.¹

Indication
ZINBRYTA is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of ZINBRYTA should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

Important Safety Information
WARNING: HEPATIC INJURY INCLUDING AUTOIMMUNE HEPATITIS and OTHER IMMUNE-MEDIATED DISORDERS

Hepatic Injury Including Autoimmune Hepatitis
- ZINBRYTA can cause severe liver injury including life-threatening events, liver failure, and autoimmune hepatitis. Obtain transaminase and bilirubin levels before initiation of ZINBRYTA. Monitor and evaluate transaminase and bilirubin levels monthly and for 6 months after the last dose
- ZINBRYTA is contraindicated in patients with pre-existing hepatic disease or hepatic impairment

Other Immune-Mediated Disorders
- Immune-mediated disorders including skin reactions, lymphadenopathy, non-infectious colitis, and other immune-mediated disorders can occur with ZINBRYTA

These conditions may require treatment with systemic corticosteroids or immunosuppressive medication.

ZINBRYTA is available only through a restricted distribution program called the ZINBRYTA REMS Program.

Contraindications
ZINBRYTA is contraindicated in patients with pre-existing hepatic disease or hepatic impairment, including alanine aminotransferase (ALT) or aspartate aminotransferase (AST) at least 2 times the upper limit of normal (ULN); a history of autoimmune hepatitis or other autoimmune condition involving the liver; or a history of hypersensitivity to daclizumab or any other components of the formulation.

Please see the following pages for additional Important Safety Information and Brief Summary of Full Prescribing Information, including BOXED WARNING.
In clinical studies, ZINBRYTA (daclizumab) significantly reduced the annualized relapse rate compared with AVONEX (interferon beta-1a) and placebo.

**DECIDE pivotal clinical trial: outcome up to 144 weeks**

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>ZINBRYTA (n=919)</th>
<th>AVONEX (n=922)</th>
<th>P-value</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized relapse rate</td>
<td>0.216</td>
<td>0.393</td>
<td>&lt;0.0001</td>
<td>45% relative reduction</td>
</tr>
</tbody>
</table>

DECIDE was a randomized, double-blind, active control study that compared ZINBRYTA 150 mg subcutaneous (n=919) every 4 weeks to AVONEX 30 mcg intramuscular (n=922) weekly. Treatment continued for 96 to 144 weeks. The primary outcome measure was the annualized relapse rate (ARR). Additional outcome measures included the proportion of patients relapsed, the proportion of patients who experienced confirmed disability progression (CDP), and the number of new or newly enlarging T2 hyperintense lesions. The study included RMS patients with an Expanded Disability Status Scale (EDSS) score of 0.0-5.0 who had either: 1) ≥2 relapses during the prior 3 years and ≥1 relapse in the year prior to randomization; or 2) ≥1 clinical relapses and ≥1 new T1 gadolinium (Gd)-enhancing or T2 hyperintense MRI lesions within the prior 2 years with at least one of these events in the prior 12 months. Patients with progressive forms of MS were excluded.

**SELECT pivotal clinical trial: outcome at 52 weeks**

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>ZINBRYTA (n=208)</th>
<th>Placebo (n=204)</th>
<th>P-value</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized relapse rate</td>
<td>0.211</td>
<td>0.458</td>
<td>&lt;0.0001</td>
<td>54% relative reduction</td>
</tr>
</tbody>
</table>

SELECT was a randomized, double-blind, placebo-controlled study that compared ZINBRYTA 150 mg subcutaneous (n=208) every 4 weeks to placebo (n=204). Treatment duration was 52 weeks. The primary outcome measure was ARR at Week 52. Additional outcome measures included new T1 Gd-enhancing lesions between Weeks 8 to 24, the proportion of patients relapsed, the proportion of patients who experienced confirmed disability progression (CDP), and the number of new or newly enlarging T2 hyperintense lesions. The study included RMS patients with an EDSS score of 0.0-5.0 who had experienced ≥1 relapse in the year prior to randomization or who had ≥1 T1 Gd-enhancing MRI lesions within 6 weeks of randomization. Patients with progressive forms of MS were excluded.

**Important Safety Information (Continued)**

**Hepatic Injury**

ZINBRYTA can cause life-threatening severe liver injury, including liver failure and autoimmune hepatitis. In controlled studies, serious drug-related hepatic injury occurred in 0.7% of ZINBRYTA-treated patients compared with 0.4% of AVONEX-treated patients (Study 1) and in 1.0% of ZINBRYTA-treated patients compared with no injury in placebo patients (Study 2). A fatal case of autoimmune hepatitis occurred in a patient re-initiating ZINBRYTA after a planned 6 month treatment interruption period. The incidence of increases in hepatic transaminases was greater in patients taking ZINBRYTA than in those taking AVONEX or placebo. Prior to starting treatment with ZINBRYTA, obtain serum transaminases (ALT and AST) and total bilirubin levels. Test transaminase levels and total bilirubin monthly and assess before the next dose of ZINBRYTA. Follow transaminase levels and total bilirubin monthly for 6 months after the last dose of ZINBRYTA. If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with ZINBRYTA, as appropriate. Discontinue ZINBRYTA if autoimmune hepatitis is suspected. Caution should be used when using hepatotoxic drugs, including non-prescription drugs, herbal products, and dietary supplements, concomitantly with ZINBRYTA.

