New AAN Study Released on Neurologist Burnout

**AAN Addressing Issue on Several Levels**

A study by the AAN of its member neurologists shows that 60 percent of respondents had at least one symptom of burnout, and burnout is common in all neurology practice settings and subspecialties. The study, believed to be the most in-depth look at burnout within a medical specialty, was published in the January 25, 2017, online issue of *Neurology®*.

“These findings confirm our recognition of burnout as a serious issue facing our profession and why the well-being of neurologists—starting with decreasing regulatory hassles—must be addressed to ensure our patients receive the highest quality care,” said AAN President Terrence L. Cascino, MD, FAAN.

Neurology is the only medical specialty that has both one of the highest rates of burnout and the lowest rates of satisfaction with work-life balance, which may cause neurologists to lose enthusiasm for their work, force some to leave practice early, and lead to fewer medical students choosing to enter neurology as a career.

Under Cascino’s leadership, the AAN has compiled a variety of tips, tools, and strategies at AAN.com/LiveWell to help its members mitigate burnout and enhance career satisfaction. At the same time, the AAN is working tirelessly

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### Get Ready to Join the Axon Registry

**axon REGISTRY®**

Having successfully completed its pilot phase, the AAN’s Axon Registry® is looking forward to additional neurologists joining in 2017. Participating in the Axon Registry provides significant benefits to those who join, says Registry Committee Chair Lyell K. Jones, MD, FAAN.

“The Axon Registry,” he said, “is by far the most effective tool to date for neurologists to meet reporting

Continued on page 8

### Improve Your Knowledge of MACRA Participation, Negotiating Contracts

MACRA’s new Quality Payment Program takes effect this year and puts into place two major reimbursement systems: the Merit-based Incentive Payment System and Advanced Alternative Payment Models. You should attend this webinar if you are not yet up to speed on how you may be affected by these changes or if you have questions about their requirements, incentives, and penalties.

Continued on page 11
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NEWS BRIEFS
BrainPAC concluded 2016 having raised $380,598 from 1,436 donors. This is a record high and represents more than a 10 percent year-over-year increase in both categories compared to 2015, when it raised $341,876 from 1,292 donors.

AAN efforts helped to cancel a Medicare Part B drug payment model. The Centers for Medicare & Medicaid Services announced in December that it will not finalize the drug payment model, a demonstration intended to cut costs by changing how physicians are reimbursed for the use of Medicare Part B drugs. The AAN helped lead the effort to fight this demonstration, which would have had an impact on a number of neurology practice groups. The AAN worked closely with other organizations to push this on Capitol Hill.

The editorial by Susan Schneider Williams, widow of actor Robin Williams, published in the September 27 issue of Neurology® was ranked the #12 most shared academic paper of 2016 by Altmetrics, which tracks 27,000 journal articles per year, due to extensive media coverage. ·
2016 Annual Report Highlights Major Accomplishments for Members

One of the best ways to get a comprehensive view of all the ways the AAN serves you, our member, is by reading our Annual Report for 2016, which you can find online at AAN.com/view/AnnualReport.

The AAN exists for the benefit of members like you, to do the things collectively that would be nearly—if not completely—impossible to do individually. With the dogged commitment and passion of thousands of volunteer members and leaders working in tandem with our professional staff, we had your back in 2016, and we’re happy to highlight some of our most significant successes of the year in this annual report. But there are a few efforts we wish to call out in this message because of their profound importance to the specialty of neurology.

**Strengthening Practices.** Some 30 percent of our US members are in solo and small practices (with five or fewer neurologists), balancing heavy patient loads with increasingly distracting reporting requirements and regulatory hassles. To ensure the Academy is providing the best value to these members, the Solo and Small Practice Task Force identified major issues affecting these members and reviewed existing AAN products and services. The task force made more than two dozen recommendations that the Board of Directors and staff have examined and will be acting upon in the months to come to strengthen our members’ practices and alleviate the pressures of regulatory burdens. The AAN is doing everything it can on the health policy front to decrease these burdens and limit the impact of new policy changes, and we had success with the final rules for MACRA and the Medicare physician fee schedule for 2017.

**Rebalancing Lives.** Neurology is the only medical specialty that has both one of the highest rates of burnout and the lowest rates of work-life balance. We know there are many external factors contributing to physician burnout including the myriad regulatory hassles that you face daily. Your health matters to the AAN and we’re here to help. The Burnout Task Force we launched in 2015 to research the issue of physician burnout reported its findings and recommendations to the Board in 2016. Consequently, we launched our new Live Well campaign and webpage at AAN.com/LiveWell with a range of resources to help address regulatory, workplace, and individual frictions that spark burnout and to help cultivate well-being and resiliency in your life. Rest assured that the AAN is fighting for you in Washington, DC, to decrease regulatory hassles and limit the impact of new policies, reporting requirements, and reimbursement changes.

**Increasing Research Support.** Research into neurologic diseases, treatments, and cures is of the highest importance. For 2016, the Academy expanded our investment in research via the AAN Research Program to $2,800,000—an increase of $400,000 over 2015—and new awards were offered.

