Breakthroughs in Neurology Conference Registration Opens This Month

Registration opens this month for the Breakthroughs in Neurology Conference, set to take place January 13 through 16, 2017, at the Sheraton Grand at Wild Horse Pass in Phoenix, AZ. This popular conference offers a unique and convenient opportunity to earn valuable CME credits in one weekend while getting a year-in-review of the best neurology science and education.

Early registration savings end December 1, so visit AAN.com/view/Breakthroughs today to learn more, view the full program listing, and secure your spot with deep discounts.

Submit Abstracts for 2017 Annual Meeting by October 24

Abstract submission is now open for the 2017 AAN Annual Meeting, to be held in Boston, MA, April 22 through 28. Abstracts are accepted in all areas of neurology and neuroscience and submissions are due by no later than 11:59 p.m. CT on October 24.

Visit AAN.com/view/17Abstracts to submit an abstract and to complete the online form. For more information, contact science@aan.com or (612) 928-6088.

Applications are now open for more than 25 prestigious AAN awards representing the most esteemed recognition of scientists—at all stages of their careers—who have made the most notable advancements in the field of neuroscience. Nominate a well-deserving colleague or apply yourself today. Awards are available for outstanding research contributions across a variety of disease states and career stages including:

Continued on page 5

Applications Now Open for Prestigious 2017 AAN Scientific Awards

Continued on page 11

How the Merit-based Incentive Payment System Will Affect Solo and Small Practices

Grow Your Small Practice—Webinar Shows How

September 8 Is Last Chance to Save $100 on Fall Conference Registration

Get Your Career in Gear with Help During Neurology Career Week

THIS ISSUE

April 22 – April 28 • Boston
# Table of Contents

<table>
<thead>
<tr>
<th>COVER</th>
<th>Breakthroughs in Neurology Conference Registration Opens This Month Submit Abstracts for 2017 Annual Meeting by October 24 Applications Now Open for Prestigious 2017 AAN Scientific Awards</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRESIDENT’S COLUMN</td>
<td>3 We Want YOU to Live Well</td>
</tr>
<tr>
<td>MEET YOUR LEADER</td>
<td>4 Stefan M. Pulst, MD, FAAN</td>
</tr>
<tr>
<td>PRACTICE</td>
<td>5 Successful Axon Registry Moves to Next Phase 6 How the Merit-based Incentive Payment System Will Affect Solo and Small Practices 7 Grow Your Small Practice—Webinar Shows How 8 Raphaelson to Serve on CMS Clinical Committee 8 AAN and UCNS Successfully Appeal Neurocritical Care Taxonomy Code</td>
</tr>
<tr>
<td>CONFERENCES</td>
<td>10 Sports Concussion Conference Draws Record Attendance 11 September 8 Is Last Chance to Save $100 on Fall Conference Registration</td>
</tr>
<tr>
<td>CME &amp; MOC</td>
<td>12 Listen to Neuroimaging Experts in Continuum Audio</td>
</tr>
<tr>
<td>RESEARCH &amp; AWARDS</td>
<td>13 October 1 AAN Research Program Application Deadline Approaching 13 Neurology Tests New Publishing Approach</td>
</tr>
<tr>
<td>MEMBERSHIP</td>
<td>14 Industry Partners Help Drive Improvements for Your Patients, Practice, and Profession 15 Apply for Neurology Today Editor-in-Chief by October 31 16 Congratulations to 2016 Diversity Leadership Program Graduates! 16 Get Your Career in Gear with Help During Neurology Career Week 16 AAN Credit Card Pays</td>
</tr>
<tr>
<td>PUBLIC POLICY</td>
<td>24 Capitol Hill Report</td>
</tr>
<tr>
<td>AMERICAN BRAIN FOUNDATION</td>
<td>25 Fellowship Allows Researcher to Apply New Imaging Techniques to Understand Memory Development in Children with Epilepsy</td>
</tr>
<tr>
<td>CAREERS</td>
<td>28</td>
</tr>
<tr>
<td>DATES AND DEADLINES</td>
<td>36</td>
</tr>
</tbody>
</table>

# NEWS BRIEF

Qualified experts are needed to review the biostatistical aspects of articles submitted to Neurology®. Experts should specialize in biostatistics with a background in experimental design and the review of randomized clinical trials, observational studies, genetic studies, and imaging studies in the neurodegenerative diseases. If interested, send CV to Morgan Sorenson at msorenson@neurology.org.
We Want YOU to Live Well

How can the AAN help more neurologists be satisfied in their jobs?

That has been a nagging question among Academy leaders for several years. We are the preeminent organization for neurologists and serve our members with an array of programs, services, and products that help you do your job better today than yesterday—and better tomorrow than today. And while these benefits may help make your job easier and enable you to be more effective in treating your patients, they don’t necessarily help you be more satisfied with your work.

We know all too well that the myriad regulatory hassles that practicing neurologists face daily take valuable time away from the reason you became a neurologist in the first place—to treat your patients. The constantly changing reporting requirements, introduction of new payment policies, and requirements for maintenance of certification can make one feel overwhelmed, frustrated, and angry. The burden of these feelings, whether conscious or subconscious, can extinguish one’s passion for our profession, and help lead to burnout.

In 2015, we launched a task force to research the issue of physician burnout—what it is, how it happens, and what can be done to deal with it effectively and improve work-life balance for our members.

Burnout is common in all practice settings and all subspecialties, but neurologists are more highly susceptible to burnout. Neurology is the only medical specialty that has both one of the highest rates of burnout and the lowest rate of work-life balance.

Burnout is described as lack of well-being due to a poor work-life balance. A sense of low personal accomplishment. A feeling of emotional exhaustion and depersonalization that can lead to the loss of interest and enthusiasm for practicing medicine.

Burnout is a significant problem in neurology, and it’s getting worse over time. Practicing neurologists experiencing burnout may not meet their potential in their jobs and their private lives. This may cause suboptimal clinical judgment, lack of empathy with patients, lack of career satisfaction, and health problems, and exacerbate work-life conflicts.

This problem impacts the health of our overall specialty, too, as more neurologists may leave practice early, fewer may enter neurology as a career choice. And since we already are facing a shortage of neurologists, this affects access to care.

We divided our task force into two groups. One, co-chaired by AAN Board member Neil A. Busis, MD, FAAN, a former chair and current member of the AAN’s Medical Economics and Management Committee, and Kerry H. Levin, MD, member of the Education Committee, studied this burnout issue intensively. The Academy randomly surveyed 5,000 US members this past winter and had a very high participation rate of 40 percent—which suggested this issue struck a chord among our members. The results of the survey are still in the process of being prepared for publication and we will use this data as leverage in our policy and advocacy discussions.

The other group of task force members led by Jennifer R. Molano, MD, FAAN, a member of the Member Engagement Committee, and Board member and Practice Committee Chair Heidi B. Schwarz, MD, FAAN, addressed how to mitigate burnout. They identified the three main sources of burnout: regulatory, workplace, and the individual. Then they set about to research and gather tools, strategies, and resources to help members prevent and mitigate burnout.

Continued on page 9
Meet Your Leader

Stefan M. Pulst, MD, FAAN

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

Stefan M. Pulst, MD, FAAN, is professor and chair of the department of neurology at the University of Utah in Salt Lake City. He was the founding chair of the AAN Section on Neurogenetics and the Basic Science Subcommittee. Pulst also served as a member of the AAN Science Committee—where he was chair from 2006 to 2011—and on the editorial board of Continuum: Lifelong Learning in Neurology®. He is the founding editor of Neurology® Genetics and currently serves on the AAN Board of Directors and as chair of the Meeting Management Committee.

What moved you to join the Board of Directors?

As chair of the Science Committee, I was occasionally invited to present at the Board of Directors meeting. While there, I was impressed by the professional atmosphere, collegiality, and diversity of opinions in the discussions about performance of the AAN and the development of a strategic vision for the future. I joined in the hope that I would be able to contribute and expand the discussions of the Board.

What experiences and viewpoints do you bring to this role?

I have served on a number of AAN committees, subcommittees, and task forces. These activities have provided me with an in-depth view of the AAN. I also bring to the Board experience as a chair of a neurology department, as a physician-scientist, and a journal editor.

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

The two opinions I hear most often are: the AAN is only for “academicians” or the AAN is only for “practicing neurologists.” Few neurologists are aware of the breadth of the AAN’s involvement in advocacy, education, and science. Membership in the Board of Directors has been diversified even in the six years that I have been part of it, but of course we could do more throughout the entire organization. In the end, misconceptions are best removed by better communication of our activities and by active participation of members.