**Immune-Mediated Disorders**

Treatment with ZINBRYTA increases the risk of immune-mediated disorders, including autoimmune disorders such as autoimmune hepatitis. Across all clinical studies (controlled and open-label), immune-mediated disorders occurred in 28% of patients on ZINBRYTA, the most common of which were skin reactions and lymphadenopathy. In the active-control study (Study 1), immune-mediated disorders were observed in 32% of ZINBRYTA-treated patients compared with 12% for AVONEX-treated patients. Some patients required invasive procedures for diagnosis (e.g., colonoscopy, liver biopsy, kidney biopsy, lung biopsy), hospitalization for fluid replacement or blood transfusion, or prolonged treatment with systemic corticosteroids or immunosuppressant drugs. Some of these events did not resolve after stopping ZINBRYTA during study follow-up. Prescribers should be vigilant regarding emergent immune-mediated disorders. For suspected immune-mediated disorders, ensure adequate evaluation to confirm etiology or to exclude other causes.

(Continued on next page)
Important Safety Information (Continued)

Immune-Mediated Disorders (Continued)

If a patient develops a serious immune disorder, consider stopping ZINBRYTA and refer the patient to an appropriate specialist for further evaluation and treatment.

- ZINBRYTA causes skin reactions. In clinical trials, skin reactions occurred in 37% of ZINBRYTA-treated patients compared with 19% of AVONEX-treated patients (Study 1) and in 18% of ZINBRYTA-treated patients compared with 13% of patients on placebo (Study 2). Skin reactions occurred at any time during treatment with ZINBRYTA. If a patient develops a serious diffuse or inflammatory rash, it is recommended that a dermatologist evaluate the patient before the next dose of ZINBRYTA. Discontinuation of ZINBRYTA may be appropriate.

- ZINBRYTA increases the incidence of lymphadenopathy. In controlled studies, lymphadenopathy or lymphadenitis occurred in 6% of ZINBRYTA-treated patients compared with 1% of AVONEX-treated patients (Study 1) and in 2% of ZINBRYTA-treated patients compared with 1% of placebo-treated patients (Study 2).

- An increased incidence of serious colitis (less than 1%) was reported in patients treated with ZINBRYTA compared with none for patients treated with AVONEX or placebo in clinical trials.

- A wide variety of other immune-mediated disorders, some serious, have occurred infrequently with the use of ZINBRYTA. If a patient develops a serious immune disorder, consider stopping ZINBRYTA.

ZINBRYTA REMS Program

ZINBRYTA is available only through a restricted program called the ZINBRYTA REMS Program, because of the risks of hepatic injury including autoimmune hepatitis, and other immune-mediated disorders. Only certified prescribers and pharmacies and patients enrolled in the REMS program can prescribe, dispense or receive ZINBRYTA.

Acute Hypersensitivity

ZINBRYTA can cause anaphylaxis, angioedema, and urticaria after the first dose or at any time during treatment. Discontinue and do not re-start ZINBRYTA if anaphylaxis or other allergic reactions occur.

Infections

ZINBRYTA increases the risk for infections. The most common types of infections observed were upper respiratory tract infections, urinary tract infections and viral infections. Avoid initiating ZINBRYTA in patients with severe active infection until the infection is fully controlled. If serious infection develops, consider withholding treatment with ZINBRYTA until the infection resolves.

- Vaccination with live vaccines is not recommended during treatment and up to 4 months after discontinuation of ZINBRYTA.

Depression and Suicide

In controlled trials, depression-related events occurred in 10% of ZINBRYTA-treated patients compared with 8% of AVONEX-treated patients (Study 1) and in 7% of ZINBRYTA-treated patients compared with 2% of patients taking placebo (Study 2). Avoid initiating ZINBRYTA in patients with severe active infection until the infection is fully controlled. If serious infection develops, consider withholding treatment with ZINBRYTA until the infection resolves.

- Advise patients and/or caregivers to immediately report any symptoms of new or worsening depression and/or suicidal ideation. If a patient develops severe depression and/or suicidal ideation, consider discontinuation of ZINBRYTA.

Adverse Reactions

The most common adverse reactions (incidence at least 5% and at least 2% higher incidence than comparator) that occurred in ZINBRYTA-treated patients were nasopharyngitis, upper respiratory tract infection, rash, influenza, dermatitis, oropharyngeal pain, bronchitis, eczema, and lymphadenopathy compared with AVONEX; and upper respiratory tract infection, depression, rash, pharyngitis, and increased ALT compared with placebo.

Please see Brief Summary of Full Prescribing Information including BOXED WARNING on following pages.

WARNINGS: HEPATIC INJURY INCLUDING AUTOIMMUNE HEPATITIS and OTHER IMMUNE-MEDIATED DISORDERS

• Hepatic Injury Including Autoimmune Hepatitis

ZINBRYTA can cause severe liver injury including life-threatening events, liver failure, and autoimmune hepatitis. In clinical trials, 1 patient died due to autoimmune hepatitis. Liver injury, including autoimmune hepatitis, can occur at any time during treatment with ZINBRYTA, with cases reported up to 4 months after the last dose of ZINBRYTA.

ZINBRYTA is contraindicated in patients with pre-existing hepatic disease or hepatic impairment [see Contraindications (4) and Warnings and Precautions (5.1)].

Prior to starting ZINBRYTA, obtain serum transaminases (ALT and AST) and bilirubin levels [see Dosage and Administration (2.3)].

Test transaminase levels and total bilirubin monthly and assess before the next dose of ZINBRYTA. Follow transaminase levels and total bilirubin monthly for 6 months after the last dose of ZINBRYTA. In cases of elevation in transaminases or total bilirubin, treatment interruption or discontinuation may be required [see Dosage and Administration (2.4) and Warnings and Precautions (5.1)].

• Other Immune-Mediated Disorders

In addition to autoimmune hepatitis, immune-mediated disorders such as skin reactions, lymphadenopathy, and non-infectious colitis can occur in patients treated with ZINBRYTA. Overall, serious immune-mediated conditions were observed in 5% of patients treated with ZINBRYTA [see Warnings and Precautions (5.2)].

