Discover the Annual Meeting Everyone’s Talking About—
Registration Opens This Month!

Registration opens soon for the world’s largest and most exciting gathering of neurologists. Discover the Annual Meeting everyone’s talking about and visit AAN.com/view/AM17 today to learn more, register, and book your hotel.

We changed the entire format and feel of the AAN Annual Meeting in 2016, with seismic shifts focused on serving attendees in new and invaluable ways. People took notice, and the excitement in the air was palpable. For 2017, we’re doing it again and adding even more changes to the docket.

When you experience the AAN Annual Meeting, you experience the most innovative neurology conference in the world with:

- **Value**
  Register for one, all-inclusive fee that eliminates pre-registration for individual courses and gives you the flexibility to move between sessions as you wish.

Continued on page 26

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**Early Registration Deadline Approaching for January Breakthroughs Conference**

*Savings End December 1*

December 1 is the last chance to take advantage of early registration savings—and book your hotel—for the 2017 Breakthroughs in Neurology Conference, set to take place January 13 through 16 at the beautiful Sheraton.

*Continued on page 27*

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**It’s Time to Renew Your Membership for 2017**

*Retain Access to Exclusive Benefits*

We’re here to support you throughout your career. Visit AAN.com/dues to renew your AAN membership today so you can continue to be a part of an esteemed network of more than 30,000 neurologists and neuroscience professionals worldwide and retain access to these career enhancing benefits—valued at up to $4,000—that only an AAN membership can afford:

- Free access to AAN online continuing education resources to help you meet all of your CME and MOC requirements
- AAN Clinical Practice Guidelines
- Publications, like Neurology® journals, featuring the latest research and breaking news

*Continued on page 27*
Because treating relapsing MS is important...

**She Deserves the Tecfidera Treatment**

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**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 x10^9/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. 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 <0.5x10^9/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 <0.8x10^9/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). In controlled and uncontrolled clinical trials, 2% of patients experienced lymphocyte counts <0.5x10^9/L for at least six months. In these patients, the majority of lymphocyte counts remained <0.5x10^9/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 <0.5x10^9/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)**

- **PLACEBO**
  - n=408
  - 46%

- **TECFIDERA**
  - n=410
  - 27%

**Half as many patients relapsed**

### Established tolerability and safety

**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.

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


For more information, visit TECFIDERAHCP.COM

More than **200K** patients treated globally—and growing

TECFIDERA has been prescribed in the US more than any other oral therapy for RMS as of September 2013

5+ years of clinical and real-world experience

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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 initial 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 capsules have 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 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 was also 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 obtain 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 less than 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, 40% of TECFIDERA treated patients experienced flushing. Flushing symptoms generally began soon after initiating TECFIDERA and usually improved or resolved over time. In the majority of patients who experienced flushing, it was mild or moderate in severity. Three percent (3%) of patients discontinued TECFIDERA for flushing and <1% had serious flushing symptoms that were not life-threatening but led to hospitalization. Administration of TECFIDERA with food may reduce the incidence of flushing. 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 1: Adverse Reactions in Study 1 and 2 reported for TECFIDERA 240 mg BID at ≥2% higher incidence than placebo

<table>
<thead>
<tr>
<th>Reaction</th>
<th>TECFIDERA N=769</th>
<th>Placebo N=771</th>
</tr>
</thead>
<tbody>
<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>
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 food intake, reduced body weight). Plasma exposure (AUC) for monomethyl fumarate (MMF), the major circulating metabolite, at the no-effect dose is approximately three times that in humans at the RHD. This dose also produced evidence of maternal toxicity (reduced food intake, reduced body weight). Plasma exposure (AUC) for monomethyl fumarate (MMF), the major circulating metabolite, at the no-effect dose is approximately three times that in humans at the RHD.

8.2 Lactation

There is no information on the effects of TECFIDERA on milk production in nursing women. Because many drugs are excreted in human milk, caution should be exercised when TECFIDERA is administered to a nursing woman.

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information) before starting TECFIDERA.

Dosing

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

Anaphylaxis and Angioedema

Advise 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. Instruct 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)].

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

Inform 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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Manufactured by:
Biogen
Cambridge, MA 02142

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2/2016
The AAN and the Child Neurology Society have been collaborating and identifying ways that the two organizations can work together to improve care for patients across the life span. This collaboration has led to initiatives such as the new Frontiers in Child Neurology program at the 2016 AAN Annual Meeting, as well as new scholarships to the Annual Meeting, with five child neurology residents receiving scholarships to cover Annual Meeting expenses as well as special programming in child neurology with the Frontiers in Child Neurology program and mentorship opportunities during the Annual Meeting. Recently, AAN President Terrence L. Cascino, MD, FAAN, President Elect Ralph L. Sacco, MD, MS, FAHA, FAAN, and Secretary-Treasurer Ann H. Tilton, MD, FAAN, spoke about these partnerships in a video that was shared at the Child Neurology Society meeting last month.

Neurology Now® magazine has received a 2016 Clarion Award in the category of current news feature in an external publication with circulation of 500,000+ for the article in the June/July 2015 issue “A Labor of Love” by Abby Ellin. The article features “Orange Is the New Black” actress Connie Shulman’s work on a documentary about her friend’s frontotemporal dementia. The awards are given by the Association of Women in Communications.

AAN Executive Director/CEO Catherine M. Rydell, CAE, was listed in the 100 Most Influential Health Care Leaders in the August 2016 issue of Minnesota Physician.
President’s Column

Fighting for You on Several Fronts

This past summer, AAN Board member Elaine C. Jones, MD, FAAN, who also chairs our Payment Policy Subcommittee, brought up an issue that had not been on our radar: the gender disparity gap in physician pay. “I know pay gaps are becoming a national issue,” she told us, “and I have had several female neurologists approach me about this issue for themselves and asking if the AAN is aware of it and what can be done.”

As Dr. Jones began to look into this, what she learned alarmed her—including this information from a July 12, 2016, article in the New York Times that cited a JAMA Internal Medicine study: A broad analysis of salary information from public medical schools found that women made almost $20,000 less a year than comparable male doctors. Neurology suffers not only from being the lowest paid of the cited specialties, but also has one of the widest discrepancies between genders.

“I would like to request that the AAN make this a priority for our profession,” Dr. Jones asked of the board. “I think a lot could be done within our own field, from educating women on negotiating, educating department chairs on the discrepancies and the need for transparency in their own departments, to mining the data we get from our surveys, etc.”

Thanks to Dr. Jones and Board member Orly Avitzur, MD, MBA, FAAN, chair of our Medical Economics and Management Committee, we have looked into this and what we have discovered is indeed shocking. Our 2016 Neurology Productivity and Compensation Survey, based on 2015 data, shows compensation reported by the female members who took the survey to average $200,000 compared to $250,000 for male members surveyed. In the AAN’s August 18, 2016, issue of Neurology Today®, these disparities were discussed by Dr. Jones and other neurology leaders, including Ann H. Tilton, MD, FAAN, secretary/treasurer of the AAN Institute

Board of Directors; and Cynthia L. Comella, MD, FAAN, chair of the AAN Women’s Leadership Group. Many of the female neurologists interviewed recognized such salary disparities from their own experiences and suggested the reasons are numerous, including greater acceptance of initial salary offers, lack of aggressiveness in negotiating salaries, perceptions of self-worth, and responsibilities at home. Literature shows females are at higher risk for burnout than males, and the Neurology Today article mentions that the salary issue may contribute to that problem.