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

Neurology now is a field with many plots ranging from care delivery to education and neuroscience. The AAN is the only organization in the US that represents neurologists working in these different areas. The AAN is also in the unique position to advocate for these different types of neurologists ranging from supporting increased NIH funding for neurological disease to organizing Neurology on the Hill. In addition, the AAN plays an increasingly important role in the global dialogue about neurology and neuroscience. Our Annual Meeting now has participation by neurologists from all over the world and has grown to be the largest neurology meeting worldwide.

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

The AAN is a multi-faceted organization serving members with very different backgrounds and professional roles. A good yardstick to evaluate success may be to evaluate whether the AAN provides the tools and the communities for one’s specific interest. The best way to achieve success, however, is for members of all backgrounds and interests to get involved with the AAN and join task forces or committees.

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

I experience work and personal life like an interwoven fabric. My work itself provides enormous and varied intellectual stimulation be it in the laboratory, in administration, or seeing patients. Everyone in my immediate family is in medicine, which blurs the work-life separation further. My wife and I love to travel and occasionally find the time to play chamber music together. And for something completely different, I enjoy playing soccer with our residents and with other more age-appropriate groups.
Successful Axon Registry Moves to Next Phase

In 2015, the AAN launched the first of four Axon Registry™ pilot cohorts in order to test technology that was said to extract quality data directly from the electronic medical record and provide feedback to physicians on their performance. The Axon Registry pilot aimed to test this technology as well as gauge member interest in quality data. With this initial phase now winding down, Registry Committee Chair Bruce Sigsbee, MD, FAAN, expressed satisfaction with the process and lessons learned. He believes we are ready to move toward a measured implementation. 

“I want to thank the practices and hundreds of AAN members who participated in these cohorts and put the Axon Registry through its paces. These early adopters of this crucial new platform for measuring and reporting quality care have done a great service for the AAN and for their colleagues who will follow.”

Currently, the Axon Registry has data from 66 practices, representing solo, small, academic medical centers, and health systems. That’s well over the 24 practices we aimed for in the pilot phase. Diversity also increased further by adding more pediatric practices alongside the adult neurology practices. In addition, the registry is extracting data from 19 different electronic health record (EHR) vendors. “To be sure, not all EHR vendors are quite so easy to work with, but the Axon Registry’s technology vendor is paving a path for better integration in the future,” said Sigsbee.

The testing phase revealed some significant lessons:

- It is possible for the software to query and extract data from text fields, notes, and hard-wired data fields; analyze the data; and report back to the users.
- Of the three data transfer methods, the pull method is the most seamless and straightforward. The push method requires significant work on behalf of the participant. Direct EHR transfer revealed some challenges as some EHRs have a lack of interoperability with registries.
- The mapping process is an important step. The practice physician champion and staff must work with the technology vendor to ensure the registry is finding the measure requirements in the practice documentation and must continue until the practice is confident that its provider documentation is accurately represented by the performance rates.
- Practices with EHRs using discrete data fields and practices using free text dictation can quickly complete their mapping calls and become fully integrated in the Axon Registry.
- The amount of data is astounding; in a rather short time frame we have data on over 1 million patient visits and over 355,000 unique patients.
- Approval as a qualified clinical data registry by CMS was essential to provide AAN members with an easy way to submit quality data to CMS and enable neurologists to participate in future Medicare value-based payment programs, such as those contained in MACRA.
- The measures matter and the ability of the data to be extracted from a variety of EHRs is essential.

Sigsbee noted that there are reports already from participants that the Axon Registry is beginning to deliver on its goal. “Overall, practices are learning the registry measures and measure performances are improving. During our registry User Group meetings, we have heard inspiring quality improvement efforts from practices. Currently, we are assessing measure and registry performance from the pilot. As others have advised us, the registry benefits to members and the AAN will exceed current projections.”

Applications Now Open for Prestigious 2017 AAN Scientific Awards

Continued from cover

- Potamkin Prize for Research in Pick’s, Alzheimer’s, and Related Diseases
- John Dystel Prize for Multiple Sclerosis Research
- Sheila Essey Award: An Award for ALS Research
- New! The Irwin Schatz Award for Autonomic Disorders
- Medical Student Essay Awards
- More

In addition to career-enhancing recognition, AAN awards offer prizes and other compensation, such as complimentary travel and registration for next year’s Annual Meeting in Boston. Visit AAN.com/view/17Awards to apply—or nominate a colleague—by the October 26, 2016, deadline.
How the Merit-based Incentive Payment System Will Affect Solo and Small Practices

The implementation by the Centers for Medicare & Medicaid Services (CMS) of the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) has led to the creation of two new payment systems for physicians: the Merit-based Incentive Payment System (MIPS) and Alternative Payment Models (reported on in the July AANnews).

MIPS is the payment program that most neurologists will enter into on the proposed start date of January 1, 2017. It combines three existing quality programs that may be familiar to you—PQRS, VBPM, and Meaningful Use of Electronic Health Records (MU)—into a single performance program, and adds one brand new component: Clinical Practice Improvement Activities (read the August AANnews to learn more about CPIAs). Under MIPS, each provider (or group) will receive a single composite performance score based on achievements in these four areas. Each area is weighted differently, and the weights change over time.

Since payment adjustments are made two years after the reporting period for now, implementation of MIPS begins in 2017 when data is being collected, with resulting payment adjustments starting in 2019.

### Composite Performance Score Weighting Over Time

<table>
<thead>
<tr>
<th>MIPS Category</th>
<th>2019*</th>
<th>2020</th>
<th>2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality (formerly Physician Quality Reporting System or PQRS)</td>
<td>50%</td>
<td>45%</td>
<td>30%</td>
</tr>
<tr>
<td>Resource Use (formerly Value-based Payment Modifier or VBPM)</td>
<td>10%</td>
<td>15%</td>
<td>30%</td>
</tr>
<tr>
<td>Advancing Care Information (formerly Meaningful Use of EHR or MU)</td>
<td>25%</td>
<td>25%**</td>
<td>25%**</td>
</tr>
<tr>
<td>Clinical Practice Improvement Activities (new)</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Total Composite Performance Score</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

* Data collection occurs two years prior (e.g., data collection for 2019 program is in 2017).

**ACI weight can drop to 15% if more than 75% of EPs are successful.

As can be seen in the table, there is an increasing emphasis on resource use (costs) over time. Note that the proportion of the CPS for quality measurement decreases in proportion to the increase of the values for costs.

The AAN Axon Registry™ has been approved by CMS as a qualified clinical data registry. This designation allows participants in the Axon Registry to submit neurology-specific measures to CMS for PQRS and, over time, also meet reporting requirements for the other MIPS components.

### MIPS Payment Adjustments

<table>
<thead>
<tr>
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<th>2019</th>
<th>2020</th>
<th>2021</th>
<th>2022</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum Bonus</strong></td>
<td>+4%*</td>
<td>+5%*</td>
<td>+7%*</td>
<td>+9%*</td>
</tr>
<tr>
<td><strong>Maximum Penalty</strong></td>
<td>-4%</td>
<td>-5%</td>
<td>-7%</td>
<td>-9%</td>
</tr>
</tbody>
</table>

* MIPS payments are budget neutral, meaning that penalty payments must be offset by bonus payments under the MIPS program. Therefore, exceptional performers may be eligible for an additional 3x bonus in order to maintain budget neutrality of the program (winners and losers). A scaling factor will never be applied to penalty amounts.

### Three Exemptions from the MIPS Program

1. The physician is in the first year of participating in the Part B Medicare program.
2. The physician provides care for 100 or fewer Medicare beneficiaries and has $10K or less in Medicare charges during the calendar year.
3. The physician is a qualifying participant in an eligible advanced alternative payment model (APM).

The AAN continues to develop tools and resources to help guide you through these evolving changes. Visit AAN.com/view/MACRA today to learn more and prepare yourself for the changes coming in 2017.

### AAN Represents Neurologists’ Concerns About MIPS

After analyzing the proposed rule issued by CMS, the AAN responded with a comment letter to the acting director outlining needed changes to the proposals for the MIPS and Alternative Payment Model (APM) payment pathways. While the new programs offer more flexibility, in some areas there remains an unnecessary level of complexity and burden, especially on smaller physician groups (one to five neurologists), which include 30 percent of US neurologists.

The letter outlined areas where CMS’s proposal may unreasonably impact small and solo neurologists and practical steps the agency can take in the final rule to alleviate the challenges facing these physicians. The Academy called on CMS to demonstrate its commitment to high-quality, patient-centered care, by taking every step necessary to protect small and solo practices in the final rule. The AAN strongly recommends that CMS strive to limit administrative burdens and streamline reporting tasks so that the delivery of patient-centered care is the principal focus in all clinical settings. The final rule is expected to be released on or around November 1, 2016.
Across the spectrum of neurology, Continuum is central to your education and practice.