If a patient develops a serious immune-mediated disorder, consider stopping ZINBRYTA and refer the patient to a specialist to ensure comprehensive diagnostic evaluation and appropriate treatment.

Some patients required systemic corticosteroids or other immunosuppressant treatment for autoimmune hepatitis or other immune-mediated disorders and continued this treatment after the last dose of ZINBRYTA [see Warnings and Precautions (5.1, 5.2)].

Because of the risks of hepatic injury, including autoimmune hepatitis, and other immune-mediated disorders, ZINBRYTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZINBRYTA REMS Program [see Warnings and Precautions (5.3)].

1 INDICATIONS AND USAGE

ZINBRYTA is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of ZINBRYTA should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dosage of ZINBRYTA is 150 milligrams injected subcutaneously once monthly [see Dosage and Administration (2.3, 2.4)].

Instruct patients to inject a missed dose as soon as possible but no more than two weeks late. After two weeks, skip the missed dose and take the next dose on schedule. Administer only one dose at a time.

2.2 Important Administration Instructions

ZINBRYTA is for subcutaneous use only. Train patients in the proper technique for self-administering subcutaneous injections using the prefilled syringe. Thirty minutes prior to injection, remove ZINBRYTA from the refrigerator to allow the drug to warm to room temperature. Do not use external heat sources such as hot water to warm ZINBRYTA. Do not place ZINBRYTA back into the refrigerator after allowing it to warm to room temperature [see How Supplied/Storage and Handling (16.2)].

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. ZINBRYTA is a colorless to slightly yellow, clear to slightly opalescent solution. Do not use ZINBRYTA if it is cloudy or there are visible particles.

Sites for injection include the thigh, abdomen, and back of the upper arm. Use each prefilled syringe one time and then place in a sharps disposal container for disposal according to community guidelines [see How Supplied/Storage and Handling (16.3)].

2.3 Assessment Prior to Initiating ZINBRYTA

Hepatic Assessment: Prior to initiating ZINBRYTA, obtain and evaluate the following: Serum transaminases (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) and total bilirubin levels. Initiation of ZINBRYTA is contraindicated in patients with pre-existing hepatic disease or hepatic impairment including ALT or AST at least 2 times the ULN [see Contraindications (4) and Warnings and Precautions (5.1)].

Assessment for Tuberculosis and Other Infections: Evaluate patients at high risk for tuberculosis infection prior to initiating treatment with ZINBRYTA [see Warnings and Precautions (5.5)]. For patients testing positive for tuberculosis, treat tuberculosis by standard medical practice prior to therapy with ZINBRYTA. Avoid initiating ZINBRYTA in patients with tuberculosis or other severe active infection [see Warnings and Precautions (5.5)].

Prior to initiation of ZINBRYTA, screen patients for Hepatitis B and C. ZINBRYTA is contraindicated in patients with pre-existing hepatic disease [see Contraindications (4)].

Vaccinations: Because vaccination with live vaccines is not recommended during treatment and up to 4 months after discontinuation of treatment, consider any necessary immunization with live vaccines prior to treatment with ZINBRYTA [see Warnings and Precautions (5.5)].

2.4 Laboratory Testing and Monitoring to Assess Safety After Initiating ZINBRYTA

Conduct the following laboratory tests at periodic intervals to monitor for early signs of potentially serious adverse effects:

Liver Tests: Test transaminase levels and total bilirubin monthly and assess before the next dose of ZINBRYTA. Follow transaminase levels and total bilirubin monthly for 6 months after the last dose of ZINBRYTA. As shown in Table 1, interruption or discontinuation of ZINBRYTA therapy is recommended for management of certain liver test abnormalities [see Warnings and Precautions (5.1)].

Table 1: ZINBRYTA Treatment Modification for Liver Test Abnormalities

<table>
<thead>
<tr>
<th>Lab Value(s)</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT or AST greater than 5 times ULN OR total bilirubin greater than 2 times ULN</td>
<td>Interrupt ZINBRYTA therapy and investigate for other etiologies of abnormal lab value(s).</td>
</tr>
<tr>
<td>ALT or AST greater than or equal to 3 but less than 5 times ULN and total bilirubin greater than 1.5 but less than 2 times ULN</td>
<td>If no other etiologies are identified, then consider continuing ZINBRYTA.</td>
</tr>
<tr>
<td>ALT or AST greater than or equal to 3 but less than 5 times ULN and total bilirubin less than 1.5</td>
<td>If other etiologies are identified, re-assess the overall risk-benefit profile of ZINBRYTA in the patient and consider whether to resume ZINBRYTA when both ALT or AST are less than 2 times ULN and total bilirubin is less than or equal to ULN.</td>
</tr>
</tbody>
</table>

In clinical trials, permanent discontinuation of therapy was required if the patient had liver test abnormalities resulting in suspension of study treatment for at least 8 consecutive weeks.

ULN = upper limit of normal

3 DOSAGE FORMS AND STRENGTHS

Injection: 150 mg/mL solution in a single-dose prefilled syringe. ZINBRYTA is a sterile, preservative-free, colorless to slightly yellow, clear to slightly opalescent solution.

4 CONTRAINdications

ZINBRYTA is contraindicated in patients with:

• Pre-existing hepatic disease or hepatic impairment, including ALT or AST at least 2 times the ULN, because ZINBRYTA could exacerbate existing liver dysfunction [see Dosage and Administration (2.3) and Warnings and Precautions (5.1)].

• A history of autoimmune hepatitis or other autoimmune condition involving the liver [see Warnings and Precautions (5.1)].