Other non-AAN studies and articles confirm that gender—and racial—disparities in salaries exist throughout the medical profession, whether practicing physicians, academic faculty, nurses, or researchers.

Clearly, both to me and the other members of the AAN Board, this is unacceptable and demands immediate action and correction. I have appointed a task force to dig deeper into the causes of this problem and recommend steps that the AAN can take to advocate on behalf of our members and promote equal pay for equal work.

I want to commend Dr. Jones for bringing this to our attention and advocating for action. Indeed, this demonstrates why a diverse board of directors—inclusive of gender, race, and work focus—is paramount to successfully leading an organization where all members are prized, all work skills are respected, and all voices are heard. I look forward to sharing with you the results of the task force’s investigation and recommendations as to what the Academy can do to help advocate for equal pay. Stay tuned.

Empowering our members to become confident leaders is at the core of our new suite of AAN Leadership Programs, and the oldest is the Palatucci Advocacy Leadership Forum, launched in 2003. Many of you might be in a position similar to Dr. Gurdesh Bedi, a 2014 graduate of the forum, who shares his remarkable story on page 12. Maybe you have seen deficiencies—or outright failures—in the delivery of quality care to patients, and have ideas about how to change the system in your workplace or community, but haven’t been able to figure out how to go about it successfully. Perhaps these conditions have eroded your zest for practicing neurology and you’re feeling marginalized. If so, I urge you to take the first step that Dr. Bedi took to become an agent of change and reinvigorate his passion for neurology: apply to participate in the 2017 Palatucci Forum, which will

Continued on page 13 ▶
Meet Your Leader

Carlayne E. Jackson, MD, FAAN

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

Carlayne E. Jackson, MD, FAAN, is professor of neurology and otolaryngology at the University of Texas Health Science Center San Antonio. She also serves as chief medical officer of UT Medicine and as assistant dean of ambulatory services for the school of medicine. Jackson serves as medical director for the South Texas ALSA Center of Excellence and the MDA ALS Research Center. With the AAN, Jackson currently serves on the Continuum® Editorial Board, Meeting Management Committee, and Leadership Development Committee. She also has served on the Science Committee, ALS Measurement Development Panel, and the Neuromuscular Topic Work Group of the Education Committee. Jackson has participated in the Palatucci Advocacy Leadership Forum, Neurology on the Hill, the Neuromuscular Ecuador Project, and as a mentor in the Emerging Leaders Forum and Diversity Leaders Program.

What moved you to join the Board of Directors? What experiences and viewpoints do you bring to this role?

Honestly, I had never considered applying for the Board until I was nominated by one of my mentors. My experience on the Board has been extremely rewarding and I would encourage members to take an active role in nominating colleagues who they feel might bring a unique perspective to the organization. Mentorship not only involves giving advice, but promoting and encouraging their mentees to serve in leadership roles.

I have spent my entire medical career at the University of Texas Health Science Center—including medical school and residency—so I have a deep understanding of the issues facing neurologists who work in a smaller academic department. I have also had the opportunity to serve as the chief medical officer of our practice plan since 2009, and as a result have been involved in the “business” of academic medicine. I have had to advocate for a diverse group of stakeholders: patients, providers, clinic staff, administrators, practice managers, medical directors, and department chairs. Through my experiences in this role, I have learned that spending time establishing relationships with my team is critical in establishing alignment around a common purpose, receiving honest feedback, and being nimble in navigating an ever-changing landscape.

From your experiences as an AAN leader, what is one of the more common misperceptions members may have about the Academy?

One of the common misperceptions about AAN leadership is that we do not understand the issues facing our membership. Since I have been on the Board, every decision we have made is based on our vision to be indispensable to our members. We have launched a series of initiatives to diversify the membership of the Board and our committees, to provide leadership training to help position neurologists in influential roles at their local hospitals and institutions, and to advocate for the value of the neurologist and neuroscientist to the legislature, CMS, and NIH. In addition, task forces have been developed to address the needs of the neurologist in private practice and to understand and minimize physician burnout. The Annual Meeting has also been revamped to provide unlimited access to educational courses.

In your view, how does the AAN benefit the field of neurology most?

The AAN is uniquely poised to be the voice of neurology to our public stakeholders: NIH, CMS, FDA, and state and federal legislators. With all of the emerging changes in health care, including changes in reimbursement strategies, it becomes imperative that all members support the AAN in advocating on behalf of their interests and the interests of the patients they serve. My Neurology on the Hill experiences establishing relationships and discussing issues with my congressmen and their staff have really solidified my belief that member engagement in advocacy is one of the most important things we can do to initiate change in health care policy.

How should members evaluate the success of the AAN and the Board of Directors in supporting their careers and neurology in general?

The best way to evaluate the success of the AAN is to stay connected with the resources provided to keep you up-to-date with our initiatives: Neurology Today, emails, AAN conferences, and AAN.com. Another way to evaluate the organization is to get involved and engage with our leadership so we can better understand your challenges and concerns. The Board actually has a “scorecard” that is reviewed and updated based on our strategic plan at least twice a year.

How do you deal with the challenges of balancing the demands of your work and personal life?

One of the key drivers of physician burnout is not being successful in obtaining an adequate work/life balance. Fortunately, I have a wonderful husband who continues to remind me when I need to put my iPhone away! I love to spend time with my daughters in Austin and San Francisco and always find time to play a round of golf with my husband at least once a week (which is possible in San Antonio). We recently moved to a garden home close by my office to minimize my commute and to allow time to attend my favorite “Body Pump” classes at the gym after work. I have learned to say “no” to projects I do not feel passionate about and have learned to continue to say “yes” to opportunities for leadership where I feel I can make a difference.
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.

Advancing Neurology. Advancing You.
Webinar Provides Overview of Health Care Technology

Discover best practices around EHR use and other emerging technologies like OpenNotes with patients. In this webinar, AAN experts will provide an interactive presentation on technology tools, especially those that focus on patient experience.

Getting the Most Out of Your Technology: HIT and Your Patients
November 8, 2016 • 12:00–1:00 p.m. ET
Deadline to Register: November 7
Directors: Allison L. Weathers, MD, FAAN

Objectives
- Familiarize yourself with current patient engagement technology used in the medical field
- Understand the core functionalities of EHR (electronic health records)
- Understand the overall pros and cons to technology in the medical field

Enjoy New Reduced 2016 Member Pricing!
- If you have scheduling conflicts, registration gives you access for one year to the recorded webinar if you miss the live event
- Physicians will earn 1 AMA PRA Category 1 Credit™ per webinar and non-physicians will receive a certificate of completion
- AAN members pay only $99 per webinar (save $50 each from 2015 fee) or subscribe to the complete 2016 webinar series for only $189 (save $10 from 2015 subscription)
- New and convenient one-hour sessions
- Includes presentation slides and access to recording

To initiate a 2016 subscription, simply start registering for a single webinar and the option to subscribe to all 10 live webinars will be presented. The 2016 subscription offer does not include registration for webinars presented in 2015, which must be made in a separate transaction.

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

FREE Webinar: Decoding the 2017 Medicare Fee Schedule and MACRA Rule

Mark your calendar to join William S. Henderson, FACMPE, and Marc Raphaelson, MD, on December 13, from 12:00 to 1:00 p.m. ET, for this FREE webinar that 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.