When questions arise, rely on Continuum: Lifelong Learning in Neurology® as the most comprehensive and authoritative go-to resource for the practicing neurology professional.

- Each issue delivers the latest expert knowledge concentrated on a specific neurologic topic, with all major topics covered in a 3-year cycle.
- Access to the Continuum archive unlocks a treasure trove of reliable information to help you provide the best care throughout the continuum of your career.
- If you need CME or maintenance of certification credits for self-assessment, Continuum can help you earn while you learn.

Subscribe or renew today and receive 65% off with your AAN member discount at LWW.com/continuum.
AAN and UCNS Successfully Appeal Neurocritical Care Taxonomy Code

Since 2014, the AAN and the United Council for Neurologic Subspecialties (UCNS) have been working hard to secure recognition of UCNS subspecialties by the National Uniform Claim Committee (NUCC). In collaboration with the Neurocritical Care Society and Society for Neuroscience in Anesthesiology and Critical Care, the AAN and UCNS have been resolute in applying for and obtaining recognition of Neurocritical Care as a subspecialty of neurology as well as the creation of a unique taxonomy code in the NUCC Health Care Provider Taxonomy code set, which may be a prerequisite for inclusion on the Medicare Physician Specialty Codes list. While the application was initially denied by the NUCC, the AAN and UCNS filed and successfully won a formal appeal.

In May, the AAN and UCNS received notice from the NUCC that the application for a Neurocritical Care taxonomy code was approved. The approved code and definition is as follows:

### 2084A2900X Neurocritical Care

The medical subspecialty of Neurocritical Care is devoted to the comprehensive, multisystem care of the critically-ill neurological patient. Like other intensivists, the neurointensivist generally assumes the primary role for coordinating the care of his or her patients in the ICU, both the neurological and medical management of the patient. They may also provide consultative services for these patients as requested within the health system.

The code is included in the July 1, 2016, release of changes to the code set and will go into effect on October 1, 2016.
We Want YOU to Live Well

Your health matters to the AAN and we’re here to help. First, I hope you recognize that we are doing everything we can on the health policy front to decrease your regulatory hassles and limit the impact of new policy issues, reporting requirements, and reimbursement changes. We also have had some success in advocating to decrease the burden of maintenance of certification and we made related education programs free for members to lessen the financial hardship. Please know that each day, AAN staff and member volunteers are fighting on your behalf to make it easier to be a successful neurologist. Change may be slow and incremental, but we do not give up.

In the meantime, we want you to be aware that it is possible to prevent burnout as well as restore well-being. Today, I’m happy to report that we have launched our new webpage at AAN.com/LiveWell with a range of resources to provide you with tips, tools, and strategies for cultivating well-being and resiliency in your life.

We know that one size does not fit all, so we have compiled a variety of didactic and interactive resources to help address regulatory, workplace, and individual frictions that spark burnout. We are planning to offer programs through our Leadership University at the 2017 Annual Meeting that will help you become a resilient leader and recapture the joy of practicing neurology. And we’re looking into convening a conference dedicated to mitigating burnout and promoting a stronger sense of well-being.

I’m also pleased to tell you that the AAN is far ahead of many other specialties and organizations in recognizing that burnout is a crisis in our midst that must be understood and addressed if we are going to be the best we can be for our patients, our families and colleagues, and our selves.

This happened because the AAN listens to its members. We exist to serve you and we care about you. And even though we already are fighting against these regulatory hassles that contribute to burnout, we knew we had to take more direct action in this area for more immediate solutions. The fact that there was more member interest for participating on our task force than there were spaces available assured us that this focus is necessary. There is tremendous determination and passion among the members on the task force to understand this problem and take the necessary steps to help solve it.

While the Academy continues to tackle the overarching regulatory issues, each of us has a personal and professional responsibility to be true to the ancient proverb, “Physician, heal thyself.” Because only when we are more whole and fully engaged and satisfied—at work, at home, and in our communities—can we have the best assurance that we will, indeed, be able to fully take care of others.

Please look into the resources we are providing at AAN.com/LiveWell. We also want you to share your experiences and suggestions on how deal with stress and refresh yourself. Whether it’s a success story about resiliency or an idea you wish to share, we want to hear it! Your feedback is invaluable as we strive to make our well-being resources meaningful and relevant to you.

Let me know if there are policy changes we should fight for—or against—to make your jobs easier, if there are other effective programs and tools that we should add, and if there are more ways the AAN can help you be more satisfied in your job.

We want to help you Live Well! •

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

Live Well
Taking Care of Your Patients Starts with Taking Care of You
AAN.com/LiveWell
Sports Concussion Conference Draws Record Attendance

The July AAN Sports Concussion Conference was a huge success, drawing a record number of attendees. More than 500 athletic trainers, physical therapists, sports medicine professionals, and neurologists convened in Chicago to discover the very latest evidence-based science for the diagnosis and management of sports concussion at the high school, collegiate, and professional levels. The multidisciplinary turnout demonstrates the interest in and support for the fact that treating concussion is a team-based approach. This year’s new Boot Camp, which kicked off the meeting, proved to be a major draw and offered attendees a chance to apply the latest diagnosis and treatment of concussion protocols, understand post-concussion syndrome and how the field is moving beyond complete rest and toward more active rehab, and better understand the continuum of the concussion model from prevention to monitoring to recovery.

See What Attendees Were Saying!

AAN Concussion PSA Among Most Top 10 Played in 2015

The AAN’s Sports Concussion public service announcement (PSA) featuring former Super Bowl champion and sports concussion advocate Ben Utecht was among the top 10 most played PSAs in the United States for 2015, according to Nielsen. Although the program officially ended in January 2016, the PSA continues to run. The PSA has been nationally broadcast on TV more than 25,000 times reaching an audience of more than 307 million people, which is the equivalent of more than $3.4 million in advertising value.
Why Should You Submit Your Abstract(s) to the 2017 Annual Meeting?

Stefan M. Pulst, MD, FAAN, chair of the Meeting Management Committee, sat down with Science Committee Chair Lisa M. DeAngelis, MD, FAAN, to learn more about 2017 Annual Meeting abstract submissions.

**Pulst:** What is unique about submitting abstracts to the AAN meeting versus other meetings?

**DeAngelis:** The AAN Annual Meeting is the premier place to present research in neurology because it brings people together from all around the world, from a wide variety of specialties. You can expect to collaborate with a diverse group of peers to further your work and gain exposure for your research. AAN abstracts are also often picked up by major media outlets including the *New York Times, USA Today, CNN, Associated Press,* and many more.

Plus, the location of this year’s meeting is ideal. Boston is such a great, historic city with so much to see and do!

**Pulst:** What are some of the new topic areas for 2017?

**DeAngelis:** While abstracts are accepted in all areas of neurology and neuroscience, we will be introducing new Neuroscience in the Clinic Sessions and will be seeking abstracts on concussion, neuroendocrinology, critical care, vision and neurodegeneration, Zika virus, functional recovery, and language and neurobiology.

**Pulst:** Are we still accepting previously presented work?

**DeAngelis:** Yes. While original research is emphasized, submission of previously presented work is encouraged if it is of interest to the field of neurology.
Reviews of neuroimaging in conditions ranging from brain tumors and spinal cord disorders to epilepsy and stroke are discussed along with a general overview of various types of imaging in the latest Continuum® Audio series.

“Practicing neurologists will find this series a great resource in helping them interpret imaging studies,” said Continuum Associate Editor and host of the Continuum Audio series Joseph S. Kass, MD, JD, FAAN, of Baylor College of Medicine in Houston, TX. "Our guest editors have chosen expert authors to provide a wide review of neuroimaging divided by disease type and location within the central nervous system. In addition to thorough discussions of MRI and CT based imaging, listeners will also hear clinically relevant discussions of gadolinium safety as well as other imaging modalities such as SPECT, PET, and ultrasound."