• A history of hypersensitivity to daclizumab or any other components of the formulation. Use in such patients may result in anaphylaxis or life-threatening multi-organ hypersensitivity [see Warnings and Precautions (5.4)].
5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Injury

ZINBRYTA can cause life-threatening severe liver injury, including liver failure and autoimmune hepatitis. In controlled studies, serious drug-related hepatic injury occurred in 0.7% of ZINBRYTA-treated patients compared with 0.4% of AVONEX-treated patients (Study 1) and 1.0% of ZINBRYTA-treated patients compared with no injury in placebo patients (Study 2). Across all clinical studies (controlled and open-label), serious drug-related hepatic injury occurred in 1% of ZINBRYTA-treated patients, with monthly monitoring of transaminases and total bilirubin. The incidence of discontinuation due to drug-related hepatic injury was 5% in ZINBRYTA-treated patients and 4% in AVONEX-treated patients.

Autoimmune Hepatitis: Across all clinical studies (controlled and open-label), 0.3% of ZINBRYTA-treated patients developed autoimmune hepatitis.

One fatal case of autoimmune hepatitis occurred in a patient re-initiating ZINBRYTA after a planned 6-month treatment interruption period. This patient subsequently received two doses of ZINBRYTA in the presence of persisting alanine aminotransferase levels (ALT) more than 5 times the upper limit of normal (ULN).

Transaminase and Total Bilirubin Elevations: The incidence of increases in hepatic transaminases was greater in patients taking ZINBRYTA than in those taking AVONEX or placebo. The incidence of ALT or AST elevations above 5 times the ULN was 6% in ZINBRYTA-treated patients compared with 3% in AVONEX-treated patients (Study 1) and 4% in ZINBRYTA-treated patients compared with 1% in patients on placebo (Study 2). Less than 1% of ZINBRYTA-treated patients had ALT or AST greater than 20 times the ULN. Elevations of hepatic transaminases of at least 3 times the ULN combined with elevated bilirubin at least 2 times the ULN and alkaline phosphatase less than 2 times the ULN occurred in 0.7% of ZINBRYTA-treated patients compared with 0.1% of AVONEX-treated patients. In clinical trials, serum transaminase elevations occurred during treatment and up to 4 months after the last dose of ZINBRYTA.

Monitoring: Prior to starting treatment with ZINBRYTA, obtain serum transaminase (ALT and AST) and total bilirubin levels [see Contraindications (4)].

Test transaminase levels and total bilirubin monthly and assess before the next dose of ZINBRYTA. Follow transaminase levels and total bilirubin monthly for 6 months after the last dose of ZINBRYTA. Treatment modifications are recommended based on serum transaminase and total bilirubin values [see Dosage and Administration (2.4)].

If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with ZINBRYTA, as appropriate. Patients with prolonged elevations of serum transaminases should be evaluated for other possible causes, such as infection, and a specialist should evaluate the patient [see Table 1]. Discontinue ZINBRYTA if autoimmune hepatitis is suspected. Treatment of autoimmune hepatitis with systemic corticosteroids and other immunosuppressive drugs may be required. Some patients may require long-term immunosuppressive therapy.

Risk of Hepatic Injury with Concomitant Use of Other Hepatotoxic Drugs: Caution should be used when using hepatotoxic drugs, including non-prescription products, concomitantly with ZINBRYTA. Also, carefully consider the need for the use of herbal products or dietary supplements that can cause hepatotoxicity [see Drug Interactions (7.1)].

5.2 Immune-Mediated Disorders

Treatment with ZINBRYTA increases the risk of immune-mediated disorders, including autoimmune disorders such as autoimmune hepatitis. Across all clinical studies (controlled and open-label), immune-mediated disorders occurred in 28% of patients on ZINBRYTA, the most common of which were skin reactions and lymphadenopathy. In the active-control study (Study 1), immune-mediated disorders were observed in 32% of ZINBRYTA-treated patients compared with 12% for AVONEX-treated patients. In Study 1, serious immune-mediated disorders were observed in 4% of patients treated with ZINBRYTA compared with less than 1% for AVONEX-treated patients. In the placebo-controlled study (Study 2), immune-mediated disorders were observed in 13% of ZINBRYTA-treated patients compared with 7% of placebo-treated patients. In Study 2, serious immune-mediated disorders were observed in 0.5% of ZINBRYTA-treated patients and in 0.5% of placebo-treated patients. In some cases, patients had concurrent or sequential occurring disorders while taking ZINBRYTA.

Some patients required invasive procedures for diagnosis (e.g., colonoscopy, liver biopsy, kidney biopsy, lung biopsy), hospitalization for fluid replacement or blood transfusion, or prolonged treatment with systemic corticosteroids or immunosuppressant drugs. Some of these events did not resolve after stopping ZINBRYTA during study follow-up.

Prescribers should be vigilant regarding emergent immune-mediated disorders. For suspected immune-mediated disorders, ensure adequate evaluation to confirm etiology or to exclude other causes. If a patient develops a serious immune-mediated disorder, consider stopping ZINBRYTA and refer the patient to an appropriate specialist for further evaluation and treatment.

Skin Reactions: ZINBRYTA causes skin reactions. In clinical trials, skin reactions occurred in 37% of ZINBRYTA-treated patients compared with 19% of AVONEX-treated patients (Study 1) and in 18% of ZINBRYTA-treated patients compared with 13% of patients on placebo (Study 2). Skin reactions occurred at any time during study treatment with ZINBRYTA. Rashes occurred in 11% of ZINBRYTA-treated patients compared to 4% of AVONEX-treated patients, and in 7% of ZINBRYTA-treated patients compared to 3% of patients on placebo. Dermatitis occurred more frequently in ZINBRYTA-treated patients compared to AVONEX-treated patients or to patients on placebo, and eczema was observed more frequently in ZINBRYTA-treated patients compared to AVONEX-treated patients [see Adverse Reactions (6.1)]. Psoriatic conditions occurred in 2% of ZINBRYTA-treated patients compared with 0.3% of AVONEX-treated patients.