Heavy Media Coverage for Revelations of Robin Williams’ Widow in Neurology Editorial

Susan Schneider Williams, widow of actor Robin Williams, issued a message to neurologists in an editorial published in the September 27 issue of Neurology® and speaks candidly in an interview on the September 27 Neurology podcast. The editorial, which was promoted by the American Brain Foundation along with its announcement that Schneider Williams has joined its Board of Directors, garnered coverage from hundreds of media outlets, including “ABC World News,” “Today Show,” “Good Morning America,” People magazine, Variety, TIME, “Entertainment Tonight,” Rolling Stone, and Huffington Post.
Neurology® Podcasts
Visit Neurology.org to listen to Neurology podcasts and earn 0.5 AMA PRA Category 1 CME Credits™ by answering the multiple-choice questions in the online podcast quiz. Interviews based on articles from Neurology® Clinical Practice, Neurology® Genetics, and Neurology® Neuroimmunology & Neuroinflammation are excluded from the CME program.

Available by November 1
- Anti-LGI1 Encephalitis: Clinical Syndrome and Long-term Follow-up
  Lara V. Marcuse, MD, BA, and Maarten J. Titulaer, MD, PhD
- Reducing Costs While Enhancing Quality of Care in MS
  B. Mark Keegan, MD, FRCP (C), and Ilya Kister, MD
- Calcium Supplementation and Risk of Dementia in Women with Cerebrovascular Disease
  Jeffrey M Burns, MD, and Silke Kern, MD
- HIV Associated Motor Neuron Disease: HERV-K Activation and Response to Anti-retroviral Therapy
  Ted M. Burns, MD, and Avindra Nath, MD

PQRS: Act Now to Avoid 2018 Payment Penalty
Neurologists should be aware that there is still time to participate in CMS’s 2016 Physician Quality Reporting System (PQRS) program and avoid the payment penalty in 2018.

For those not currently participating in the pilot of the AAN’s Axon Registry™ or those looking for an alternative reporting method, the AAN once again is offering Academy members a discounted registration through the PQRSwizard at AAN.com/page/index/4040.

For now, and as in previous years, participating neurologists will need to choose nine individual measures across three national quality strategy (NQS) domains including at least one cross-cutting measure. The measures must meet the 50-percent reporting criteria. Or, depending on the reporting mechanism, neurologists can choose a measures group and report on one or more measures groups for at least 20 Medicare patients.

Neurologists participating via a qualified clinical data registry (QCDR) such as AAN’s Axon Registry will be required to report nine measures across three NQS domains, at least two of which must be outcomes measures.

Neurologists should also keep in mind that the value-based payment modifier (VBPM) program combines PQRS participation with cost data and involves a separate, additional payment penalty.

If you have questions regarding participating in PQRS, contact Gina Gjorvad at ggjorvad@aan.com, or visit AAN.com/practice/medicare/physician-quality-reporting-system for more information.
Public Policy

Palatucci Forum Leads to Fulfillment of Member’s Dreams for Patients

More than 400 AAN members have participated in the Palatucci Advocacy Leadership Forum. They have been changing how neurology is practiced across the world, from Pakistan to Austria to Wyoming—and to St. Croix Falls, WI, where Gurdesh Bedi, MD, is the first medical director of the Kinisi Institute of Movement, a new musculoskeletal center serving western Wisconsin and eastern Minnesota.

Bedi, a son of physicians in his native India, had trained in the US and taken up practice in this scenic riverside area. It was a successful practice, but he didn’t know what to do next. He wanted to build a larger center, advocate for his patients’ rights, be a policy maker, change the world. But he didn’t know where to start.

Bedi applied to attend the 2014 forum after an enthusiastic recommendation from a “PALFer” from the first class. He was accepted, and his life was changed by the weekend of intensive training and the AAN members he met who would become his best friends and mentors.

“I was like Alice in Wonderland,” he said later. “I got to learn and debate with policy makers and system rebels, local heroes and cross-border caregivers, dreamers of starts-ups and serial entrepreneurs. These discussions were stimulating, and my world view radically expanded.”

The lesson that change doesn’t always have to happen at the highest levels revolutionized Bedi’s thinking. “I discovered that I was a believer in change from the ground up. So I went back and got engaged in a Rotary Club in my town.” Soon he signed up for the county and the Wisconsin state medical societies. Within a month of PALF, he was sitting on two Wisconsin medical councils, presiding over its young physician society, and on the way to becoming Wisconsin’s delegate to the AMA. Within a year, he was on the board of the 175-year-old, 13,000-member Wisconsin medical society. Around the same time, he found his niche at the national level and got involved with the efforts of the AAN and AMA in Washington, DC.

“I also realized that change needed to happen in my everyday microenvironment. I had a healthy, traditional practice. I personally did well in this environment. I grew, controlled my schedule, had good support staff, and had a good income. But all along, as much as I loved my job, I had felt that something was missing. I had pitched ideas of ambitious projects to my hospital leadership and board before, but knew that I wasn’t communicating right. On the flight back from my rookie PALF year, I realized where the gap was. PALF helped me realize it.”

Bedi said the Palatucci Forum works on the principle of putting the patient in the center of the conversation. After PALF 2014, Bedi saw having a logic-based, common-sense, respectful attitude toward patients as a right, and not a forlorn desire. The forum gave him the tools to restate his previously hazy view of this utopian clinical approach into achievable action plans, setting SMART (Specific, Measurable, Attainable, Realistic, Timely) goals. With this revised approach, his team approached the hospital board with a hefty project to redesign its clinics from the ground up (using a PALF-inspired SMART action plan).

The result is the Kinisi Institute for Movement (a name that embodies the principles behind this new musculoskeletal center) and the first of these smart-clinics launched in July 2016, with Bedi appointed as the center’s first medical director. The clinic and its systems have been designed by staff who have been trained to anticipate, rather than react to, patient needs and expectations. Bedi now feels he has a real shot at making health care more humane in the region.

“None of this would have ever been possible, may have not even been imagined, had I not been urged to apply for the forum and been accepted just two years ago,” Bedi says. “I wrote
more emails, had clearer thoughts, and was much better skilled to handle organizational challenges after PALF. It was such an intense intellectual high that I craved a second shot, and went back as an advisor in 2015. The results were even better—like a booster vaccination.” He wanted to participate a third time, in 2016, but a family situation prevented him.

The Palatucci Forum is one of several programs offered by the AAN to train leaders to meet the many challenges in today’s world of neurology. What Bedi says about the forum can be said of all of the leadership programs.

“I don’t think that the Shakespearean concept of leaders being born or having leadership thrust upon them is true anymore. Leadership cannot be gifted or thrust upon any unprepared individual. It must be acquired—through hard work, skills, development, and training. While capability is a basic requirement, molding capable individuals into perpetual problem solvers requires structured leadership training. That is the road the Palatucci Forum opened for me.”

President’s Column

Fighting for You on Several Fronts

Continued from page 3

be held next May. You will be trained by experts and your peers, mentored by successful graduates, and reinvigorated by a new mission that is achievable and consequential.

Building sustained relationships with members of Congress is a vital component of successful advocacy. As you can read on page 14, some of our members have met with lawmakers when they returned home, either in the district office or at the neurologist’s clinic, during the recent congressional recess. Both settings eliminate the chance of distractions of roll call votes or committee meetings, and clinic visits provide a show-and-tell opportunity that more vividly presents the perspectives of doctor and patient.