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

Hour 1:
- Introduction to Magnetic Resonance Imaging for Neurologists / Ernst-Wilhelm Radue, MD
- Positron Emission Tomography and Single-Photon Emission Computed Tomography in Neurology / Robert S. Miletich, MD, PhD, FAAAS
- Ultrasound in Neurology / Andrei V. Alexandrov, MD, RVT
- Safety Considerations in Magnetic Resonance Imaging of Patients With Implanted Medical Devices / Marcus Ponce de Leon, MD, FAAN

Hour 2:
- Imaging of Ischemic Stroke / David S. Liebeskind, MD, FAAN
- Imaging of Hemorrhagic Stroke / Ryan Hakimi, DO, MS
- Imaging for Adults With Seizures and Epilepsy / Gregory D. Cascino, MD, FAAN
- Imaging of Congenital Malformations / Jennifer W. McVige, MA, MD

Hour 3:
- Imaging of Brain Tumors / Laszlo L. Mechtler, MD, FAAN
- Imaging of Intracranial Cysts / John A. Bertelson, MD
- Imaging of Pituitary and Parasellar Disorders / Ajay Abad, MD
- Legal Implications for Physician Investment and Ownership in Health Care Enterprises / Joseph S. Kass, MD, JD, FAAN

Hour 4:
- Imaging in Patients With Visual Symptoms / Gabriella Szatmary, MD, PhD
- Imaging of Spinal Cord Disorders / Laszlo L. Mechtler, MD, FAAN
- Imaging of Central Nervous System Demyelinating Disorders / Konstantin Balashov, MD, PhD, FAAN
- Potential Safety Issues Related to the Use of Gadolinium-based Contrast Agents / Nandor K. Pinter, MD

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.
October 1 AAN Research Program Application Deadline Approaching

October 1 is the last chance to apply for one of the following prestigious AAN awards, including two new, large-scale awards, which mark the AAN’s pledge to support all types of research across all career levels and discovery stages:

- **NEW! $450,000 Career Development Award**
  - Provides $150,000 per year for three years. Eligible applicants will have completed residency within five to 10 years of the July 1, 2017, award start date.

- **NEW! $130,000 Neurology Research Training Scholarship**
  - Provides $65,000 over two years. The award is designed for basic and translational research proposals in neurology, and eligible applicants will have completed residency no more than five years prior to the July 1, 2017, award start date.

- Clinical Research Training Scholarship
- Practice Research Training Scholarship
- Clinician-Scientist Development Three-Year Award in ALS Research
- Clinical Research Training Fellowship in ALS
- Robert Katzman Research Training Fellowship in Alzheimer’s and Dementia Research
- Research Training Fellowship in Ataxia
- Susan S. Spencer Clinical Research Training Fellowship
- Clinical Research Training Fellowship in Epilepsy
- Clinical Research Training Fellowship in Muscular Dystrophy
- Clinical Research Training Fellowships in Parkinson’s Disease
- Clinical Research Training Fellowship in Tourette Syndrome

For more information and to apply, visit AAN.com/view/ResearchProgram.

Neurology Tests New Publishing Approach

“**What is the journal of the future? What do readers want?**”

With the Neurology® journal due for redesign, the Academy’s editorial and publishing teams began discussions last year about publishing trends and meeting readers’ needs. They talked to various journal editors in the field and explored working examples of some of the latest industry changes.

The results of these efforts will be evident to recipients of the September 6 issue of Neurology. They will get to experience the new “electronic long, paper short” (ELPS) approach the journal is piloting. The ELPS concept introduces flexibility in content presentation and weds print and electronic media to deliver more of what readers want: shorter articles that can be consumed quickly in print, with longer versions of the same articles or additional imagery online, where readers can dig deeper if so inclined. The short articles also will be available online for those who prefer reading online.

According to the issue’s editorial from Editor-in-Chief Robert A. Gross, MD, PhD, FAAN, “Our working hypothesis, then, is that most readers will prefer a shorter article that they can read in its entirety, while those seeking the full content (and possibly longer articles) can go online. Our aim for this issue is to test this hypothesis. Herein is a current version of Neurology with a batch of articles that are exemplars of the one-page treatment. We’ve added context: what is known, how this work fills a gap, next steps. There is enough discussion to identify the limitations, but also the strength of the findings, and to highlight the actionable results. The advantages are several. More readers (from patients to reporters) may be enticed by our content, and may find it more accessible. Neurologists may be encouraged to read more outside their areas of interest. And there is no loss of content, as the full version is online.”

Readers can make their thoughts known about this pilot issue by completing a feedback survey at http://tinyurl.com/Neurology2016. The survey will be open until September 27.
Industry Partners Help Drive Improvements for Your Patients, Practice, and Profession

Industry Roundtable (IRT) partners collaborate with the AAN to share vision, intellect, and financial resources in the areas of education, sponsorship, leadership…and research—an area not only critical to the future of neurology, but one that is in dire need of funding. Federal support for neurologic research has remained flat and competition for funds from the National Institutes of Health has intensified.

“Scientific and medical communities have called the shortage of investigators a crisis that will impact far more than the 50 million Americans currently affected by a neurologic disease,” said AAN President Terrence L. Cascino, MD, FAAN.

Recognizing this critical need for research, the AAN has made it a priority to promote neurology and neuroscience research and training by pledging to support all types of research across all career levels and discover stages. But it can’t do it alone—which is why partnerships with industry who share the same vision and goals is essential to the AAN Research Program, and what will ultimately drive needed improvement for your patients, practice, and profession.

To date, the AAN and American Brain Foundation have invested more than $20 million to provide researchers the resources they need to answer important questions about preventions, treatments, and cures for brain disease, and a significant part of that research funding has come from valued industry partners—nearly $2.5 million in the last five years alone.

Meet Our AAN Research Program Partners

Three decision makers from valued Industry Roundtable partners share what neurology research—and collaboration with the AAN—means to them.

Daniele Bravi, MD
Acting Chief Medical Officer, Vice President US Drug Development, Lundbeck

“All over the world, CNS disorders are a growing burden, not only for individuals but for families and societies as well. During the last 100 years, Lundbeck has heavily invested in advancing science in psychiatric and neurological disorders. Lundbeck is very proud to support this program as a reflection of the company’s commitment to bringing innovative therapies forward for patients, and shaping the future of neuroscience.”

Armin Szegedi, MD, PhD
Vice President Clinical Development CNS, Allergan

“At Allergan, we are committed to improving patients’ lives through efforts in research and development that advance potentially breakthrough treatments and cures for neurological and psychiatric conditions. Through our ongoing partnership with the American Academy of Neurology, we are proud to work together on a shared mission of advancing critical research and education to discovering causes, improving treatments, and developing cures for neurological diseases and conditions that affect millions of people around the world.”

Darlene Jody, MD
Head of Global Medical Affairs, MS and Immunology, Sanofi Genzyme

“Sanofi Genzyme is proud to support the AAN’s efforts to provide grants to neurology researchers as part of our ongoing commitment to improving the lives of people living with devastating diseases such as multiple sclerosis. There are many medical needs that remain unmet in MS, and while we continue to move forward with our own research efforts, we believe that collaborating with organizations like the AAN will help to speed the discovery of important scientific advancements.”

To make a donation to the American Brain Foundation to help support vital research into cures for brain disease, visit ABF.convio.net/donate.

Thank You to Our Recent Industry Funders*

- Allergan Foundation
- Biogen
- Genentech
- Genzyme
- Lundbeck
- Teva

*Since 2012
Apply for Neurology Today Editor-in-Chief by October 31


Published since 2001, Neurology Today is an AAN member benefit that reports on breaking news, issues, and trends in the practice and science of neurology, reaching more than 26,000 professionals. In addition to ensuring the timely production and management of print and digital editions of Neurology Today and the digital editions of the Neurology Today Conference Reporter, the editor-in-chief sets the future editorial vision and direction for the publication while continuing the strong tradition of providing reliable, accurate, neurologist edited and curated news covering the field of neurology.

The position is open to Active or Fellow AAN members in good standing who possess solid leadership skills and knowledge about AAN programs, priorities, and policies, as well as connections to leaders in the neurology field. This position has an initial five-year term, eligible for reappointment for up to five additional years. A transition period with the outgoing editor-in-chief will run from April through June 2017, with the editorial term running from July 1, 2017, to June 30, 2022.

Address inquiries and applications to Andrea Weiss at aweiss@aan.com. Applications must be received by October 31, 2016.

Dr. Gabriele De Luca’s work was enhanced by the additional time in the laboratory that his AAN Research Award provided. The opportunity has had a lasting effect on his career, and the funding was crucial in the pursuit of his dreams to be a clinician-scientist.

I am deeply indebted to the AAN, donors, and sponsors who provide the financial and academic support needed to nurture the next generation of clinician-scientists.

—Gabriele C. De Luca, MD, PhD
2010 John F. Kurtzke, MD, FAAN, Clinician-Scientist Development Award Recipient

2017 AAN Research Program
Apply now for any of the 20 research funding opportunities.

Deadline: October 1, 2016 • AAN.com/view/ResearchProgram
Congratulations to 2016 Diversity Leadership Program Graduates!