Serious skin reactions occurred in 2% of patients treated with ZINBRYTA compared with 0.1% of patients on AVONEX (Study 1) and in 1% of patients treated with ZINBRYTA compared with none treated with placebo (Study 2). Serious skin reactions resulted from infectious complications following a serious cutaneous reaction. In patients with a history of skin conditions, including eczema or psoriasis, use of ZINBRYTA may exacerbate those conditions.

Treatment of skin reactions included treatment with topical or systemic steroids or immunosuppressant drugs, including tacrolimus. In clinical trials, discontinuation because of skin reactions was 4% in ZINBRYTA-treated patients. Rashes took a mean of 3 months to resolve; some were unresolved at the time of the last evaluation. If a patient develops a serious diffuse or inflammatory rash, it is recommended that a dermatologist evaluate the patient before the next dose of ZINBRYTA. Discontinuation of ZINBRYTA may be appropriate.

Lymphadenopathy: ZINBRYTA increases the incidence of lymphadenopathy. In controlled studies, lymphadenopathy or lymphadenitis occurred in 6% of ZINBRYTA-treated patients compared with 1% of AVONEX-treated patients (Study 1) and in 2% of ZINBRYTA-treated patients compared with 1% of placebo-treated patients (Study 2). Onset of lymphadenopathy or lymphadenitis occurred throughout the treatment period. Serious events related to lymphadenopathy or lymphadenitis included infections, benign salivary neoplasms, skin reactions, thrombocytopenia, and intestinal lung changes [see Warnings and Precautions (5.3)]. The majority of cases resolved with or without continued treatment with ZINBRYTA and took a mean of 3 months to resolve. Lymphadenopathy resulted in discontinuation in 0.6% of ZINBRYTA-treated patients.

Some patients with lymphadenopathy underwent diagnostic biopsy. In the event that lymph node biopsy is considered, full diagnostic evaluation should be conducted by a specialist.

Non-Infectious Colitis: An increased incidence of serious colitis (less than 1%) was reported in patients treated with ZINBRYTA compared with none for patients treated with AVONEX or placebo in clinical trials. Consider referring patients who develop symptoms of colitis (e.g., abdominal pain, fever, prolonged diarrhea) to a specialist.

Other Immune-Mediated Disorders: A wide variety of other immune-mediated disorders were observed, including multi-organ, systemic, and autoimmune hepatitis. These include single organ or systemic multi-organ inflammatory reactions. Many events occurred in only one patient, and the relationship to ZINBRYTA is unknown [see Adverse Reactions (6.1)]. Some required treatment with systemic corticosteroids. Some required several months for resolution after the last dose of ZINBRYTA.

For suspected immune-mediated disorders, ensure adequate evaluation to confirm etiology or to exclude other causes. If a patient develops a serious immune-mediated disorder, consider stopping ZINBRYTA and refer the patient to an appropriate specialist for further evaluation and treatment.

5.3 ZINBRYTA REMS Program

ZINBRYTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZINBRYTA REMS Program, because of the risks of hepatic injury including autoimmune hepatitis, and other immune-mediated disorders [see Warnings and Precautions (5.1, 5.2)].

Notable requirements of the ZINBRYTA REMS Program include the following:

• Prescribers must be certified with the program by enrolling and completing training.
• Patients must enroll in the program and comply with ongoing monitoring requirements [see Warnings and Precautions (5.1, 5.2)].
• Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive ZINBRYTA.

Further information, including a list of qualified pharmacies/distributors, is available at 1-800-456-2255.

5.4 Acute Hypersensitivity

ZINBRYTA can cause anaphylaxis, angioedema, and urticaria after the first dose or at any time during treatment. Discontinue and do not restart ZINBRYTA if anaphylaxis or other allergic reactions occur [see Contraindications (4)].
5.5 Infections

ZINBRYTA increases the risk for infections. In controlled trials, infections occurred in 69% of ZINBRYTA-treated patients compared with 57% of AVONEX-treated patients (Study 1), and in 50% of ZINBRYTA-treated patients compared with 44% of patients taking placebo (Study 2). Serious infections occurred in 4% of ZINBRYTA-treated patients compared with 2% of AVONEX-treated patients (Study 1) and in 3% of ZINBRYTA-treated compared with none on placebo (Study 2).

The most common types of infections observed were upper respiratory tract infections, urinary tract infections and viral infections. In clinical trials, cases of tuberculosis occurred in countries where tuberculosis is endemic. Evaluate high-risk patients for tuberculosis infection prior to initiating treatment with ZINBRYTA. For patients testing positive for tuberculosis, treat by standard medical practice prior to therapy with ZINBRYTA [see Dosage and Administration (2.3)].

Avoid initiating ZINBRYTA in patients with severe active infection until the infection is fully controlled. If serious infection develops, consider withholding treatment with ZINBRYTA until the infection resolves.

Vaccination: The safety of immunization with live viral vaccines during treatment with ZINBRYTA has not been studied. Vaccination with live vaccines is not recommended during treatment and up to 4 months after discontinuation of ZINBRYTA [see Dosage and Administration (2.3)].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of ZINBRYTA cannot be directly compared with rates in clinical trials of other drugs and may not reflect the rates observed in practice.

In all controlled and uncontrolled trials performed in patients with relapsing multiple sclerosis, 2236 patients received ZINBRYTA for a total of 5214 person-years. Of these patients, 1576 received ZINBRYTA for at least 1 year, 1259 for at least 2 years, and 888 for at least 3 years. In the controlled studies, approximately 67% were female, 92% were Caucasian, and the mean age was 36 years at study entry.