I hope these examples will inspire you to take advantage of the opportunity to participate in our Neurology on the Hill visit to Washington next February 27 and 28. I want to emphasize that you do not need any experience to join us. Our staff will present an overview of the issues we will address with members of Congress. You also will hear from some key players in health care policy who will share their insights and experiences. You’ll have the chance to meet and network with fellow Academy members—a great way to share common interests, concerns, and solutions that have been successful elsewhere. And that’s just the first day! On the second day, you’ll don your complimentary Academy green necktie or scarf and meet with your senator and/or representative to help educate them on these issues and make our case on behalf of our patients. While our political system may be far from perfect, we citizens do have the right to have our voices heard, to be grassroots lobbyists, to speak truth to power. If we neglect this responsibility, if we fail to speak up and educate those who make the decisions that affect us, it diminishes our authority to complain about the outcome.

You can learn more about Neurology on the Hill and submit your application by November 20, 2016, at AAN.com/view/2017NOH. The deadline for the Palatucci Forum is January 9, 2017, and more information and the application are at AAN.com/view/2017PALF. To host a congressional visit at your practice, please contact Becky Horton at bhorton@aan.com.

The AAN’s mission includes supporting your career satisfaction. On many different fronts, in a variety of ways, your Academy is fighting for you. I hope you will keep this in mind when you receive your membership renewal notice for 2017 in the mail. The AAN has your back.

Terrence L. Cascino, MD, FAAN
President, American Academy of Neurology
tcascino@aan.com
Public Policy

Across the Country, AAN Members and Leaders Advocate for Neurology

Over the past few months, President Terrence L. Cascino, MD, FAAN; President Elect Ralph L. Sacco, MD, MS, FAHA, FAAN; Executive Director/CEO Catherine M. Rydell, CAE; and other AAN colleagues have been advocating for neurology to members of Congress and key shapers of health care policy. Leading topics of discussion were pushing for passage of the Furthering Access to Stroke Telemedicine (FAST) Act and reducing regulations that unfairly burden neurologists.

Congressional Site Visits

AAN Board of Directors member and practicing neurologist Sarah M. Benish, MD, FAAN, hosted Rep. Erik Paulsen (R-MN) at the Minneapolis Clinic of Neurology in Edina, MN. Benish, along with Kurt Neil, executive director, provided an overview of their day-to-day activities in a physician-owned private practice. The Minneapolis Clinic of Neurology—co-founded in 1955 by Joseph A. Resch, MD, FAAN, who had prompted A.B. Baker, MD, FAAN, to launch the AAN in 1948—is the largest physician-owned single-specialty neurology clinic in the nation. This gave Paulsen unique insight into the challenges of practicing medicine while operating a small- to mid-sized business. Benish and Neil gave the congressman a tour of the facility and highlighted different equipment, particularly their mobile MRI machine. They also discussed issues affecting their practice such as reporting through PQRS, the impending MACRA implementation, and specialty drug costs.

Government Relations Committee Chair Nicholas E. Johnson, MD; Jennifer J. Majersik, MD, MS; Awais Riaz, MD, PhD, FAAN; and Steve O’Donnell, MD, met with Sen. Orrin Hatch’s health policy staff at the University of Utah Center for Neurosciences. They focused their discussion on the importance of stroke telemedicine and the FAST Act, especially as it continues to gain cosponsors in the House of Representatives. Also in attendance was the Utah government relations director for the American Heart Association/American Stroke Association to provide a patient perspective on the importance of the FAST Act. The neurologists also provided their perspectives on relevant issues such as drug pricing and MACRA implementation.

The AAN facilitates visits from members of Congress to neurology practices. Contact Becky Horton at bhorton@aan.com if you’re interested in hosting your representative at your practice.

In-district Meetings

The AAN launched a pilot program to facilitate meetings between members and their lawmakers when they are in their home districts during congressional recesses. Members of the Government Relations Committee participated in the first meetings.

Johnson, Majersik, Riaz, and O’Donnell collaborated again with the American Heart Association/American Stroke Association to meet with staff of Rep. Chris Stewart (R-UT). They discussed the FAST Act, the BRAIN Initiative, and regulatory burden.

Brett M. Kissela, MD, FAAN, met with Rep. Steve Chabot (R-OH) and his legislative assistant at the congressman’s office. Kissela’s purpose was to discuss the FAST Act and explain that expanding stroke telemedicine could result in a net savings of $1.2 billion per year for federal health programs. Kissela said he felt that meeting was a “game-changer” because they could take ample time to discuss the issue, without the added distractions of Washington, DC.

Partha Thirumala, MD, discussed the FAST Act with Rep. Keith Rothfus (R-PA) and his health legislative assistant. Thirumala had previously met Rothfus and was building on this existing relationship.
Steve Holtz, MD, FAAN, and Robyn Young, MD, met with staff of Rep. Barbara Lee (D-CA). According to Holtz, they had a “very fruitful discussion” with Lee’s congressional aide and discussed the “FAST Act, the importance of cognitive neurology, and the need to make Meaningful Use less obstructive to patient care.” They were able to spend a significant amount of time on these issues, and Holtz said that “Congresswoman Lee is very much on board with issues that are important to our community of neurologists.”

Meanwhile, at the White House

The White House hosted “Making Health Care Better,” a five-part series that highlighted the significant progress made in improving the health system over the past seven years. AAN President Terrence L. Cascino, MD, FAAN; President Elect Ralph L. Sacco, MD, MS, FAHA, FAAN; and Executive Director/CEO Catherine M. Rydell, CAE, attended the session that focused on advancements in cardiovascular health research, delivery and quality of care, and coverage.

2017 Neurology on the Hill Will Meet with New Congress

Apply by November 20; Openings Are Limited!

We will know soon if the November 8 elections change the balance of power in Congress. What is for sure is that when it convenes next year, urgent matters affecting neurologists will be on the table, and the AAN will advocate for them during the 2017 Neurology on the Hill.

Applications are being accepted online for this event, which will be held February 27 and 28 at the Ritz-Carlton Pentagon City, in Washington, DC. The 15th Neurology on the Hill will follow the successful format of briefing participants about the leading issues and the legislative process on the first day, and then going to the Capitol on the second day to meet with members of Congress and their staffs.

“The AAN is highly regarded in Washington as the primary voice of neurology,” said Nicholas E. Johnson, MD, chair of the Government Relations Committee. “Our influence has never been stronger. But the elections mean we may see more new faces next February, so it’s very important we get in there and educate them on how they can make it easier for our patients to get the care they need, when they need it.”

Neurology on the Hill is open to all US members, except medical students. Selected applicants will receive complimentary airfare and hotel accommodations. There is a general registration fee of $150, or $50 for residents, fellows, and members residing in the Washington, DC, area.

The deadline for applying to participate is November 20. Spaces fill quickly for this event, which last year drew a record number of 182 neurologists. To learn more and to apply, visit www.aan.com/view/2017NOH.

The 2017 Election: Who Wins?

The AAN invites you to attend “What Do the Elections Mean for Your Practice?,” a FREE webinar examining the results of the 2017 federal elections, on November 17 from 7:00 p.m. to 8:00 p.m. ET. The webinar will be hosted by Senior Legislative Counsel Mike Amery, Esq., who leads the AAN’s advocacy team in Washington. Visit http://bit.ly/2ewrRYy to register.
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.