The following 11 AAN members were selected and participated in the 2016 AAN Diversity Leadership Program, which is designed to promote greater diversity among AAN leaders by identifying, mentoring, and engaging members from underrepresented minority groups.

- Richard Benson, MD, PhD
- Edgar Samaniego, MD
- Jerome Lisk, MD
- Michael Stitzer, MD
- Chinasa Nwankwo, MD
- Alejandro Tobon Gonzalez, MD
- Hope O’Brien, MD
- Carol Ulloa, MD
- Yazmin Oidia, MD
- Dario Beltran, MD
- Temitayo Oyegbile, MD

The Diversity Leadership Program is supported in part by Allergan, Inc., Medtronic, Inc., and Supernus Pharmaceuticals, Inc. Learn more at AAN.com/view/DiversityLeadershipProgram.

Get Your Career in Gear with Help During Neurology Career Week

The AAN’s popular Neurology Career Week will take place October 3 to 7. Academy members seeking new job opportunities and work search insights will want to take advantage of some exclusive offers, including a chance to win $500 in a sweepstakes for those who create or update their job search profile between September 1 and October 7.

The AAN also is offering free CV reviews to first 100 responders between September 1 and October 7. And the first 25 job searchers who register between September 1 and October 7 can enjoy free coaching sessions to help them with interview preparation.

Coaching sessions will be scheduled the weeks of October 3 and 10.

Employers who are seeking job candidates can participate in the Online Job Fair with advertising that runs for as little as $350. The Neurology Career Week jobs email will be sent October 4 to all AAN members. Reserve your space by September 20 for only $500 plus the cost of an online web post on AAN.com.

To learn more about Neurology Career Week, visit AAN.com/careers.

AAN Credit Card Pays

As an exclusive benefit, AAN members can carry the only credit card with the Academy logo that helps support the AAN while providing you with cash back. The long-term loyalty credit card, offered through Bank of America, provides one-percent cash back on everyday purchases, two percent on groceries, and three percent on gas.

Additional perks include:
- $100 cash rewards bonus if you make at least $500 in purchases in the first 90 days*
- Earn rewards automatically
- No expiration on rewards
- No rotating categories

Apply for the BankAmericard Cash Rewards card at AAN.com/view/CashRewards.

* Grocery store and gas bonus rewards apply to the first $1,500 in combined purchases in these categories each quarter.
QUIETING MS Quietly*
for your patients with relapsing MS

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

MS = multiple sclerosis.

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

IMPORTANT SAFETY INFORMATION

WARNING: HEPATOTOXICITY AND RISK OF TERATOGENICITY

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

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.

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. Decreases in white blood cell counts, mainly of neutrophils and lymphocytes, and platelets have been
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.\textsuperscript{1,3,4}
- AUBAGIO 7 mg did not demonstrate a significant reduction in risk of sustained disability progression in either trial.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{1}
TOPIC: A double-blind, placebo-controlled clinical trial in patients with relapsing 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.\textsuperscript{1,4}

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AUBAGIO is one tablet, once a day.\textsuperscript{1}

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

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

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

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

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

Reported with AUBAGIO. 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. Administration of live vaccines is not recommended. The risk of malignancy, particularly lymphoproliferative disorders, or infection may be increased with the use of some medications with immunosuppressive potential, including teriflunomide. Peripheral neuropathy, including polyneuropathy and mononeuropathy, has been reported with AUBAGIO. Age >60 years, concomitant neurotoxic medications, and diabetes may increase the risk. If peripheral neuropathy is suspected, consider discontinuing treatment and performing accelerated elimination.

Interstitial lung disease and rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with leflunomide; a similar risk would be expected for teriflunomide. If a severe skin reaction develops with AUBAGIO, stop treatment and use accelerated elimination.

Blood pressure increases and hypertension have occurred with AUBAGIO. Measure blood pressure at treatment initiation and manage any elevations during treatment.
CUSTOMIZED 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.

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 cell count (CBC) within 6 months before the initiation of treatment with AUBAGIO. Further monitoring should be based on signs and symptoms of infection [see Warnings and Precautions (5.4)].
- Prior to initiating AUBAGIO, screen patients for latent tuberculosis infection with a tuberculin skin test or blood test for mycobacterium tuberculosis infection [see Warnings and Precautions (5.4)].
- Check blood pressure before start of AUBAGIO treatment and periodically thereafter [see Warnings and Precautions (5.7)].

4 CONTRAINDICATIONS
AUBAGIO is contraindicated in:

- Patients with severe hepatic impairment [see Warnings and Precautions (5.1)].
- Pregnant women or women of childbearing potential not using reliable contraception. AUBAGIO may cause fetal harm [see Warnings and Precautions (5.2) and 5.3) and Use in Specific Populations (8.1)].
- Patients with a history of a hypersensitivity reaction to teriflunomide, leflunomide, or to any of the inactive ingredients in AUBAGIO. Reactions have included anaphylaxis, angioedema, and serious skin reactions [see Warnings and Precautions (5.5)].
- 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 could 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. These elevations occurred mostly within the first year of treatment. Half of the cases returned to normal without drug discontinuation. In clinical trials, if ALT elevation was greater than three times the ULN on two consecutive tests, AUBAGIO was discontinued and patients underwent an accelerated elimination procedure [see Warnings and Precautions (5.3)]. Of the patients who underwent discontinuation and accelerated elimination in controlled trials, half returned to normal or near normal values within 2 months.

One patient in the controlled trials developed ALT 32 times the ULN and jaundice 5 months after initiation of AUBAGIO 14 mg treatment. The patient was hospitalized for 5 weeks and recovered after plasmapheresis and cholestyramine accelerated elimination procedure. AUBAGIO-induced liver injury in this patient could not be ruled out. Obtain serum transaminase and bilirubin levels within 6 months before initiation of 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, weakness, anorexia, or jaundice. 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 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 not be started on AUBAGIO until pregnancy is excluded and it has been confirmed that they are using reliable contraception. Before starting AUBAGIO, patients must be advised that if pregnancy occurs on the treatment, it is possible that rapidly lowering the plasma concentration of teriflunomide by instituting an accelerated elimination procedure may decrease the risk to the fetus from AUBAGIO [see Warnings and Precautions (5.3)].

Upon discontinuing AUBAGIO, it is recommended that all women of childbearing potential undergo an accelerated elimination procedure. Women receiving AUBAGIO treatment who wish to become pregnant must discontinue AUBAGIO and undergo an accelerated elimination procedure, which includes verification of teriflunomide plasma concentrations less than 0.02 mg/L (0.02 mcg/mL). Human plasma concentrations of teriflunomide less than 0.02 mg/L (0.02 mcg/mL) are expected to have minimal risk [see Contraindications (4), Warnings and Precautions (5.3) and Use in Specific Populations (8.1)].

5.3 Procedure for Accelerated Elimination of Teriflunomide
Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, it takes on average 8 months to reach plasma concentrations less than 0.02 mg/L, although because of individual variations in drug clearance it may take as long as 2 years. An accelerated elimination procedure could be used at any time after discontinuation of AUBAGIO. Elimination can be accelerated by either of the following procedures:

- Administration of cholestyramine 8 g every 8 hours for 11 days. If cholestyramine 8 g three times a day is not well tolerated, cholestyramine 4 g three times a day can be used.
- Administration of 50 g oral activated charcoal powder every 12 hours for 11 days.

If either elimination procedure is poorly tolerated, treatment days do not need to be consecutive unless there is a need to lower teriflunomide plasma concentration rapidly.

At the end of 11 days, both regimens successfully accelerated teriflunomide elimination, leading to more than 98% decrease in teriflunomide plasma concentrations.

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

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 WBC count occurred during the first 6 weeks and WBC count remained low during treatment. In placebo-controlled studies, neutrophil count < 1.5×10^9/L was observed in 12% and 16% of patients receiving AUBAGIO 7 mg and 14 mg, respectively, compared with 7% of patients receiving placebo. Lymphocyte count < 1.5×10^9/L was observed in 2% 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. Similar risks would be expected for AUBAGIO [see Clinical Pharmacology (12.3 in the full prescribing information)].

Cases of thrombocytopenia with AUBAGIO, including rare cases with platelet counts less than 50,000/mm^3, have been reported in the postmarketing setting. Obtain a complete blood cell count (CBC) within 6 months before the
initiation of treatment with AUBAGIO. Further monitoring should be based on signs and symptoms suggestive of bone marrow suppression.