In the active-controlled study (Study 1), 919 patients received ZINBRYTA (150 mg SQ, every 4 weeks) and 922 patients received AVONEX (interferon beta-1a 30 mcg IM, weekly) for a minimum of 2 years and up to 3 years, with 1952 person-years of exposure to ZINBRYTA; the median length of treatment was approximately 27 months. The adverse reactions from Study 1 are presented in Table 2.

In the placebo-controlled study (Study 2), 417 patients received ZINBRYTA with 423 person-years of exposure, of which 208 received 150 mg, and 204 received placebo every 4 weeks for up to 1 year; the median length of treatment was approximately 11 months. The adverse reactions from Study 2 are presented in Table 3.

The most common adverse reactions (incidence at least 5% and at least 2% higher incidence than comparator) that occurred in ZINBRYTA-treated patients were nasopharyngitis, upper respiratory tract infection, rash, influenza, dermatitis, ophthalmalgia, pain, bronchitis, eczema, and lymphadenopathy compared with AVONEX; and upper respiratory tract infection, depression, rash, pharyngitis, and increased alanine aminotransferase (ALT) compared with placebo.

The most common adverse reactions leading to discontinuation in up to 5% of patients treated with ZINBRYTA were hepatic events including elevations of serum transaminases and cutaneous events.

Patients were excluded from the clinical studies for abnormal laboratory values including hemoglobin, complete blood count with differential, serum transaminases, or serum creatinine. Patients were excluded if they had a history of seizure disorder or of having a seizure within 6 months of beginning the study, or suicidal ideation or severe depression within 3 months of beginning the study. During Study 1, concomitant use of ZINBRYTA with the hepatotoxic drugs valproic acid, carbamazepine, lamotrigine, phenytoin, isoniazid, and propylthiouracil was not permitted except in patients already receiving the drugs at the time of study entry.

In clinical studies, serum chemistry was evaluated at baseline and monthly.

Table 2: Adverse Reactions in Adults with RMS with an Incidence at Least 2% More for ZINBRYTA 150 mg SQ Every 4 Weeks than AVONEX 30 mcg IM Once Weekly (Study 1)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZINBRYTA 150 mg SQ Every 4 Weeks N = 919 %</th>
<th>AVONEX 30 mcg IM Once Weekly N = 922 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Rash</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Influenza</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Eczema</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Acne</td>
<td>3</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Table 3: Adverse Reactions in Adults with RMS with an Incidence at Least 2% More for ZINBRYTA 150 mg SQ Every 4 Weeks than Placebo (Study 2)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZINBRYTA 150 mg SQ Every 4 Weeks N = 208 %</th>
<th>Placebo N = 204 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Depression</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Increased AST</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>3</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

1 includes upper respiratory tract infection and viral upper respiratory tract infection
2 includes erythematous rash, exfoliative rash, macular rash, maculopapular rash, papular rash, pruritic rash, rash, and vesicular rash
3 includes allergic dermatitis, atopic dermatitis, bullous dermatitis, dermatitis, exfoliative dermatitis, and seborrheic dermatitis
4 includes dyshidrotic eczema, eczema, and nummular eczema

Other clinically relevant adverse reactions observed at <2% difference included abnormal liver function tests, increased lymphocytes count, diarrhea, dry skin, erythema, folliculitis, increased hepatic enzyme, laryngitis, lymphadenitis, pneumonia, pruritus, psoriasis, respiratory tract infection, skin exfoliation, toxic skin eruption, and viral infection.
8.6 Hepatic Impairment
Clinical trials did not include patients with ALT or AST more than two times the ULN. Patients with signs and symptoms of hepatic impairment may be at increased risk for hepatotoxicity from ZINBRYTA [see Dosage and Administration (2.3, 2.4), Contraindications (4), and Warnings and Precautions (5.1, 5.2)].

17 PATIENT COUNSELING INFORMATION
Advising the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Hepatic Injury: Inform the patient of the risk of severe hepatic injury associated with ZINBRYTA. Advise patients of the symptoms of hepatic dysfunction, and instruct patients to report such symptoms to their healthcare provider immediately [see Warnings and Precautions (5.1, 5.2)].

Discuss with the patient the importance of measuring hepatic laboratory values and having them evaluated by the healthcare provider monthly while taking ZINBRYTA and for up to 6 months after the last dose of ZINBRYTA.

Discuss with the patient the risk of concomitant use of other hepatotoxic medications, over the counter medications, herbal products, or dietary supplements.

Inform the patient that they will be given a ZINBRYTA Patient Wallet Card that they should carry with them at all times. This card describes symptoms which, if experienced, should prompt the patient to immediately seek medical evaluation.

Advise the patient to show the ZINBRYTA Patient Wallet Card to other treating healthcare providers.

Immune-Mediated Disorders: Advise patients that ZINBRYTA can cause their immune system to attack healthy cells in their body and that this can affect any organ system.

Skin Reactions: Advise patients that ZINBRYTA can cause dermatologic reactions that can range from mild rashes to serious reactions that could require treatment with other medications or result in hospitalization. Instruct patients to seek immediate medical attention if dermatologic reactions occur [see Warnings and Precautions (5.2)].

Lymphadenopathy: Inform patients that ZINBRYTA may cause lymphadenopathy that can range from mild events that can resolve on their own to serious lymphadenopathy that may require invasive procedures for diagnosis. Instruct patients of the symptoms and instruct patients to contact their healthcare provider if they develop lymphadenopathy [see Warnings and Precautions (5.2)].

Non-Infectious Colitis: Inform patients that ZINBRYTA may cause gastrointestinal reactions that may be serious and could require treatment. Advise patients of the symptoms of colitis and instruct patients to promptly contact their healthcare provider if they experience these symptoms [see Warnings and Precautions (5.2, 5.3)].