**Reinventing Learning.** We reinvented the AAN Annual Meeting with seismic shifts, from a new one-rate registration fee to novel Experiential Learning Areas unchained from didactic classroom presentations. The result was a meeting imbued with new energy, variety, and enthusiasm that we will build upon in our planning for the 2017 Annual Meeting in Boston. We hope to see you there.

Continued on page 7 ▶
Catherine M. Rydell, CAE

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

Catherine M. Rydell, CAE, has been the AAN’s executive director and chief executive officer since 1999 and serves as an ex-officio member of the AAN and AAN Institute boards. Prior to joining the AAN, Rydell served as executive director of the North Dakota Medical Association. From 1984 through 1996, Rydell served as a state representative in the North Dakota State Legislature where she chaired the House Human Services Committee and the House Education Committee. She also sponsored key health legislation, including the North Dakota Clean Indoor Air Act.

What brought you to the AAN and what keeps you here?

My entire professional life has involved working with physicians in a variety of settings. It began when I served in my home state’s legislature. I chaired the committee that dealt with health care and worked closely with medical associations and individual physicians on health-related issues. My admiration for their dedication, their intellect, and their compassion had me hooked. I also was a hospital administrator, which opened the door for my role as CEO of the state medical association, which in turn led me to the AAN. Accepting the position of CEO for the Academy was the best decision of my professional life. There are no words to adequately express my admiration for the neurologists I’ve met, many of whom I consider lifelong friends. The leaders, the volunteers, and the amazing staff are a joy to work with. Every day is a new challenge, an opportunity to grow and boredom is not an option—that’s what keeps me here.

How has the AAN changed during your tenure?

The AAN of today is unrecognizable from the AAN of 1999. The growth has been phenomenal. In 1999, the AAN was an organization known for an outstanding journal and a successful Annual Meeting. The health care world was changing at a rapid pace, and because of visionary leaders the AAN evolved to address those changes. Thanks to the new directions set forth in the first-ever AAN strategic plan developed in the late 1990s, the organization set the stage so the Academy could effectively meet the needs of the members. Membership in 1999 was 16,772 and now is more than 30,000. The operating budget was $15.9M and now is $53M. We had 82 staff, and as of 2017 will have 183. The ongoing growth of programs and services to meet our members’ needs is always evolving—we touch every aspect of our members’ professional lives. The Academy provides practice management tools and resources, education, and CME at all levels, expanded support for science, valued patient resources, expanded conferences and an innovative Annual Meeting, integration of technology in programs and services, leadership development programs, increased presence on social media, justification of fair reimbursement, tools to meet certification requirements, federal, state and regulatory advocacy, additional highly respected publications, clinical data registry, critical practice guidelines and quality measures development, public and community relations, tools to mitigate neurologist burnout—and the list goes on and on.

How does your role as an ex-officio member of the Board of Directors differ from that of the neurologists on the board?

While it is important that I am at the table to participate in deliberations, I am a non-voting member of the board. I work closely with the president and president elect to set the agenda for the board. I like to say the “secret sauce” of the AAN is the mutually respectful relationship between our volunteers and the staff. While this is true at all levels, it is no more evident than with the Board of Directors and the executive staff. The board sets the policy of the organization and I work with my executive team to make sure it is implemented and that board goals are met or exceeded.

What are you most proud of in your role as CEO?

That’s the easiest question to answer—the development of a world class staff. The dedication and commitment of the AAN staff is truly an inspiration to me. I marvel at their ability to accept a challenge, find innovative solutions, and exceed expectations. They are consistently looking for ways to make the AAN indispensable to our members. I dare say nearly everyone on our staff has family or friends who have dealt with one form of neurologic disease or another. So they, too, have a very personal stake in our success, and they come to work every day with a commitment and passion that is palpable.

What challenges do you see ahead for the AAN?

In this time of uncertainty in health care, we are committed to do all we can to help our members navigate the challenges they will face. We strive to be proactive with all governmental and regulatory entities to assure the needs of our members and their patients are identified and addressed. It has never been more important that we listen to all segments of our membership, understand their concerns, and act on their behalf. To that end, we are determined to decrease the burden of regulatory hassles so our members are confident they have the time to do what they love—positively affect the lives of people afflicted with neurologic disorders.
Investing in Quality Improvement. The AAN successfully piloted the Axon Registry® with four cohorts involving nearly 900 neurologists and more than 1 million patient records. The Centers for Medicare & Medicaid Services approved the Axon Registry as a Qualified Clinical Data Registry, meaning AAN members will be able to easily submit quality data to CMS and participate in future Medicare value-based payment programs under MACRA. In addition, the American Board of Psychiatry and Neurology stated participating in Axon Registry will meet Maintenance of Certification Performance in Practice requirements. The Axon Registry demonstrates our commitment to improving the quality and value of neurologic care.

Inspiring Tomorrow’s Neurologists. The Conrad N. Hilton Foundation awarded a grant to the AAN to help increase the percentage of medical students entering neurology by 25 percent over a three-year period. This will help us determine what factors lead medical students to choose neurology as a career and develop materials to inspire more students to go into our specialty.

Nurturing Tomorrow’s Neurology Leaders. Future success depends on tomorrow’s leaders. We evaluated and rebranded our Leadership Programs, launched the Transforming Leaders Program for mid-career neurologists, and developed the Women Leading Neurology Program for implementation in 2017.