The AAN took a major step in advancing our neurology alternative payment models (APMs) last week, when Joel Kaufman, MD, FAAN, and Marc Raphaelson, MD, from the AAN’s Payment Alternative Team, and AAN staff met with leadership from the Centers for Medicare & Medicaid Services (CMS). We were really encouraged by CMS’ interest in our epilepsy and headache care payment models (and thank you to all the AAN members who responded to our request for comments and feedback). Agency staff asked many questions and provided us with steps to take so that our models could potentially be tested by CMS and qualify as Advanced APMs under MACRA. We will continue talking with CMS staff. This comes after we have received many comments from members and worked to incorporate improvements into the models. The AAN is on the leading edge of APM development and garnering national attention.

Dr. Kaufman, chair of the AAN’s Payment Alternative Team, said, “The AAN is reaching out to insurers, other specialty societies, and now the Innovation Center. We are casting a wide net to get feedback on our models. These are working documents and will get stronger with broader input.” Dr. Kaufman described these models in an April 2016 AANnews® article. We committed to ensuring that our members have options under the new MACRA system, which allows professionals to pick between two options: the Merit-based Incentive Payment System (MIPS) pathway or participating in what CMS describes as an Advanced APM. We remain hopeful that our models will qualify under the APM track of MACRA and allow neurologists to negotiate new arrangements with payers. *

Guidelines

AAN Publishes Practice Advisory on EEG in ADHD Diagnosis

The AAN’s new “Practice Advisory: The Utility of EEG Theta/Beta Power Ratio in ADHD Diagnosis” was published online ahead of print on October 19, 2016, and in the November 29, 2016, print issue of Neurology®. According to the AAN advisory, quantitative EEG (QEEG) theta/beta power should not be used to diagnose ADHD, confirm an ADHD diagnosis, or support further testing after a clinical evaluation, unless such diagnostic assessments take place within the limits of a research study. Furthermore, the combination of QEEG theta/beta ratio and frontal beta power should not replace the clinical examination in ADHD diagnosis.

In their examination of the evidence on QEEG use for this indication, the advisory authors combined the results of two large studies in a statistical analysis and found a rate of overall diagnostic accuracy of approximately 89 percent, suggesting that use of QEEG for this indication can produce a false-positive rate of greater than five percent.

“We compared the data from our analysis with a threshold of acceptable diagnostic error of five percent, a rate obtained from large observational studies of diagnostic errors in outpatient care in the United States,” said David Gloss, MD, FAAN, lead author of the practice advisory. “Although some of the evidence on QEEG in ADHD diagnosis was strong, we considered the combined rate of greater than five percent diagnostic inaccuracy to be unacceptable, particularly for children whose lives may be significantly altered by a false ADHD diagnosis.”

Read the advisory and access PDF summaries for clinicians and patients, a slide presentation set, and a payment policy perspectives article on AAN.com. For more information, contact Julie Cox at jcox@aan.com or (612) 928-6069. *
Meet Your Year-end CME and MOC Requirements with Free Online Resources from the AAN

As you prepare for your year-end CME and MOC requirements, don’t forget about a variety of quality online resources included free with your AAN membership. These handy courses can be accessed from virtually anywhere—home or office—and allow you to meet your end-of-year CME and MOC needs, as required by the ABPN.

- **NeuroPiSM**
  This online performance improvement program meets the ABPN MOC Part 4 Performance in Practice component requirements in addition to offering 20 CME credits.

- **NeuroSAE®**
  The AAN’s convenient online self-assessment examination assesses your knowledge of neurology to assist you in building your learning plan and compares your performance to other neurologists.

- **NeuroLearn™**
  This exclusive multimedia suite of online education courses is designed to be taken at your own time and pace, address relevant clinical neurology and timely practice topics, and offer up to two CME credits upon successful completion.

- **Neurology CME**
  Stay current with the most recent advances in the field with the AAN’s peer-reviewed, premier medical journal. Earn up to 1.5 hours of AMA PRA Category 1 Credits™ per issue—or up to 72 for a full year.

- **Neurology Podcast**
  Earn .5 AMA PRA Category 1 Credit when you listen to weekly podcasts from Neurology and answer the accompanying online questions.

Access these CME and MOC programs—and more—at AAN.com/cme-and-moc/online-learning-programs. *

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**Earn Up to 147.5 CME with Annual Meeting On Demand**

In addition to a host of free online CME and MOC resources, AAN members receive a deep discount on AAN Annual Meeting On Demand, the virtual library of the 2016 AAN Annual Meeting. This convenient resource offers a variety of topics and options to tailor your CME learning and allows you to participate in the sessions you were not able to attend during the meeting, or revisit your favorite sessions. With your On Demand program you’ll receive:

- Access to more than 500 hours of presentations
- Downloadable PDFs of the presentation slides and syllabi
- The opportunity to earn up to 147.5 AMA PRA Category 1 Credits™
- A complimentary hard drive to view presentations offline
- iPosters: online access to scientific posters presented at the Annual Meeting

Get started today at AAN.com/view/AMOD. *

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**Online CME & MOC Programs FREE with Your AAN Membership!**

Learn more at AAN.com/view/MOC
Use Workout or Commute Time for Update on Muscle Disease with Continuum Audio

Get updated on the latest in muscle diseases such as myotonias, myopathies, and muscular dystrophies during your workout time or commute with the latest Continuum Audio series.

“Neurologists will appreciate these thoughtful overviews of muscle disease from authorities in the field,” said Continuum Audio series Editor Aaron E. Miller, MD, FAAN, of Mount Sinai School of Medicine in New York, NY. “The series also covers the role of electrodiagnostic testing, imaging, and muscle biopsy in the investigation of muscle disease, as well as the ethical considerations of genetic testing for presymptomatic people at risk for progressive myopathy and registry participation for those who want to know how to get started with that.”

The first two hours of the series are currently available; the second two hours will be available in December.

Hour 1:
- The Role of Electrodiagnostic Testing, Imaging, and Muscle Biopsy in the Investigation of Muscle Disease / Laura K. Rosow, MD
- Autoimmune Myopathies / Andrew L. Mammen, MD, PhD
- Inclusion Body Myositis / Hannah R. Briemberg, MD, FRCPC

Hour 2:
- The Dystrophic and Non-dystrophic Myotonias / Valeria A. Sansone, MD
- Facioscapulohumeral Muscular Dystrophy / Jeffrey M. Statland, MD
- The Limb-Girdle Muscular Dystrophies and the Dystrophinopathies / John T. Kissel, MD, FAAN

Hour 3:
- Approach to the Patient with HyperCKemia / Shannon L. Venance, MD, PhD, FRCPC
- Toxic and Endocrine Myopathies / Hans D. Katzberg, MD
- Metabolic Myopathies / Mark A. Tarnopolsky, MD, PhD

Hour 4:
- An Overview of Congenital Myopathies / Jean K. Mah, MD, MSc, FRCPC
- Myasthenia Gravis and Lambert-Eaton Myasthenic Syndrome / Michael W. Nicolle, MD
- Genetic Testing of Pre-symptomatic Individuals at Risk for Progressive Myopathy: Ethical Considerations / Zachary Simmons, MD, FAAN

Continuum Audio is a biweekly audio CME program based on discussions with the authors of articles published in Continuum: Lifelong Learning in Neurology®, the official CME journal of the AAN. Continuum Audio is available in multiple formats, including apps for iOS and Android devices. This program may be used to meet self-assessment and CME requirements for maintenance of certification as mandated by the American Board of Psychiatry and Neurology. To learn more and subscribe, visit Audio-digest.org/Continuum.
**QUIETING MS** Quietly

* for your patients with relapsing MS

**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.

Please see additional Important Safety Information and Brief Summary of Full Prescribing Information, including **boxed WARNING**, on the following pages.
• Use in Women of Childbearing Potential:

• Hepatotoxicity:

WARNINGS AND PRECAUTIONS

• 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.