**Risk of Infection / Tuberculosis Screening**

- AUBAGIO is not recommended for patients with severe immunodeficiency, bone marrow disease, or severe, uncontrolled infections.
- Medications like AUBAGIO that have immunosuppressive 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 Kveimobacteria pneumonia sepsis occurred in a patient taking AUBAGIO 14 mg for 1.7 years. Fatal infections have been reported in the post-marketing setting in patients receiving leflunomide, especially Pneumocystis jiroveci pneumonia and aspergillosis.
- Most of the reports were confounded by concomitant immunosuppressant therapy and/or comorbid illness which, in addition to rheumatoid disease, may predispose patients to infection.
- In clinical studies with AUBAGIO, cytomegalovirus hepatitis reactivation has been observed.

- In clinical studies with AUBAGIO, cases of tuberculosis have been observed. Prior to initiating AUBAGIO, screen patients for latent tuberculosis infection with a tuberculin skin test or with a blood test for mycobacterium tuberculosis infection. AUBAGIO has not been studied in patients with a positive tuberculosis screen, and the safety of AUBAGIO in individuals with latent tuberculosis infection is unknown. AUBAGIO has not been studied in patients with a positive tuberculosis 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.

**5.4 Malignancy**

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

**5.5 Hypersensitivity and Serious Skin Reactions**

- AUBAGIO can cause anaphylaxis and severe allergic reactions [see Contraindications (4)]. Signs and symptoms have included dyspnea, urticaria, and angioedema including lips, eyes, throat, and tongue.

- Cases of serious skin reactions, including cases of Stevens-Johnson syndrome (SJS) and a fatal case of toxic epidermal necrolysis (TEN), have been reported with AUBAGIO.
- In patients treated with leflunomide, the parent compound, very rare cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported.
- Inform patients of the signs and symptoms of anaphylaxis and angioedema and signs and symptoms that may signal a severe 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 (2.3)]. 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 polyneuropathy and mononeuropathy (e.g., carpal tunnel syndrome), occurred more frequently in patients taking AUBAGIO than in patients taking placebo. The incidence of peripheral neuropathy confirmed by nerve conduction studies was 1.4% (13 patients) and 1.9% (17 patients) of patients receiving 7 mg and 14 mg of AUBAGIO, respectively, compared with 0.4% receiving placebo (4 patients). Treatment was discontinued in 0.7% (8 patients) with confirmed peripheral neuropathy (3 patients 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 -0.6 mmHg for placebo. The change from baseline in diastolic blood pressure was +1.4 mmHg and +1.9 mmHg for AUBAGIO 7 mg and 14 mg, respectively, and -0.3 mmHg for placebo. Hypertension was an adverse reaction in 3.1% and 4.3% of patients treated with 7 mg or 14 mg of AUBAGIO compared with 1.8% for placebo. Check blood pressure before start of AUBAGIO treatment and periodically thereafter. Elevated blood pressure should be appropriately managed during treatment with AUBAGIO.

**5.8 Respiratory Effects**

- Intestinal lung disease, including acute interstitial 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. Discontinue also potentially result in return of disease activity if the patient had been responding to AUBAGIO treatment [see Warnings and Precautions (5.3)].

### 6 ADVERSE REACTIONS

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

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

**6.1 Clinical Trials Experience**

- Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
- A total of 2047 patients receiving AUBAGIO (7 mg or 14 mg once daily) constituted the safety population in the pooled analysis of placebo controlled studies in patients with relapsing forms of multiple sclerosis; of these, 71% were female. The average age was 37 years.
- Table 1 lists adverse reactions in placebo-controlled trials with rates that were at least 2% for AUBAGIO patients and also at least 2% above the rate in placebo patients. The most common were headache, an increase in ALT, diaphoresis, alopecia, and nausea. The adverse reaction most commonly associated with discontinuation was an increase in ALT (3.3%, 2.6%, and 2.3% of all patients in the AUBAGIO 7 mg, AUBAGIO 14 mg, and placebo treatment arms, respectively).

**Table 1. Adverse Reactions in Pooled Placebo-Controlled Studies in Patients with Relapsing Forms of Multiple Sclerosis**

<table>
<thead>
<tr>
<th>AUBAGIO&lt;sup&gt;®&lt;/sup&gt; (teriflunomide) tablets, for oral use</th>
<th>mg</th>
<th>mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Reaction</strong></td>
<td><strong>(N=1045)</strong></td>
<td><strong>(N=1002)</strong></td>
</tr>
<tr>
<td>Headache</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>Increase in Alamine</td>
<td>13%</td>
<td>15%</td>
</tr>
<tr>
<td>Diarhea</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>10%</td>
<td>13%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>8%</td>
<td>9%</td>
</tr>
<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 premarketing database. These cardiovascular deaths occurred during uncontrolled extension studies, one to nine years after initiation of treatment. A relationship between AUBAGIO and cardiovascular death has not been established.

**Acute Renal Failure**

- In placebo-controlled studies, creatinine values increased more than 100% over baseline in 8/1045 (0.8%) patients in the 7 mg AUBAGIO group and 6/1002 (0.6%)
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 phosphorous levels of at least 0.6 mmol/L, compared to 7% of placebo-treated patients; 4% of AUBAGIO-treated patients had hypophosphatemia with serum phosphorous levels at 0.3 mmol/L but less than 0.6 mmol/L, compared to 0.6% of placebo-treated patients. No patient in any treatment group had a serum phosphorous 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)]
- Thoratomy [see Warnings and Precautions (5.4)]
- Interstitial lung disease [see Warnings and Precautions (5.8)]
- Pancreatitis

7. DRUG INTERACTIONS

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

Effect of AUBAGIO on warfarin
Coadministration of AUBAGIO with warfarin requires close monitoring of the international normalized ratio (INR) because AUBAGIO may decrease peak INR by approximately 25%. Effect of AUBAGIO on oral contraceptives
AUBAGIO may increase the systemic exposures of ethinylestradiol and levonorgestrel. Consideration should be given to the type or dose of contraceptives used in combination with AUBAGIO [see Clinical Pharmacology (12.3 in the full prescribing information)].

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

Effect of AUBAGIO on organic anion transporter 3 (OAT3) substrates
Teriflunomide inhibits the activity of OAT3 in vivo. In patients taking AUBAGIO, exposure of drugs which are OAT3 substrates (e.g., celafloxacin, cinofloxacin, penicillin G, ketoprofen, furousemide, methotrexate, zidovudine) may be increased. Monitor these patients and adjust the dose of the concomitant drug(s) which are OAT3 substrates as required [see Clinical Pharmacology (12.3 in the full prescribing information)].

Effect of AUBAGIO on BCRP and organic anion transporting polypeptide B1 and B3 (OATP1B1/1B3) substrates
Teriflunomide inhibits the activity of BCRP and OATP1B1/1B3 in vivo. For a patient taking AUBAGIO, the dose of rosuvastatin should not exceed 10 mg once daily. For other substrates of BCRP (e.g., mitoxantrone) and drugs in the OATP family (e.g., methotrexate, rifampin), especially HMG-Co reductase inhibitors (e.g., atorvastatin, rosuvastatin, tateplindine, pravastatin, repaglinide, and simvastatin), consider reducing the dose of these drugs and monitor patients closely for signs and symptoms of increased exposures to the drugs while patients are taking AUBAGIO [see Clinical Pharmacology (12.3 in the full prescribing information)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

Administration of teriflunomide (oral doses of 1, 3.5, or 12 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in high incidences of fetal malformation (primarily craniofacial, and axial and appendicular skeletal defects) and embryofetal death at doses associated with minimal maternal toxicity. Maternal plasma exposure at the no-effect dose (1.0 mg/kg/day) for embryofetal developmental toxicity in rabbits was less than that in humans at the MRHD.

In studies in which teriflunomide (oral doses of 0.05, 0.1, 0.3, 0.6, or 1.0 mg/kg/day) was administered to rats during gestation and lactation, decreased growth, eye and skin abnormalities, and high incidences of malformation (limb defects) and postnatal death were observed in the offspring at doses not associated with maternal toxicity.

Maternal plasma exposure at the no-effect dose for pre- and postnatal developmental toxicity in rats (0.10 mg/kg/day) was less than that in humans at the MRHD. In animal reproduction studies of leflunomide, embryolethality and teratogenic effects were observed in pregnant rat and rabbit at or below clinically relevant plasma teriflunomide exposures (AUC). In published reproduction studies in pregnant mice, leflunomide was embryolethal and increased the incidence of malformations (craniofacial, axial skeletal, heart and great vessel). Supplementation with exogenous uridine reduced the teratogenic effects in pregnant mice, suggesting that the mode of action (inhibition of mitochondrial enzyme dihydroorotate dehydrogenase) is the same for therapeutic efficacy and developmental toxicity. At recommended doses in humans, teriflunomide and leflunomide result in a similar range of plasma concentrations of teriflunomide.