Collaborating with Child Neurology. The AAN developed a Child Neurology Work Group in late 2015 with representation from the AAN and the Child Neurology Society to collaborate and identify ways that the two organizations can work together to improve care for patients across the life span. This collaboration has led to initiatives such as new programming at the Annual Meeting including scientific presentations, networking opportunities, and panel discussions, as well as new scholarships to the Annual Meeting for five child neurology residents. In addition, more child neurologists have been integrated into AAN leadership opportunities such as committees and subcommittees, science and education program groups for Annual Meeting programs, and as participants in AAN Leadership Programs.

Committing to Innovation. As leaders, we are committed to advancing the AAN through innovation. Last year, we started work on redesigning all of our publications and their websites, including AAN.com—which receives more than 1 million visitors each year. We’ve engaged some of the top design agencies from around the world to deliver a highly attractive, easy-to-digest user experience. In addition, we started work on a new powerful search engine across all of our websites to make finding AAN content easier and more relevant. Furthermore, we’re embarking on new personalization strategies to help deliver relevant and timely content when and how you like to learn. Even more exciting, we have begun to develop a new website for patients, caregivers, and the public that will serve as a new tool for members looking to provide their patients content from the most trusted authority on managing neurologic disease—the AAN.

Addressing Gender Disparity in Neurology. Appointed in October 2016 in response to startling salary data that shows neurology has one of the widest discrepancies between genders, the Gender Disparity Task Force is studying compensation, professional advancement, leadership opportunities, and work/life balance. It will make recommendations for strategies to improve the identified disparities.

Please know that each day, AAN member volunteers and our staff are fighting on your behalf to make it easier to be a successful neurologist. We’ve got your back.

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

Catherine M. Rydell, CAE
Executive Director and CEO,
American Academy of Neurology
The February/March 2017 issue of *Neurology Now* features “The Sopranos” actress Jamie-Lynn Sigler, who was diagnosed with multiple sclerosis at age 20. Now 35, Sigler has disclosed her disease publicly to help others learn to live with the condition. The Brain Health by the Decade feature explains how the brain develops and grows during different life stages and includes 20 expert tips for lifelong brain health. A story in the Living Well department looks at the reasons, such as cost and fear of side effects, why patients don’t take their medications and provides solutions for each of them.

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

In the new issue of *Neurology* Clinical Practice, a variety of practice topics are explored including validation of olfactory deficit as a biomarker of Alzheimer’s disease, treatment options for obstructive sleep apnea, and optimizing extended-release carbidopa/levodopa (ER CD-LD) in Parkinson’s disease and consensus on conversion from standard therapy.

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

## Get Ready to Join the Axon Registry

requirements, prove value to payers, satisfy Part IV of the ABPN’s Maintenance of Certification, and work to assess and improve their quality of care.”

The Academy will onboard 30 practices each quarter, starting in early 2017. This makes it possible to work with a large number of practices yet give each of the practices up to three months to work through the integration process before bringing on more practices. It also gives the registry vendor, FIGMD, the time to provide more individualized support.

Due to the Centers for Medicare & Medicaid Services timelines for submitting data for quality reporting programs, practices that join the Axon Registry in the fourth quarter of 2017 will only be able to submit for the Merit Based Incentive Payment System (MIPS) if they are able to get through the initial implementation by November 1.

“Whether using the Axon Registry for 2017 MIPS reporting or not, new participants can start working on quality improvement initiatives and the AAN will help with options for practices unable to submit via the Axon Registry,” said Jones.

AAN members interested in joining their colleagues in the Axon Registry should go to AAN.com/View/Axon and fill out the interest form. As practices sign up, they will be placed on a wait list and contacted when their number is reached. For more information about whether your EHR vendor is successfully working with the Axon Registry, review the EHR list available online at http://bit.ly/2heFB8G. For information about the process, contact registry@aan.com.
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Available by February 1

- **Neurology:** The Effects of Orthostatic Hypotension on Cognition in Parkinson’s Disease  
  Justin Cerri, PhD, and Matthew J. Barrett, MD, MSc
- **Neurology:** A Randomized, Double-blind, Placebo-controlled Trial of Coenzyme Q10 in Huntington’s Disease  
  Michelle Fullard, MD, and Andrew J. McGarry, MD
- **Neurology:** Glucocorticoid-associated Worsening in Reversible Cerebral Vasoconstriction Syndrome  
  Andrew M. Southerland, MD, MSc, and Aneesh Bhim Singhal, MD
- **Neurology:** Relationship Between Risk Factor Control and Vascular Events in the SAMMPRIS Trial  
  Joseph Carrera, MD, and Tanya N. Turan, MD, MSCR
- **Neurology:** Progressive Rural-Urban Disparity in Acute Stroke Care  
  Andrew M. Southerland, MD, MSc, and Allison W. Willis, MD, MSCI
- **Neurology: Clinical Practice:** Incidence of Meningeal Enhancement on Brain MRI Secondary to Lumbar Puncture  
  Jonathan Perk, MD, PhD, and Sarah Flanagan Wesley, MD, MPH
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  David A. Lapides, HS, and Jan Dirk Blom, MD, PhD
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  Eliot Dimberg, MD, and Hiroshi Mitsumoto, MD, DSc
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February 7, 2017  |  12:00 p.m.–1:00 p.m. ET
Register by February 6