• Hypersensitivity and Serious Skin Reactions:

• Peripheral Neuropathy:

• Increased Blood Pressure:

• Bone Marrow Effects/Immunosuppression Potential/Infections:

IMPORTANT SAFETY INFORMATION (continued)

CONTRAINDICATIONS

• 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.

• 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 acute or chronic infections should not be started until the infection(s) is resolved.
to quieting* relapsing MS

2 trials impacting disability progression

- 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.1,3,4
- AUBAGIO 7 mg did not demonstrate a significant reduction in risk of sustained disability progression in either trial.1
- 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.1

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) once 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=408), or placebo (n=389) once 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.1,6

11.2% with AUBAGIO 7 mg, and 7.5% with placebo (n=389) once daily.1

AUBAGIO 14 mg (n=366), or placebo (n=363) once daily for 108 weeks.1

A UBAGIO 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.1,3,4

Health care professionals should run certain tests before prescribing AUBAGIO and should monitor patient liver enzyme levels monthly for the first 6 months.1

AUBAGIO is one tablet, once a day.1

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.1,2

RMS=relapsing forms of MS.

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

Brief Summary of Prescribing Information

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 (5.2), and Use in Specific Populations (8.1)].

1 INDICATIONS AND USAGE

AUBAGIO® is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

2 DOSAGE AND ADMINISTRATION

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

Monitoring to assess safety

• Obtain transaminase and bilirubin levels within 6 months before initiation of AUBAGIO therapy. Monitor ALT levels at least monthly for six months after starting AUBAGIO [see Warnings and Precautions (5.1)].
• Obtain a complete blood 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 to 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 twice 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. In clinical trials of AUBAGIO, cases of prolonged and severe transaminase increase greater than three times the ULN occurred in 0.6% of patients receiving AUBAGIO and 0.5% of patients receiving placebo. 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. An 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, 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 some other probable 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 be counseled on the potential for serious risk to the fetus. The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must notify the physician immediately for pregnancy testing and, if positive, be counseled for discontinuation of AUBAGIO therapy.

5.3 Procedure for Accelerated Elimination of Teriflunomide

Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, it takes on average 8 months to reach plasma concentrations less than 0.02 mcg/mL (0.02 mg/L). Human plasma concentrations of teriflunomide less than 0.02 mcg/mL (0.02 mg/L) are expected to have minimal risk [see Contraindications (4), Warnings and Precautions (5.1) and Use in Specific Populations (8.1)].

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 monitoring of teriflunomide plasma concentrations less than 0.02 mg/L (0.02 mcg/mL). Human plasma concentrations of teriflunomide less than 0.02 mcg/mL (0.02 mg/L) are expected to have minimal risk [see Contraindications (4), Warnings and Precautions (5.1) and Use in Specific Populations (8.1)].

The procedure for AUBAGIO is recommended in the postmarketing setting. Obtain a complete blood cell count (CBC) within 6 months before the initiation of the procedure. Notify the physician immediately for pregnancy testing and, if positive, the physician must discuss the option of continuing AUBAGIO with the patient and the 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)].

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.

5.4 Bone Marrow Effects/Immunosuppression Potential/Infections

Bone Marrow Effects

A mean decrease in white blood cell (WBC) count of approximately 15% (mainly neutrophils and lymphocytes) and in platelet count of approximately 10% was observed in placebo-controlled trials with 7 mg and 14 mg of AUBAGIO compared to baseline. The decrease in mean WBC count occurred during the first 6 weeks and WBC count remained low during treatment. In placebo-controlled studies, neutrophil count <1.5x10^9/L was observed in 12% and 18% of patients receiving AUBAGIO 7 mg and 14 mg, respectively, compared with 7% of patients receiving placebo; lymphocyte count <0.8x10^9/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 serious pancytopenia 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)]. A mean decrease in platelet counts less than 50,000/mm³ have been reported in the postmarketing setting. Obtain a complete blood count (CBC) within 6 months before the
initiation of treatment with AUBAGIO. Further monitoring should be based on signs and symptoms suggestive of bone marrow suppression.

Risk of Infection / Tuberculosis Screening

Patients with active acute or chronic infections should not start treatment until the infection is resolved. If a patient develops a serious 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 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 individuals with latent tuberculosis infection is unknown. For patients testing positive in tuberculosis screening, treat by standard medical practice prior to therapy with AUBAGIO.

Vaccination

No clinical data are available on the efficacy and safety of 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.

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 clearly not 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 polynuropathy 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% (17 patients) with confirmed peripheral neuropathy in 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, and +3.6 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.

6.6 Respiratory Effects

Intestinal lung disease, including acute intestinal pneumonitis, has been reported with AUBAGIO in the postmarketing setting. Intestinal lung disease and worsening of pre-existing intestinal lung disease have been reported during treatment with leflunomide. Intestinal 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)].

6. ADVERSE REACTIONS

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

- Bone marrow toxicity [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)]

5.1 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 (3.5% of 6.6% and 2.3% of all patients in the AUBAGIO 7 mg, AUBAGIO 14 mg, and placebo treatment arms, respectively).

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>AUBAGIO 7 mg</th>
<th>AUBAGIO 14 mg</th>
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<tbody>
<tr>
<td>Headache</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>Increase in ALT</td>
<td>13%</td>
<td>15%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13%</td>
<td>14%</td>
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<tr>
<td>Alopecia</td>
<td>10%</td>
<td>13%</td>
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<tr>
<td>Nausea</td>
<td>8%</td>
<td>11%</td>
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<td>Paresthesia</td>
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<tr>
<td>Arthralgia</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3%</td>
<td>4%</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 postmarketing 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 8/1045 (0.8%) patients in the 7 mg AUBAGIO group and 8/1002 (0.8%)
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, 18% 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.

- Hypersensitivity reactions, 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 (5.4)]
- Intestinal ulcer 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 theophylline

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 (craniofacial, axial and appendicular skeletal defects) and maternal toxicity. Maternal plasma exposure (primarily craniofacial, and axial and appendicular skeletal defects) and embryofetal death at doses associated with minimal maternal toxicity. Maternal plasma exposure (primarily craniofacial, and axial and appendicular skeletal defects) and embryofetal death at doses associated with maternal toxicity. Maternal plasma exposure (primarily craniofacial, and axial and appendicular skeletal defects) and embryofetal death at doses associated with maternal toxicity. Maternal plasma exposure (primarily craniofacial, and axial and appendicular skeletal defects) and embryofetal death at doses associated with maternal toxicity. Maternal plasma exposure (primarily craniofacial, and axial and appendicular skeletal defects) and embryofetal death at doses associated with maternal toxicity. Maternal plasma exposure (primarily craniofacial, and axial and appendicular skeletal defects) and embryofetal death at doses associated with maternal toxicity.
Speakers Named for 2017 Frontiers in Neuroscience Plenary Session

Five expert speakers will outline their recent findings, along with clinical implications, during the Frontiers in Neuroscience Plenary Session to be held Wednesday, April 26, from 9:15 a.m. to 11:30 a.m. during the AAN Annual Meeting in Boston.