Use in Males

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

Pregnancy Registry

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

8.2 Nursing Mothers

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

8.3 Pediatric Use

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

8.4 Geriatric Use

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

8.5 Hepatic Impairment

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

8.6 Renal Impairment

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

10 OVERDOSAGE

There is no experience regarding teriflunomide overdose or intoxication in humans. Teriflunomide 70 mg daily up to 14 days was well tolerated by healthy subjects. In the event of clinically significant overdose or toxicity, cholestyramine or activated charcoal is recommended to accelerate elimination [see Warnings and Precautions (5.5)].

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
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June 2016

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Capitol Hill Report

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

The AAN has dedicated itself to developing a proactive regulatory advocacy strategy on behalf of our members. Recent actions by the Centers for Medicare & Medicaid Services (CMS), a regulatory agency that enacts health care policy “behind the scenes,” show this effort is making significant progress. In the past, CMS sometimes seemed indifferent to the regulatory and practice burdens facing neurologists. In response, the AAN strategically emphasized the value of cognitive services and patient care in regulatory comment letters and meetings with CMS leadership. Whereas previous CMS rules discussed the importance of primary care, this year’s proposed physician payment rule repeatedly refers to “primary care, care management and coordination, and cognitive services.” Many in Congress have changed their statements to include cognitive care, and now our regulatory efforts have helped broaden CMS’ recognition that payment inequality applies not only to primary care, but also to neurologists and other cognitive specialists.

These results have come from our constant presence involving several meetings with CMS leadership over the last year. These meetings have included many of the AAN’s top leadership including President Terrence L. Cascino, MD, FAAN, and several Medical and Economics Management (MEM) Committee members. Other results can be seen in the proposed Physician Fee Schedule for 2017, where AAN recommendations have been significantly endorsed by CMS to:

- Recognize and reimburse existing CPT codes for non-face-to-face services including chronic care management
- Recognize and reimburse a new G-code for evaluation of patients with cognitive impairment
- Simplify requirements to provide chronic care management services

The AAN also has successfully advocated to shorten the meaningful use program’s reporting period to 90 days, while also securing expanded hardship exceptions that benefit our members.

AAN members should be reassured that the MEM Committee and AAN staff are securing significant victories for neurologists in the process..
Selective temporal resection can be effective for children with refractory temporal lobe epilepsy; however, research investigating reliable pre-surgical guides is necessary to predict and minimize the adverse impact of temporal lobe surgery on memory functioning.

Leigh N. Sepeta, PhD, is tackling this problem, with the support of the American Brain Foundation, American Epilepsy Society, and the Epilepsy Foundation through the Susan S. Spencer Clinical Research Training Fellowship in Epilepsy awarded in 2015. Although her background was originally in autism research, Sepeta became interested in studying epilepsy through her clinical work with this population and the evolving use of research tools such as functional MRI (fMRI) and diffusion tensor imaging (DTI) for clinical purposes with these patients.

Sepeta, who is now an assistant professor at George Washington University School of Medicine and a pediatric neuropsychologist at Children’s National Health System in Washington, DC, is taking advantage of advanced imaging techniques with fMRI and DTI to better understand memory function in children.

“Important differences exist between children and adults with epilepsy and temporal resection effects on memory networks, suggesting a longer window for memory plasticity than language systems,” said Sepeta. “In typically developing adults, each hippocampus is thought to be specialized to process specific types of information with verbal encoding resulting in left hippocampal lateralization and visual encoding in right (material specificity).

Thus, dominant temporal resections may lead to post-operative verbal memory decline in adults. However, memory functioning in children does not significantly decline after surgery, according to the majority of neuropsychological studies.

Sepeta’s research challenges presumptions of material specificity across the age span and hypothesizes that hippocampal specialization for specific types of material occurs later in development. “If true, this would have a significant impact on our understanding of the development of memory, as well as epilepsy interventions such as resection. The AAN’s Clinical Research Training Fellowships provide essential protected time for me and other investigators pursuing clinical research that is critical for making scientific discoveries important to improve health care outcomes.”

In their joint letter recommending Sepeta for the fellowship, her mentors William D. Gaillard, MD, and Madison M. Berl, PhD, of Children’s National Health System, said, “There are few well-trained investigators in this area, and only a handful who can utilize advanced imaging of the type Dr. Sepeta proposes, with the clinical insight to take full advantage of new technologies.”

Berl added, “I am proud to be associated with the work that Dr. Sepeta is doing in temporal lobe epilepsy as she strives to develop new mechanisms that provide better treatment for people living with epilepsy.”

The two-year fellowship provides Sepeta an annual salary of $55,000 plus $10,000 per year for tuition to support education in clinical research methodology.

Donations to the American Brain Foundation support the AAN’s Research Program, which has been expanded to include awards for basic and translational research. To support future promising research like Sepeta’s, visit AmericanBrainFoundation.org.
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$0 Co-Pay Offer* | + |
5 Dosage Strengths, Including 150 mg | + |

$0 CO-PAY*

*Eligible Patients Pay $0. Covers $200/Prescription, Maximum Annual Savings of $2,400.

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Neurology Position with Central Maine Medical Center: 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 angio, EMG, Evoked Potentials, EEG, and 24-72 Hour Ambulatory EEG. We also have an active Telenursing 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 Gena Mallozi, Central Maine Medical Center, 300 Main Street, Lewiston, ME 04240. Fax: (207) 795-5696, email: MalloziG@cmhc.org, or call: (800) 445-7431. Not a J1 Opportunity.

Neurologist: Excellent Opportunity in NY: St. Peter’s Health Partner’s Medical Associates, P.C., is seeking qualified candidates for two new full time Neurology positions for immediate placement. Positions include general, office based, neurology with inpatient consultation, and hospital only neurology (neuro-hospitalist.) These are excellent opportunities to join a respected and expanding team of seven physicians as the organization develops its neuroscience service line across the Capital District of NY. Applicants should be able to perform EMG/NCS and EEG. Some sleep study reading is available in the outpatient setting. We recently opened a beautiful new office space. We offer a supportive practice environment with established patient bases with strong demand. These are exciting opportunities to join a dynamic and growing organization as it takes its neurology program to the next level of integration. Send applications to mgallucci@sphcs.org.

Two Stroke (Vascular) Neurology positions – Assistant, Associate or Full Professor: The Department of Neurology at the University of Washington is seeking two neurologists with expertise in vascular neurology to join the Comprehensive Stroke Center at Harborview Medical Center. The Stroke Program at Harborview represents a dynamic environment to practice Vascular Neurology, both inpatient and outpatient. A TeleStroke program is in place and expanding. You will interact with eight Vascular Neurologists, two Interventional Neurosurgeons, two Interventional Neuroradiologists, and an outstanding Emergency Department. These are both full-time appointments and will be at the Assistant Professor rank (without tenure for reasons due to funding, job code 0113) in the clinician-educator academic pathway. Candidates with exceptional qualifications may be considered for appointment at the rank of Associate Professor (without tenure for reasons due to funding, job code 0112) or Professor (without tenure for reasons due to funding, job code 0111). Send a letter of interest and curriculum vitae to: Kass Klemz, Assistant to the Chairman, University of Washington Department of Neurology, Box 356465, Seattle, WA 98195. Email: kass@uw.edu. These positions are open until filled. University of Washington is an affirmative action and equal opportunity employer. All qualified applicants will receive consideration for employment without regard to race, color, religion, sex, sexual orientation, gender identity, national origin, age, protected veteran or disabled status, or genetic information.

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, P.C., RIVERWALK, 354 Merrimack Street, Lawrence, MA 01843, or email to jft@neneuro.com. Visit us on the web at www.neneuro.com.

Fellowship in Neuroradiography: Winchester Neurological Consultants, Inc., in conjunction with Virginia Commonwealth University and Winchester Medical Center, is offering a clinical Neuroradiology Fellowship for BC/BE neuroscience 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. There is also an opportunity to combine the Imaging Fellowship with a NeuroHospitlist Fellowship over a two year training period with a salary of $80,000.00 per year. CVs should be emailed to gsteele@winchesterneurological.com

Neurologist: A large highly regarded Neurology practice in Northern New Jersey is seeking full or part time subspecialty trained Neurologists. The practice provides adult and pediatric neurological care at a single office and single hospital, with multiple established sub-specialties. We are seeking to expand existing and establish additional areas of expertise in the following fields: Multiple Sclerosis, Neuro-oncology, Dementia/Cognitive Disorders, Neuro-hospitalist, Headaches/Chemodenervation. The practice is physician owned and a partnership track is offered. The practice is located in an affluent suburban community thirty minutes from NYC, with excellent lifestyle and school system. Email CV to hjtmaer@neurobergen.com; www.neurobergen.com

The hottest jobs meet the top candidates at the AAN Neurology Career Center.