Directors: Lyell K. Jones, MD, FAAN, and William S. Henderson, FACMPE

Upon completion, you should be able to:
- Understand MACRA's two major payment systems: Merit-based Incentive Payment System (MIPS) and Advanced Alternative Payment Models (APM)
- Implement strategies to report under MIPS
- Explore opportunities to participate in Advanced APMs
- Calculate the potential changes and difference in reimbursement based on the new MIPS and APMs systems

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Getting What You Deserve—A Primer on Contracting

March 8, 2017  |  12:00 p.m.–1:00 p.m. ET
Register by March 7

Directors: Brad C. Klein, MD, MBA, FAAN, and David A. Evans, MBA

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Lyell K. Jones, MD, FAAN
William S. Henderson, FACMPE
Brad C. Klein, MD, MBA, FAAN
David A. Evans, MBA
Policy

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.

AAN Leaders Attend First Day of 115th Congress

By Mike Amery, Esq., Senior Legislative Counsel

Nothing beats the first day of a congressional session. Everyone is in a great mood. After long and likely expensive campaigns, they won elections in November and are finally taking their seats in Congress, some for the first time. The 115th US Congress opened last week with the swearing in of 435 House members, including 52 freshmen, and 34 senators, including seven freshmen.

Senior Congressional Affairs Representative Derek Brandt and I were joined for opening day by AAN President Terrence L. Cascino, MD, FAAN; President-elect Ralph L. Sacco, MD, MS, FAHA, FAAN; and Executive Director/CEO Catherine M. Rydell, CAE. We spent all day walking the halls of Congress congratulating members, talking a little politics and, of course, talking about neurology.

Many congressional offices hold open houses throughout the day and we took full advantage to meet personally with a couple dozen members of the House, including Rep. Phil Roe, MD (R-TN), chair of the House Veterans Affairs Committee; Rep. Frank Pallone (D-NJ), lead Democrat on the House Energy & Commerce Committee; and Rep. Mike Thompson (D-CA), a leader on the House Ways & Means Committee, all of whom have major influence over health policy issues.

Opening day isn’t the time to get deep into the issues, but Drs. Cascino and Sacco had several opportunities to talk about regulatory hassles physicians deal with that have no impact on patient care and lead to physician burnout. They also thanked several cosponsors of the Furthering Access to Stroke Telemedicine (FAST) Act, a bill that the AAN has built momentum for over the last two years, and reminded them that the legislation will be an early priority in 2017.

The House and Senate office buildings are situated on opposite sides of Capitol Hill. The House side contains three buildings for member offices. The oldest is Cannon, built in 1908. Longworth opened in 1933 and Rayburn in 1965. As you walk through these buildings on the first day of a new Congress you can sense the joyous atmosphere as you see the new members’ families there to celebrate the beginning of their service. The thing I noticed this year was how crowded the Cannon Building was, where groups of people clogged every hallway, but not so many in the Longworth building and very few in Rayburn.

First-time members of Congress bring a lot of people to DC to help them celebrate. More experienced members often have a “been there, done that” attitude and bring fewer. Cannon is where a lot of the freshman offices are, with fewer...
in Longworth and almost none in Rayburn. The reason for this is because office space on Capitol Hill is determined by one criterion—seniority.

The dean of the House is Rep. John Conyers (D-MI), who was first elected in 1964. Conyers selected 2426 Rayburn for his office space. Many of Conyers’ colleagues with seniority also pick Rayburn’s spacious offices with views of the Capitol dome. On the other side of the spectrum are the 52 freshmen who drew numbers to determine their order of selecting office space. By the time the last 20 or so are left, they are all on the upper floors of the older, smaller Cannon building. Freshman Rep. Charlie Christ (D-FL) drew last place in the 115th Congress and selected, or settled, with 427 Cannon.

It was in Cannon that we met several of the newest members of Congress, including Rep. Jason Lewis (R-MN), who I have known for several years, and Rep. Jimmy Panetta (D-CA), whose spouse is a friend of Cathy Rydell. We also met with third-term Rep. Tom Emmer (R-MN) who moved from the fifth floor of Cannon down to 315 where he has already hung several pictures of President John F. Kennedy. The reason is pretty cool: 315 Cannon was JFK’s US House office from 1947 to 1953.

In Longworth and Rayburn, we saw fewer crowds, but met with more established representatives such as Billy Long (R-MO), Brett Guthrie (R-KY), Tony Cardenas (D-CA), and Paul Tonko (D-NY), all members of the important House Energy & Commerce Committee (E&C).

With swearing-in day behind us and the change in presidential administration nearing, lobbyists and advocates will replace the families in the hallways and Congress will get to work. Republicans have majorities in both houses, but Senate Democrats still have a powerful tool in the threatened filibuster, which requires the Senate to garner a supermajority of at least 60 votes to move most legislation forward. The sailing will not be smooth and the joy of opening day will fade until the first Tuesday in January…2019. •
Pennsylvania Neurological Society Marks Tenth Year

State neurological societies provide important educational, networking, and grassroots advocacy opportunities for neurologists. AAN member Brad C. Klein, MD, MBA, FAAN, knew his Pennsylvania colleagues would benefit from one, and he attended the 2006 Palatucci Advocacy Leadership Forum (PALF) with an ambitious action plan to start a neurological society in his home state.