Advances in Translational Research in Epilepsy
Amy Brooks-Kayal, MD
University of Colorado School of Medicine, Aurora, CO

Inherited Neuropathies
Mary Reilly, MD, FRCP, FRCP(C)
National Hospital for Neurology and Neurosurgery, London, United Kingdom

Amyloid-beta Protein Vaccine Therapy for Alzheimer’s Disease
Eliezer Masliah, MD
National Institute on Aging/National Institutes of Health, Bethesda, MD

Vesicle Communication in the Tumor-bearing Brain
Xandra O. Breakefield, PhD
Massachusetts General Hospital, Charlestown, MA

Lethal Microcephaly
M. Elizabeth Ross, MD, PhD
Weill Cornell Medical College, New York, NY

Presenters and titles are subject to change.
It’s Time to Renew Your Membership for 2017

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Membership

Continued from cover

Early Registration Deadline Approaching for January Breakthroughs Conference  
Continued from cover

Grand at Wild Horse Pass in Phoenix, AZ. This popular conference will offer a unique and convenient opportunity to get a year-in-review of the best neurology science and education; network with faculty and colleagues; and earn up to 28.5 CME, 11.25 of which qualify for self-assessment CME. Visit AAN.com/view/breakthroughs today to view the full program and to secure your spot.

Highlights:

- **New! Neuroscience in the Clinic Sessions**: Learn how to incorporate the latest scientific research into your daily practice. A mix of scientists and clinicians will present on real-life cases covering a variety of disease states.

- **New! Curbside Consults**: Bring your challenging cases to discuss one-on-one with an expert in aging/dementia, neuro-oncology, or movement disorders, offered from 3:15 p.m. to 4:15 p.m. within the Saturday Neuroscience in the Clinic sessions.

- **Best of the Annual Meeting**: Hear from top leading researchers within the Hot Topics and Controversies in Neurology Plenary Sessions.

- **Neurology MOC Prep Course**: Get help preparing for the ABPN recertification exam and earn 11.25 self-assessment CME.

- **Leadership for Women**: Gain inspiration and training to grow your leadership potential.

- **Practice Management Programs**: Discover the latest on MACRA and MIPS requirements.

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More Options

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Give Your Topiramate Patients MORE with Qudexy® XR!

<table>
<thead>
<tr>
<th>Qudexy® XR¹</th>
<th>Topamax® (topiramate) Tablets²</th>
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<tbody>
<tr>
<td>100% Extended-Release Bead Formulation</td>
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<td>Smooth Pharmacokinetic Profile</td>
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<td>FDA-Approved Sprinkle Administration Option in All Strengths</td>
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<td>$0 Co-Pay Offer*</td>
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<td>5 Dosage Strengths, Including 150 mg</td>
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*Eligible Patients Pay $0. Covers $200/Prescription, Maximum Annual Savings of $2,400.

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Now Accepting Applications for 2017 Diversity Leadership Program

Application Deadline: December 10

Applications are now open for the 2017 AAN Diversity Leadership Program. The prestigious program seeks to identify, orient, and cultivate high-potential members from diverse and underrepresented ethnic backgrounds who will be lifetime, engaged contributors to the Academy.

Up to 10 participants will be selected to engage with AAN leadership and staff, develop their own leadership skills, and contribute to a group project. Qualified applicants must be US AAN members belonging to one or more of the following race/ethnicity groups: African American/Black, Hispanic or Latino, American Indian, Native Hawaiian, or Alaska Native.

“The representation of underrepresented minorities in leadership at the AAN does not adequately reflect the membership nor the communities that its members serve,” said Jose G. Merino, MD, MPhil, FAAN, chair of the AAN Leadership Development Committee. “Exceptional nonprofits recognize that diversity is essential to the organization’s success. They understand that successful inclusive organizations must have people from diverse backgrounds in leadership roles. In addition, 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.”

Selected program participants to this prestigious and interactive eight-month program will receive:

- Introduction to the AAN structure and interaction with AAN leadership at the April 2017 AAN Annual Meeting in Boston
- Leadership training that will start with face-to-face meetings at the 2017 AAN Annual Meeting and continue over eight months with:
  - Monthly coaching conference calls with professional consultant and suggested readings and activities
  - Individual regular conversations with an AAN leader who will serve as a mentor for the program
  - Participation in a collaborative group project focused on strategies for the AAN’s diversification strategy that will be presented to the AAN Board at the fall 2017 meeting in Minneapolis

Added Merino, “Homogeneous leadership can result in nearsightedness and group think. The AAN recognizes and is committed to the idea that diverse leadership enhances the organization by offering a wider spectrum of views and cultural experiences. Such diversity will help the AAN meet the needs of its members and, as a result, their patients.”

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

Jose G. Merino, MD, MPhil, FAAN

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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 Teleneurology service that is affiliated with Massachusetts General Hospital. Central Maine Medical Center is the flagship hospital of Central Maine Healthcare. The medical center has 250 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, 200 Main Street, Lewiston, ME 04240. Fax: (207) 795-5696; email: MallozGi@cmhc.org, or call: (800) 445-7431. Not a J1 Opportunity.

Partnership Track Position in Princeton, NJ
Princeton Area Partners is seeking a BC/BE neurologist to join an established group of 6 neurologists. Opportunity, a light call schedule, a change of scenery or all of the above. This is a wonderful area of the state to raise a family. We are situated one hour from New York City, Philadelphia and the Jersey Shore. Visit our website at www.prneurology.com. Please fax CV to Audrey Leffberg, Practice Administrator at (732) 246-3089 or email aleffberg@prneurology.com

General Neurologist Practice Opportunity—UNC Health Care Affiliated Hospital
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Neurologists
Well-established, quality oriented neuroscience group seeks to add additional neurologists. Opportunity for subspecialists and general neurologist. We are a multidisciplinary neuroscience group providing a strong team oriented environment and opportunities for professional growth. Our location offers easy access to the cultural institutions of Boston, as well as outstanding private and public school opportunities. Send CV to Howard M. Gardner, MD, Medical Director, New England Neurological Associates, PC., RIVERWALK, 354 Merrimack Street, Lawrence, MA 01843, or email to jtf@theoneuro.com. Visit us on the web at www.neneuro.com.

Fellowship in Neuroimaging
Winchester Neurological Consultants, Inc., in conjunction with Virginia Commonwealth University and Winchester Medical Center, is offering a clinical Neuroimaging Fellowship for BC/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 gsteelie@winchesternerveurological.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><em>P</em>-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) ≥2 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><em>P</em>-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 12-week 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). Administer ZINBRYTA with caution to patients with previous or current depressive disorders. 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.


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Brief Summary for ZINBRYTA (daclizumab) injection, for subcutaneous use
Consult Full Prescribing 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. 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 case 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 gener ally 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 (5.3)].

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). If no other etiologies are identified, then discontinue ZINBRYTA. 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

- 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 in 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 placebo patients (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 0.5% of ZINBRYTA-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 levels (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, or 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 immunosuppressant drugs may be required. Some patients may need long-term immunosuppression.

Risk of Hepatic Injury with Concomitant Use of Other Hepatotoxic Drugs: Caution should be used when using hepatotoxic drugs, including non-steroidal anti-inflammatory drugs, 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% of 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-control 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 removal, 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 treatment with ZINBRYTA. Rashes occurred in 11% of ZINBRYTA-treated patients compared with 4% of AVONEX-treated patients 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. See Adverse Reactions (6.1). Pustular conditions occurred in 2% of ZINBRYTA-treated patients compared with 0.3% of AVONEX-treated patients. Photosensitivity also occurred.