ZINBRYTA REMS Program
ZINBRYTA is available only through a restricted program called the ZINBRYTA REMS Program [see Warnings and Precautions (5.3)]. Inform the patient of the following notable requirements:

- Patients must enroll in the program and comply with ongoing monitoring requirements [see Warnings and Precautions (5.1, 5.2, 5.3)].

ZINBRYTA is available only from certified pharmacies participating in the program. Therefore, provide patients with the telephone number and website for information on how to obtain the product.

Allergic Reactions and Anaphylaxis: Advise patients of the symptoms of allergic reactions and anaphylaxis, and instruct patients to seek immediate medical attention if these symptoms occur [see Warnings and Precautions (5.4)].

Risk of Infections: Inform patients that they may be more likely to get infections when taking ZINBRYTA, and that they should contact their healthcare provider if they develop symptoms of infection [see Warnings and Precautions (5.5)].

Depression and Suicide: Advise patients of the symptoms of depression and suicidal ideation as they have occurred with the use of ZINBRYTA and instruct patients to report symptoms of depression or thoughts of suicide to their healthcare provider immediately [see Warnings and Precautions (5.6)].

Instructions for Self-Injection Technique and Procedures: Provide appropriate instruction for methods of self-injection, including careful review of the ZINBRYTA Instructions for Use. Instruct the patient in the use of aseptic technique when administering ZINBRYTA. Inform the patient that a healthcare provider should show them or their caregiver how to inject ZINBRYTA before administering the first dose. Tell the patient not to re-use needles or syringes, and instruct the patient on safe disposal procedures. Inform the patient to dispose of used needles and syringes in a puncture-resistant container.

Manufactured by:
Biogen Inc.
Cambridge, MA 02142
U.S. License # 1697

Distributed by:
AbbVie Inc.
North Chicago, IL 60064

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**Dates and Deadlines**

**DECEMBER 1**
Application Deadline: UCNS Fellowship Program Accreditation
UCNS.org

**DECEMBER 1**
Registration Deadline: RITE®
(Residency In-service Training Examination)
AAN.com/trainees/resident-resources/residency-in-service-training-examination

**DECEMBER 1**
Early Registration Deadline: Breakthroughs in Neurology
AAN.com/view/Breakthroughs

**DECEMBER 10**
Application Deadline: Diversity Leadership Program
AAN.com/view/Diversity

**DECEMBER 13**
FREE Webinar: Decoding the 2017 Medicare Fee Schedule and MACRA Rule
AAN.com/view/pmw16

**JANUARY 9**
Application Deadline: Palatucci Advocacy Leadership Forum
AAN.com/view/2017PALF

**JANUARY 13–16**
Breakthroughs in Neurology
Phoenix, AZ
AAN.com/view/Breakthroughs

**JANUARY 17**
Application Deadline:
UCNS Neuro-oncology Certification and Recertification Examinations Deadline
UCNS.org/go/subspecialty/neo-oncology/certification

**JANUARY 18**
Webinar: How to Approach Advance Care Planning
(Register by January 17)
AAN.com/view/pmw17

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UCNS.org

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(Residency In-service Training Examination)
AAN.com/trainees/resident-resources/residency-in-service-training-examination

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UCNS Neuro-oncology Certification and Recertification Examinations Deadline
UCNS.org/go/subspecialty/neo-oncology/certification

**JANUARY 18**
Webinar: How to Approach Advance Care Planning
(Register by January 17)
AAN.com/view/pmw17

**FEBRUARY 7**
Webinar: Successfully Participate in MACRA
(Register by February 6)
AAN.com/view/pmw17

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**SAVE THE DATES!**

**APRIL 22–28, 2017**
AAN Annual Meeting, Boston
WARNINGS: SERIOUS DERMATOLOGIC REACTIONS AND APLASTIC ANEMIA AND AGRANULOCYTOSIS

Serious Dermatologic Reactions and HLA-B*1502 Allele
Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), have occurred in patients treated with carbamazepine. These syndromes may be accompanied by mucocutaneous manifestations, such as mucositis, pharyngitis, or purpuric rash. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations, but the risk in patients of Asian descent is estimated to be about 10 times higher. These dermatologic reactions may be associated with increased risk of death. The risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. Test for HLA-B*1502, prior to initiating EQUETRO in patients with an increased likelihood of harboring this allele. A new use of EQUETRO in patients testing positive for the allele unless the benefit clearly outweighs the risk. Discontinue EQUETRO if you suspect that the patient has a serious dermatologic reaction [see Warnings and Precautions, Laboratory Tests].

Aplastic Anemia and Agranulocytosis
Aplastic anemia and agranulocytosis can occur during treatment with EQUETRO. The risk of developing these reactions with EQUETRO is 5-8 times greater than in the general population. However, the overall risk in the general population is low (6 cases in a population of one million per year for aplastic anemia and two cases in a population of one million per year for agranulocytosis). Obtain a complete blood count before beginning treatment with EQUETRO, and monitor CBC periodically. Consider discontinuing EQUETRO if significant bone marrow depression develops [see Warnings and Precautions].

INDICATION: EQUETRO is indicated for the treatment of:

- partial seizures with complex symptomatology (e.g., psychomotor, temporal lobe)
- generalized tonic-clonic seizures (grand mal)
- mixed seizure patterns, which include the seizure types listed here or other partial or generalized seizures.

EQUETRO is not indicated for the treatment of absence seizures (petit mal). Carbamazepine has been associated with increased frequency of generalized convulsions in these patients.