As the Pennsylvania Neurological Society (PNS) celebrated its first decade during its annual meeting last fall, Klein looked back on how it started, with small dinner meetings to bring local neurologists together, and how PALF and the AAN helped him get it launched.

“I attended the PALF program in 2006, during my third year as a resident,” he said. “At the forum, I realized the necessity of neurologists in leading change for our profession and our patients. It became abundantly clear that if we, physicians and patients, were not at the table we would be on the menu. While my state has a very active medical society, representing all medical and surgical fields, specialties like neurology could easily get lost in the shuffle given how many responsibilities and competing interests the state medical society manages. The medical society also did not have a formal relationship with Pennsylvania’s neurologists, so decisions on neurology could occur without oversight. Effectively, there was no organization that represented the specific challenges that neurologists and patients with neurological issues face. It was an unmet need in the state.”

At the Palatucci Forum, Klein’s view of the importance and value of state neurological advocacy found strong backing from fellow neurologists and the Academy. “PALF introduced me to phenomenal neurologists across the world as well as AAN leadership, who were willing to support my efforts to bring an organized voice for neurology into Pennsylvania. The development of the organization truly became a team effort involving not only other Pennsylvania neurologists, but the support of the AAN and the resources they provided.”

Klein used the skills he acquired and developed at the Palatucci Advocacy Leadership Forum—the AAN’s award-winning advocacy skills development curriculum with the mission of training AAN members to advocate for the interests of their patients and profession—and continues to move the neurosociety forward. The PNS has grown and evolved over the past decade and holds well-attended annual meetings around the state of Pennsylvania. Last fall’s annual meeting in Bethlehem offered attendees nine CME credits on wide ranging topics such as migraine, ALS, epilepsy, MACRA, Alzheimer’s, and physician burnout, to name a few. In addition to a robust agenda, US Representative Charlie Dent (R-PA 15th District) stopped by to meet with PNS members and hear their concerns facing their practices and their patients.

Demonstrating the value of state societies—or advocacy in general—can be challenging, Klein acknowledged. He has seen that many neurologists still do not appreciate the potential return on their investment by getting involved in advocacy. “I think this occurs for a number of reasons. I think it’s very hard for many physicians to see the value because the tangible benefits often take more time than we would expect (potentially years). There are often compromises in our goals as well because of the number of stakeholders and we may not feel comfortable with the outcomes, yet we need to keep in mind that the results we get are often better than what happens without our involvement. Further, sometimes advocacy ‘successes’ are not creating new legislative bills, but preventing bad legislation from moving forward, and these successes are not always apparent and tangible enough for many. I think many people also see legislatures as unreachable and/or not people with whom they can talk, even though they are just individuals like us. And lastly, too few of us have overcome our hesitancy to take on new skill sets, even though the skills simply require improving our abilities to communicate with others. For all these reasons, a state neurological society can be challenged in its ability to expand its value.”

From left, Brad C. Klein, MD, MBA, FAAN; US Congressman Charlie Dent (R-PA 115th District); and Jonathan P. Hosey, MD, FAAN.
Nonetheless, the hard work and energy invested in advocacy can have a significant payoff on a number of levels. For Klein and the PNS, an important aspect is the recognition and value of the Pennsylvania society as the “go to” organization for neurological issues in the state—just as the AAN is on a federal level with Congress and other health policy agencies. "Because of its coordinated voice, the organization has directly changed state legislative bills to support and protect neurology patients. Further, the state medical society, as well as the state legislature, will reach out to us when they need expert opinion on issues involving neurological concerns. I believe that the organization has helped play a small role in the growth of other neurologists’ interest in their own advocacy efforts. It is also exciting to see the leadership of our current president, Dr. Anthony May, and our outstanding board guide the organization into the future."

Not surprisingly, Klein believes that every state can benefit from a neurological society. "Unquestionably, our direct role can impact how we practice and how patient care is delivered. A state neurological society does not need to be large to be impactful. If you wish to start a society in your state, start small, set reasonable expectations and goals, and continue to grow. Neurologists also need to feel empowered to know that if they want to make this happen, they just need to reach out to the AAN to start a discussion, develop the support, find the right people to connect with, and then move forward."

Visit the AAN’s Neurosociety page at AAN.com/membership/state-societies to get connected with your state neurosociety and get involved today. And if your state does not have such a society, you may be the one to follow in Klein’s footsteps!

Here are more ways to help you get started:

- Take a deeper dive into advocacy by viewing webinars on Advocacy 101 and legislative issues at AAN.com/public-policy/public-policy-education/webinars.
- Learn what your colleagues have to say in the “Advocating for Neurology” video on YouTube at Youtube.com/watch?v=gtlseviPaSo.
- Keep up on the latest neurology news from Washington, DC, by reading the Capitol Hill Report email sent twice monthly and posted at AAN.com/public-policy/capitol-hill-report.
- Access the free NeuroLearnSM advocacy course, “Become an Effective Advocate for Your Patients and Specialty,” available at http://bit.ly/2gkxTg9 and earn one CME credit as you learn how to recognize the core skills necessary to effectively engage with the public policy system, and identify the impact of public policy on neurology.