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

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

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

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

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

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

These conditions may require treatment with systemic corticosteroids or immunosuppressive medication.
ZINBRYTA is available only through a restricted distribution program called the ZINBRYTA REMS Program.

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

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

DECIDE pivotal clinical trial: outcome up to 144 weeks

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

DECIDE was a randomized, double-blind, active control study that compared ZINBRYTA 150 mg subcutaneous (n=919) every 4 weeks to AVONEX 30 mcg intramuscular (n=922) weekly. Treatment continued for 96 to 144 weeks. The primary outcome measure was the annualized relapse rate (ARR). Additional outcome measures included the proportion of patients relapsed, the proportion of patients who experienced confirmed disability progression (CDP), and the number of new or newly enlarging T2 hyperintense lesions. The study included RMS patients with an Expanded Disability Status Scale (EDSS) score of 0-5.0 who had either: 1) ≥2 relapses during the prior 3 years and ≥1 relapse in the year prior to randomization; or 2) ≥1 clinical relapses and ≥1 new T1 gadolinium (Gd)-enhancing or T2 hyperintense MRI lesions within the prior 2 years with at least one of these events in the prior 12 months. Patients with progressive forms of MS were excluded.

SELECT pivotal clinical trial: outcome at 52 weeks

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

SELECT was a randomized, double-blind, placebo-controlled study that compared ZINBRYTA 150 mg subcutaneous (n=208) every 4 weeks to placebo (n=204). Treatment duration was 52 weeks. The primary outcome measure was ARR at Week 52. Additional outcome measures included new T1 Gd-enhancing lesions between Weeks 8 to 24, the proportion of patients relapsed, the proportion of patients who experienced 12-week CDP, and the number of new or newly enlarging T2 hyperintense lesions. The study included RMS patients with an EDSS score of 0-5.0 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.

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 (2.2)].

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 reaction, lymphadenopathy, and non-infectious colitis can occur in patients treated with ZINBRYTA. Overall, serious immune-mediated conditions were observed in 5% of patients treated with ZINBRYTA [see Warnings and Precautions (5.2)].

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

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

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

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

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

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

2.2 Important Administration Instructions

ZINBRYTA is for subcutaneous use only.

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

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. ZINBRYTA is a colorless to slightly yellow, clear to slightly opalescent solution. Do not use ZINBRYTA if it is cloudy or there are visible particles. Sites for injection include the thigh, abdomen, and back of the upper arm. Use each prefilled syringe one time and then place in a sharps disposal container for disposal according to community guidelines [see How Supplied/ Storage and Handling (16.3)].

2.3 Assessment Prior to Initiating ZINBRYTA

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

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

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

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

2.4 Laboratory Testing and Monitoring to Assess Safety After Initiating ZINBRYTA

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

ZINBRYTA is contraindicated in patients with:

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

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

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

5.1 Hepatic Injury

ZINBRYTA can cause life-threatening severe liver injury, including liver failure and hepatitis. In controlled studies, liver injury occurred in 1% 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 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). 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).

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 6 month treatment interruption period. This patient subsequently received two doses of ZINBRYTA in the presence of persisting alanine aminotransferase levels (ALT) more than 5 times the upper limit of normal (ULN).

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

Monitoring: Prior to starting treatment with ZINBRYTA, obtain serum transaminases (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 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 immunosuppressants 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 nonprescription products, concomitantly with ZINBRYTA. Also, carefully consider the need for the use of herbal products or dietary supplements that can cause hepatotoxicity [see Drug Interactions (7.1)].

5.2 Immune-Mediated Disorders

Treatment with ZINBRYTA increases the risk of immune-mediated disorders, including autoimmune disorders such as autoimmune hepatitis. Across all clinical studies (controlled and open-label), immune-mediated disorders occurred in 28% of patients on ZINBRYTA, the most common of which were skin reactions and lymphoproliferation. In the active-control study (Study 1), immune-mediated disorders were observed in 32% of ZINBRYTA-treated patients compared with 12% for AVONEX-treated patients. In Study 1, serious immune-mediated disorders were observed in 4% of patients treated with ZINBRYTA compared with less than 1% for AVONEX-treated patients. In the placebo-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 0.4% of placebo-treated patients.

In some cases, patients had concurrent or sequential occurring disorders while taking ZINBRYTA.

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

Prescribers should be vigilant regarding emergent immune-mediated disorders. For suspected immune-mediated disorders, ensure adequate evaluation to confirm etiology or to exclude other causes. If a patient develops a serious immune-mediated disorder, consider stopping ZINBRYTA and refer the patient to an appropriate specialist for further evaluation and treatment. Skin Reactions: ZINBRYTA causes skin reactions. In clinical trials, skin reactions occurred in 37% of ZINBRYTA-treated patients compared with 19% of AVONEX-treated patients (Study 1) and in 18% of ZINBRYTA-treated patients compared with 13% of patients on placebo (Study 2). Skin reactions occurred at any time during treatment with ZINBRYTA. Rashes occurred in 11% of ZINBRYTA-treated patients compared to 4% of AVONEX-treated patients, and in 7% of ZINBRYTA-treated patients compared to 3% of patients on placebo. Dermatitis occurred frequently in ZINBRYTA-treated patients compared to AVONEX-treated patients or to patients on placebo, and eczema was observed more frequently in ZINBRYTA-treated patients compared to AVONEX-treated patients [see Adverse Reactions (6.1)]. Psoriatic conditions occurred in 2% of ZINBRYTA-treated patients compared with 0.3% of AVONEX-treated patients. Photosensitivity also occurred.

Serious skin reactions occurred in 2% of patients treated with ZINBRYTA compared with 0.1% of patients on AVONEX (Study 1) and in 1% of patients treated with ZINBRYTA compared with none treated with placebo (Study 2). 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, 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). Other than removal or biopsy, no specific treatments were required. Lymphadenopathy 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, 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, 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 1-800-456-2355.

5.4 Acute Hypersensitivity

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

ZINBRYTA increases the risk for infections. In controlled trials, infections occurred in 65% 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)].

5.6 Depression and Suicide

Depression-related events occurred more frequently in patients receiving ZINBRYTA than in patients receiving AVONEX or placebo. 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). In Study 1, serious events related to depression, including suicidal-related or suicide attempts, occurred in 0.4% of ZINBRYTA-treated patients and in 0.7% of AVONEX-treated patients. None occurred in Study 2 (placebo-controlled).

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, weekly) for a minimum of 2 years and up to 3 years, with 1952 person-years of exposure to ZINBRYTA, the median length of treatment was approximately 27 months. The adverse reactions from Study 1 are presented in Table 2.

In the placebo-controlled study (Study 2), 417 patients received ZINBRYTA with 423 person-years of exposure, of which 208 received ZINBRYTA 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, ophthalmologic 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>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Influenza</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Ophthalmologic pain</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Eczema</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Acne</td>
<td>3</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

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

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>Rash2</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4</td>
<td>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, 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.
The effects on the breastfed child, or the effects of the drug on milk production.

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% (752/3913) 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 predominantly 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 with 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 nonprescription products, concomitantly with ZINBRYTA. Carefully consider the need for the use of herbal products or dietary supplements that can cause hepatotoxicity [see Warnings and Precautions (5.1)].

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. 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 days 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
Advising the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

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

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

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

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

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

Immunemediated 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 and take medical attention if these symptoms occur [see Warnings and Precautions (5.4)].

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

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

Instructions for Self-Injection Technique and Procedures: Provide appropriate instruction for methods of self-injection, including careful review of the ZINBRYTA Instructions for Use. Instruct the patient in the use of an 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.

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## Dates and Deadlines

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**SEPTEMBER 8**
- Fall Conference Early Registration Deadline
  - AAN.com/view/Fall

**SEPTEMBER 13**
- Webinar: Solo, But Not Alone: Thriving in Small Neurology Practices
  - (Register by September 12)
  - AAN.com/view/pmw16

**OCTOBER 1**
- Application Deadline: 2017 AAN Research Program Awards and Scholarships
  - AAN.com/view/ResearchProgram

**OCTOBER 3–7**
- Neurology Career Week
  - AAN.com/careers

**OCTOBER 11**
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