Prior to initiating treatment with EQUETRO, test patients in genetically at-risk populations for the presence of the HLA-B*1502 allele. Complete pretreatment blood counts, baseline and periodic liver, eye, urinalysis and BUN testing should be made. Therapy should be prescribed only after critical risk-to-benefit appraisal in patients with a history of adverse hematologic reaction to any drug may be particularly at risk of bone marrow depression. Withdrawal Precipitated Seizure, Status Epilepticus:

Drug Reaction with Eosinophilia and Systemic Symptoms/Multiorgan Sensitivity
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multorgan hypersensitivity, has occurred with carbamazepine. Some of these events have been fatal or life-threatening. DRESS typically presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement. Early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately.

Hypersensitivity. Hypersensitivity reactions to carbamazepine have been reported in patients who previously experienced this reaction to anticonvulsants including phenytoin, primidone, and phenobarbital. A history of hypersensitivity reactions should be obtained for patients and their immediate family members and if present, benefits and risks should be carefully considered, and patients monitored if carbamazepine is initiated.

Suicidal Behavior and Ideation. Antiepileptic drugs (AEDs), including EQUETRO, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Anyone considering prescribing EQUETRO must balance the risk of suicidal thought or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality, and an increase in suicidal thoughts and behavior should not be regarded as drug induced. If suicidal thoughts or behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviors, and should be closely observed for a worsening of existing symptoms, development of new symptoms, or the emergence of symptoms such as agitation, anxiety, ampersadism, depression, or unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Should suicidal thoughts or behavior occur, the patient should be carefully observed, and the family and caregivers should be instructed to monitor the patient, to observe and report any symptoms, and to report any worsening and to immediately consult a healthcare provider.

Abrupt Discontinuation and Risk of Seizure. Do not discontinue EQUETRO abruptly, because of the risk of seizure and other withdrawal signs/symptoms.

Usage in Pregnancy. EQUETRO can cause fetal harm when administered to a pregnant woman. Congenital malformations, including spina bifida may result. The prescribing physician should weigh the benefits of therapy against the risks when treating women of childbearing potential.

Physicians are advised to recommend that pregnant patients taking EQUETRO enroll in the North America Antiepileptic Drug (NAAED) Pregnancy Registry by calling the toll-free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org.

Hypotension. Hypotension can occur as a result of treatment with EQUETRO, in many cases, by the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The risk of developing SIADH with EQUETRO treatment appears to be dose-related with elderly patients and patients treated with diuretics at greater risk. Consider discontinuing EQUETRO in patients with symptomatic hypotension. Signs and symptoms of hypotension may include headache, new or increased seizure frequency, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls.

Potential for Cognitive and Motor Impairment. EQUETRO has the potential to cause impairment in judgment, attention, and motor function. Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that EQUETRO does not affect them adversely.

Potential for Loss of Virologic Response to Non-nucleoside Reverse Transcriptase Inhibitors. Non-nucleoside reverse transcriptase inhibitors that are substrates for CYP3A4 with Concomitant use of EQUETRO. Concomitant use of EQUETRO and non-nucleoside reverse transcriptase inhibitors may decrease the drug levels of CYP3A4 substrates. Consider using other non-nucleoside reverse transcriptase inhibitors that are not substrates for CYP3A4. Avoid use of EQUETRO in patients who previously experienced this reaction to anticonvulsants including phenytoin, primidone, and phenobarbital. A history of hypersensitivity reactions should be obtained for patients and their immediate family members and if present, benefits and risks should be carefully considered, and patients monitored if carbamazepine is initiated. Avoid use of EQUETRO in patients with symptomatic hyponatremia. Hyponatremia can occur as a result of treatment with EQUETRO; in many cases, by the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The risk of developing SIADH with EQUETRO treatment appears to be dose-related with elderly patients and patients treated with diuretics at greater risk. Consider discontinuing EQUETRO in patients with symptomatic hyponatremia. Signs and symptoms of hyponatremia may include headache, new or increased seizure frequency, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls.

Potential for Cognitive and Motor Impairment. EQUETRO has the potential to cause impairment in judgment, attention, and motor function. Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that EQUETRO does not affect them adversely.

Potential for Loss of Virologic Response to Non-nucleoside Reverse Transcriptase Inhibitors. Non-nucleoside reverse transcriptase inhibitors that are substrates for CYP3A4 with Concomitant use of EQUETRO. Concomitant use of EQUETRO and non-nucleoside reverse transcriptase inhibitors may decrease the drug levels of CYP3A4 substrates. Consider using other non-nucleoside reverse transcriptase inhibitors that are not substrates for CYP3A4. Avoid use of EQUETRO in patients who previously experienced this reaction to anticonvulsants including phenytoin, primidone, and phenobarbital. A history of hypersensitivity reactions should be obtained for patients and their immediate family members and if present, benefits and risks should be carefully considered, and patients monitored if carbamazepine is initiated. Avoid use of EQUETRO in patients with symptomatic hyponatremia. Hyponatremia can occur as a result of treatment with EQUETRO; in many cases, by the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The risk of developing SIADH with EQUETRO treatment appears to be dose-related with elderly patients and patients treated with diuretics at greater risk. Consider discontinuing EQUETRO in patients with symptomatic hyponatremia. Signs and symptoms of hyponatremia may include headache, new or increased seizure frequency, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls.
Equetro® (carbamazepine) Extended-Release Capsules
Approved for Use in Treating Epilepsy*

Equetro is indicated for the treatment of
• Partial seizures with complex symptomatology
• Generalized tonic-clonic seizures
• Mixed seizures

Limitations of usage: Equetro is not indicated for the treatment of absence seizures (petit mal).

For more information and the Equetro Savings Card, visit Equetro.com.

*PLEASE SEE SPECIFIC INDICATIONS ON BACK.
PLEASE SEE IMPORTANT SAFETY INFORMATION ON BACK INCLUDING BOXED WARNING, CONTRAINDICATIONS, AND WARNINGS AND PRECAUTIONS.