Consider applying for the 2018 Palatucci Advocacy Leadership Forum or Neurology on the Hill at AAN.com/public-policy.

Tell Us Your Story

4 categories to enter… 4 chances to win $1,000!

Submit a video in the category that best suits your story about brain disease, and helps build awareness of the importance of neuroscience research for patients and the physicians and scientists who treat and work to find cures.

1. “Why I think Neuroscience Is...™ Cool” — Tell us why the brain is fascinating
2. “Why I think Neuroscience Is...™ Rewarding” — Tell us how discovery opens doors
3. “Why I think Neuroscience Is...™ Essential” — Tell us why research is important
4. “Why I think Neuroscience Is...™ Critical” — Tell us why advocacy makes an impact

SUBMISSION DEADLINE: March 10, 2017

Visit NeuroFilmFestival.com for complete contest rules, idea tips, and submission instructions.
Upgrade Your Professional Credentials with the FAAN Designation

The AAN is seeking applications and nominations for its highly regarded Fellow of the American Academy of Neurology (FAAN) member category. The FAAN designation will:

- Set you apart both within the Academy and in many other circumstances throughout your professional career
- Provide the recognition you deserve for your exemplary contributions to the field of neurology
- Offer exclusive eligibility to serve on the AAN Board of Directors, a unique opportunity that could allow you to have a significant impact on the future direction of the AAN and the field of neurology

To apply, nominate a colleague, or learn about qualifications, visit AAN.com/view/FAAN today. For more information, contact AAN Member Services at memberservices@aan.com or (800) 879-1960.

Congratulations New FAANs!

The AAN congratulates the following members who were named Fellows between October and December, 2016.

Fadi Karim Abou-Mrad, MD, PhD, FAAN
Beau M. Ances, MD, PhD, MS, FAAN
Hossein Ansari, MD, FAAN
Abdulaziz Ashkanani, BMBCH, FRCP, FAAN
Amer Awad, MD, FAAN
Sheldon Benjamin, MD, FAAN
Geetha Chari, MD, FAAN
Claudia J. Chaves, MD, FAAN
Tanuja Chitnis, MD, FAAN
Kelvin L. Chou, MD, FAAN
David Corbin, MB, FRCP, FAAN
Elliot Dimberg, MD, FAAN
David W. Dodick, MD, FAAN
Daniel A. Drubach, MD, FAAN
Barbara A. Dworetzky, MD, FAAN
Diana M. Escolar, MD, FAAN
Richard E. Ferguson, MD, FAAN
Anne Foundas, MD, FAAN
Peter Fuhr, MD, FAAN
Jeffrey Marc Gelfand, MD, MAS, FAAN
David J. Gill, MD, FAAN
Vanessa K. Hinson, MD, PhD, FAAN
Teresa L. Jacobs, MD, FAAN
Sayona John, MD, FAAN
Kathleen Kennelly, MD, PhD, FAAN
Richard D. King, MD, PhD, FAAN
Bruce R. LeForce, MD, PhD, FAAN
Thomas Leist, MD, PhD, FAAN
Michael Levy, MD, FAAN
Christian J. Lueck, MD, FAAN
Raman K. Malhotra, MD, FAAN
Justin Malone, MD, FAAN
Olga L. Mcabee, MD, FAAN
Peter J. Myers, MD, FAAN
Katherine H. Noe, MD, PhD, FAAN
Bjorn E. Oskarsson, MD, FAAN
Joseph J. Pysh, DO, PhD, FAAN
Mary Ellen Quiceno, MD, FAAN
Matthew S. Robbins, MD, FAAN
Kirk Roberts, MD, FAAN
Michael Rosenbloom, MD, FAAN
Bruce S. Rubin, MD, FAAN
Jonathan S. Rutchik, MD, MPH, FAAN
Amitabh Y. Shukla, MD, FAAN
Abdelazim Sirelkhatim, MD, FAAN
Yutaka Tanaka, MD, FAAN
Pariwat Thaisetthawatkul, MD, FAAN
Gregory P. Van Stavern, MD, FAAN
Galina Vorobeychik, MD, FRCP, FAAN

Neurology Career Center: New Features Help Launch New Careers

The newly enhanced AAN Neurology Career Center makes it easier than ever to be successful at your job search. Improvements include:

- Receive notification of new positions by just providing your email address
- Apply for an open position as easily as sending an email
- Store up to 12 career-related documents in your profile
- Access the Career Center via smartphone, tablet, or desktop

Visit Careers.AAN.com—the only job board site featuring neurology-only job opportunities—today!
with policy makers in Washington, DC, to decrease the regulatory hassles neurologists face in this ever-changing health care environment so they can spend more time with their patients and less time with administrative chores.