Some 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). One death 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 (Studies 1 and 2), serious 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 interstitial lung changes [see Warnings and Precautions (5.5)]. 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, some serious, have occurred infrequently with the use of ZINBRYTA. 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)].
- Prescribers 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)].
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 patients 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)]. Administer ZINBRYTA with caution to patients with previous or current depressive disorders. Advise patients and/or caregivers to immediately report any symptoms of new or worsening depression and/or suicidal ideation to their healthcare provider. If a patient develops severe depression and/or suicidal ideation, consider discontinuation of ZINBRYTA.

**6 ADVERSE REACTIONS**

The following serious adverse reactions are described elsewhere in labeling:

- **Hepatic Injury** [see Warnings and Precautions (5.1)]
- **Immune-Mediated Disorders** [see Warnings and Precautions (5.2)]
- **Acute Hypersensitivity** [see Warnings and Precautions (5.4)]
- **Infections** [see Warnings and Precautions (5.5)]
- **Depression and Suicide** [see Warnings and Precautions (5.6)]

**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, every 4 weeks) 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, oropharyngeal 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. Hematology was evaluated at baseline, monthly for 6 months, and then every 3 months. Thyroid function was measured at baseline and every 6 months.

**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>
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</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>25</td>
<td>21</td>
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<tr>
<td>Upper respiratory tract infection¹</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Rash¹</td>
<td>11</td>
<td>4</td>
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<tr>
<td>Influenza</td>
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<td>6</td>
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<tr>
<td>Dermatitis¹</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>
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<tr>
<td>Eczema¹</td>
<td>5</td>
<td>2</td>
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<tr>
<td>Lymphadenopathy</td>
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<td>&lt;1</td>
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<td>Tonsillitis</td>
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<tr>
<td>Acne</td>
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</table>

¹ includes upper respiratory tract infection and viral upper respiratory tract infection

**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>Depression¹</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Rash¹</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>
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<td>Rhinitis</td>
<td>4</td>
<td>1</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>Dermatitis¹</td>
<td>3</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

¹ includes depressed mood and depression

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

Other clinically relevant adverse reactions observed at <2% difference included abnormal liver function test, decreased lymphocyte 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.
Seizures: In Study 1, seizures occurred in 1% of ZINBRYTA-treated patients, compared with 0.3% of AVONEX-treated patients. In Study 2, no seizures occurred in either treatment group.

Immune-Mediated Disorders: Types of immune-mediated or autoimmune conditions that were observed in 2 or more ZINBRYTA-treated patients include type I diabetes, celiac disease, autoimmune thyroiditis, immune hemolytic anemia, thrombocytopenia, pancreatitis, glomerulonephritis, sarcoidosis, rheumatoid arthritis, thyroiditis, and sialadenitis [see Warnings and Precautions (5.2)]. The relationship of these events to ZINBRYTA is unknown.

Breast Cancer: In controlled studies, 1 ZINBRYTA-treated woman developed breast cancer compared with none in the AVONEX-treated group. Across all controlled and open-label clinical studies, 8 of 1485 (0.5%) ZINBRYTA-treated women developed breast cancer, and 1 of 751 (0.1%) ZINBRYTA-treated men developed breast cancer. It is unclear whether this represents an incidence increase over background rate.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. In Study 1, patients were tested for anti-drug (daclizumab) antibodies at Week 4 and approximately every 3 months thereafter. Anti-drug antibodies and neutralizing antibodies were observed in 19% (175/913) and 8% (71/913) of patients, respectively. Anti-drug antibody responses were transient in 12% (110/913) of patients and persistent in 7% (65/913) of patients. Anti-drug and neutralizing antibody responses predominately occurred during the first year of treatment, and their frequency declined with continued ZINBRYTA treatment. In patients with neutralizing antibodies, daclizumab clearance was increased on average by 19% [see Clinical Pharmacology (12.3)]. There was no apparent correlation of anti-drug antibody or neutralizing antibody development to clinical response, adverse reactions, or pharmacodynamic profile of ZINBRYTA. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to daclizumab in the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

7.1 Hepatotoxic Drugs

Caution should be used when using hepatotoxic drugs, including non-narcotic analgesics, anticonvulsant drugs, and potent inducers of the cytochrome P450 system that can affect the metabolism of ZINBRYTA to daclizumab. Caution should also be used when using drugs that can cause immune-mediated or autoimmune 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)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary: There are no adequate data on the developmental risk associated with use of ZINBRYTA in pregnant women. Administration of ZINBRYTA to monkeys during gestation resulted in embryofetal death and reduced fetal growth at maternal exposures greater than 30 times that expected clinically [see Data]. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data: Animal Data: In monkeys administered ZINBRYTA (0, 10, 50, or 200 mg/kg) weekly by subcutaneous injection during organogenesis (gestation day 20 through 50), there was a decrease in fetal body weight and crown-rump length, and an increase in embryofetal death at the highest dose tested. Plasma exposure (AUC) at the no-effect dose of 50 mg/kg was approximately 30 times that in humans at the recommended human dose (RHD) of 150 mg. In monkeys administered ZINBRYTA (50 mg/kg) weekly by subcutaneous injection from gestation day 50 to birth, there were no effects on pre- or postnatal development for up to 6 months after birth. Plasma exposure (AUC) at the administered dose was 55 times that in humans at the RHD.

8.2 Lactation

Risk Summary: There are no data on the presence of daclizumab in human milk, the effects on the breastfed child, or the effects of the drug on milk production. Daclizumab was excreted in the milk of ZINBRYTA-treated monkeys. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ZINBRYTA and any potential adverse effects on the breastfed child from ZINBRYTA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of ZINBRYTA in patients less than 17 years old have not been established. Use of ZINBRYTA is not recommended in pediatric patients due to the risks of hepatic injury and immune-mediated disorders [see Warnings and Precautions (5.1, 5.2)].

8.5 Geriatric Use

Clinical studies of ZINBRYTA did not include a sufficient number of patients aged 65 and over to determine whether they respond differently than younger patients.

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)].

17 PATIENT COUNSELING INFORMATION

Advise 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)].

Discuss with the patient the importance of measuring hepatic laboratory values and having the hepatitis virus antibody test performed 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. Inform 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)].

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)].

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 (5.2)].

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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05/2016 ZIN-US-0466
## Dates and Deadlines

### NOVEMBER 2016

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**November 8**
Webinar: Getting the Most Out of Your Technology: HIT and Your Patients
(Register by November 7)
AAN.com/view/pmw16

**November 17**
FREE Webinar: What Do the Elections Mean for Your Practice?

**November 20**
Application Deadline: 2017 Neurology on the Hill
AAN.com/view/2017NOH

**November 30**
Application Deadline: Fellow Scholarship to the Annual Meeting
http://tools.aan.com/science/awards/?fuseaction=home.info&id=85

**November 30**
Nomination Deadline: Resident Scholarship to the Annual Meeting
AAN.com/research-and-awards/resident-scholarship-to-the-annual-meeting

**November 30**
Nomination Deadline: Program Director Recognition Award
http://tools.aan.com/science/awards/?fuseaction=home.info&id=40

**November 30**
Application Deadline: Program Coordinator Recognition Award
http://tools.aan.com/science/awards/?fuseaction=home.info&id=86

### DECEMBER 2016

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

**December 1**
Registration Deadline: RITE® (Residency In-service Training Examination) Exam
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 2017

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

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

### SAVE THE DATES

**January 13–16, 2017**
Breakthroughs in Neurology, Phoenix, AZ
AAN.com/view/Breakthroughs

**April 22–28, 2017**
AAN Annual Meeting, Boston
AAN.com/view/AM17