The study involved 1,671 neurologists with a median age of 51 years and an average 17 years in practice. Of the group who completed the questionnaire, 65 percent were men. Participants reported working an average of 56 hours per week, with three-fourths of that time spent in clinical care. One-third of neurologists worked in academic practice, or a university setting, and the rest in clinical practice.

The study found 60 percent of neurologists reported at least one symptom of burnout (high emotional exhaustion or high depersonalization). A majority, 53 percent, of neurologists had high emotional exhaustion, 41 percent felt high depersonalization, and 21 percent had a low personal accomplishment score. Clinical practice neurologists had a higher burnout rate than academic neurologists (63 percent versus 56 percent).

Hours worked per week, nights on call per week, number of outpatients seen each week, and amount of clerical work were associated with greater burnout risk. Lower risk was associated with effective support staff, job autonomy, meaningful work, age, and subspecializing in epilepsy.

“US neurologists deal with diseases of the brain and other parts of the nervous system that are extremely complex, and most of these disorders are chronic and severely debilitating,” said study author Neil A. Busis, MD, FAAN. “At the same time, neurologists are faced with excessive workloads, loss of autonomy, clerical burden, and inadequate support staff—isues that are associated with the high prevalence of burnout and low rates of satisfaction with career and work-life integration.”

Other key findings of the study:

■ 61 percent of neurologists would choose to become a physician again while 67 percent would choose to become a neurologist again.
■ 67 percent of neurologists were satisfied with their job.
■ One in three neurologists indicated their work schedule left enough time for personal/family life.
■ 60 percent of neurologists reported they have significant autonomy in determining how they do their job.

■ Most neurologists (88 percent) reported their work is meaningful to them.
■ A minority of neurologists indicated the amount of time spent on clerical tasks was reasonable, both directly (23 percent) and indirectly (16 percent) related to patient care.
■ 56 percent of neurologists indicated that they had too little support staff to assist them in their work.

Neurologists work a median of 55 hours per week compared to 50 hours for all US physicians.

In addition, 32 percent of neurologists indicated their work schedule leaves enough time for personal/family life compared to 41 percent of all physicians, a rate lower than every other medical specialty.

According to the study, effective approaches to address these issues and cultivate meaning and engagement in neurology practice could include efforts within the neurologist’s work unit and organization to improve efficiency, optimize workload, decrease clerical burden, provide greater flexibility and control over work, and enhance support staff. Physician-friendly national policies that decrease regulatory burden and mandated clerical tasks would also enhance neurologists’ engagement in the practice of neurology.

“Today, demand for neurologist services exceeds supply in most states, and demand is growing faster than supply. By 2025, it’s estimated that we will need nearly 20 percent more neurologists than are available. The high rate of neurologist burnout may contribute to—and be exacerbated by—this shortage,” said Cascino, who spearheaded the AAN’s efforts to study the issue of burnout and work-life balance and identify ways to reduce or prevent burnout and improve work-life balance. ¶
AAN Guideline Suggests fMRI Useful in Epilepsy Surgery Evaluation

The AAN’s new “Practice Guideline: Use of fMRI in the Presurgical Evaluation of Patients with Epilepsy” was published online ahead of print on January 11, 2017, and was published in the January 24, 2017, print issue of Neurology®. This new guideline is the first to provide a summary of the available studies on the use of functional MRI (fMRI) in predicting cognitive outcomes of patients who undergo surgery for the treatment of epilepsy. The guideline will support further efforts to develop and implement the use of fMRI in presurgical evaluation of patients with epilepsy. The guideline evidence suggests fMRI may be used as an option in place of the intracarotid amobarbital procedure (IAP) in many instances; however, the guideline authors emphasize that the choice of procedure depends on many factors and should be made on a per-case basis. Limitations of IAP include the limited time available for testing and the expense and discomfort of the procedure.

“This guideline provides a framework for understanding the literature on fMRI in the evaluation of epilepsy patients, including the evaluation of the commonly used fMRI tasks for predicting postsurgical outcomes,” said Jerzy Szafarski, MD, PhD, FAAN. “The data show that fMRI may be considered in place of IAP for some purposes such as language and memory lateralization and prediction of language and memory outcomes after epilepsy surgery, although clinicians should determine the appropriate procedure on an individual basis.”

Read the guideline and access PDF summaries for clinicians and patients, and a slide presentation set on AAN.com. For more information, contact Julie Cox at jcox@aan.com or (612) 928-6069.

Conferences

The Best Beds in Boston Beckon for Your Business by March 8

The only reservations you should have about attending the AAN Annual Meeting in Boston are hotel reservations! Be sure to book your accommodations by March 8 to ensure you have a place to rest and relax after a busy day at the meeting everyone’s talking about.

Please be advised of unofficial solicitations and websites to secure housing for the AAN Annual Meeting. Convention Management Resources, Inc., is the only official housing company for the AAN. The companies Congress Makers and HICORD may represent themselves as official housing companies for the AAN, but they are not affiliated with the AAN in any way, nor are they authorized to represent the AAN and should be avoided.

Visit AAN.com/view/AM17 today to learn more, book your hotel by March 8, and register by March 30 to get the early registration discount savings.

Last Call: Submit Emerging Science Program Abstracts by February 9

The February 9 deadline is near to submit abstracts to be considered for the 2017 Annual Meeting’s Emerging Science program. Major research must have been conducted since the October 24, 2016, abstract deadline. Visit AAN.com/view/17emergingscience for eligibility requirements and to conveniently submit online. For more information, contact science@aan.com or (612) 928-6088.
IN THE MANAGEMENT OF RMS

THINK BEYOND RELAPSES

RMS = relapsing forms of 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. 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 activated charcoal. AUBAGIO is contraindicated in patients with severe hepatic impairment. Patients with pre-existing liver disease may be at increased risk of developing elevated serum transaminases when taking AUBAGIO.
• AUBAGIO is contraindicated for use in pregnant women and in women of reproductive potential who are not using effective contraception because of the potential for fetal harm. Teratogenicity and embryolethality occurred in animals at plasma teriflunomide exposure lower than that in humans. Exclude pregnancy before the start of treatment with AUBAGIO in females of reproductive potential. Advise females of reproductive potential to use effective contraception during AUBAGIO treatment and during an accelerated drug elimination procedure after AUBAGIO treatment. Stop AUBAGIO and use an accelerated drug elimination procedure if the patient becomes pregnant.

CONTRAINDICATIONS
• Patients with severe hepatic impairment.
• Pregnant women and females of reproductive potential not using effective contraception.
• Patients with a history of hypersensitivity reaction to teriflunomide, leflunomide, or to any of the inactive ingredients in AUBAGIO.
• Co-administration with leflunomide.
Start or switch to AUBAGIO® (teriflunomide) 14 mg—the only oral DMT with a proven impact on disability progression in 2 Phase III trials

The majority of patients remained free from disability progression* with AUBAGIO 14 mg

![Figure: AN ESTIMATED 80% IN TEMSO OVER 108 WEEKS (P=0.03)†](image)

![Figure: AN ESTIMATED 84% IN TOWER OVER 108 WEEKS (P<0.05)†](image)

*Disability progression was a secondary endpoint in TEMSO and TOWER.†

TEMSEO: 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.

TOWER: A double-blind, placebo-controlled trial in patients with relapsing forms of MS (N=1149). Patients were randomized to receive AUBAGIO 14 mg (n=372), AUBAGIO 7 mg (n=408), or placebo (n=369) once daily with results for up to 40 months of treatment.

WARNINGS AND PRECAUTIONS

- **Hepatotoxicity:** Patients with pre-existing acute or chronic liver disease, or those with serum ALT >2 times the upper limit of normal (ULN) before initiating treatment, should not normally be treated with AUBAGIO. In clinical trials, if ALT elevation was >3 times the ULN on 2 consecutive tests, patients discontinued AUBAGIO and underwent accelerated elimination. Consider additional monitoring if co-administering AUBAGIO with other potentially hepatotoxic drugs; monitor patients who develop symptoms suggestive of hepatic dysfunction (eg, unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine).

- **Teratogenicity:** AUBAGIO may cause fetal harm when administered in pregnant women. Teratogenicity and embryo-fetal lethality occurred in animal reproduction studies in multiple animal species at plasma teriflunomide exposures similar to or lower than that in humans at the maximum human recommended dose of 14 mg/day. AUBAGIO is contraindicated for use in pregnant women and females of reproductive potential not using effective contraception. Women who become pregnant while taking AUBAGIO may enroll in the AUBAGIO pregnancy registry by calling 1-800-745-4447, option 2.

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

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

(continued on back)

Please see additional Important Safety Information and Brief Summary of Full Prescribing Information, including boxed WARNING, on the following pages.

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1 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. 

2 AUBAGIO is available in 14 mg and 7 mg tablets.
Proven impact in newly diagnosed RMS patients

In patients who had a first clinical event characteristic of RMS, AUBAGIO® (teriflunomide) provided freedom from relapses

72% REMAINED RELAPSE FREE IN TOPIC VS 62% WITH PLACEBO

71% of patients remained relapse free with AUBAGIO 7 mg in the TOPIC trial

TOPIC is the only trial of an oral RMS therapy that studied patients who had a first clinical event consistent with acute demyelination occurring within 90 days of randomization

MAKE AUBAGIO YOUR FIRST CHOICE FOR NEWLY DIAGNOSED RMS PATIENTS

IMPORTANT SAFETY INFORMATION (continued)

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

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

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

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

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

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

Use in Specific Populations: Women who wish to become pregnant should discontinue AUBAGIO and undergo an accelerated elimination procedure. Use of effective contraception should be continued until plasma concentrations of teriflunomide are <0.02 mcg/mL. Nursing mothers should not use AUBAGIO. 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 effective contraception. Men wishing to father a child should discontinue therapy and either undergo accelerated elimination or verify plasma teriflunomide concentration is <0.02 mcg/mL.

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


SANOFI GENZYME

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GZUS.AUBA.15.01.0245(3) December 2016

AUBAGIO is available in 14 mg and 7 mg tablets.
AUBAGIO® (teriflunomide) tablets, for oral use
Rx Only

Brief Summary of Prescribing Information

WARNING: HEPATOTOXICITY and RISK OF TERTAGENICITY

• 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. Concurrent 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)]. 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

AUBAGIO is contraindicated for use in pregnant women and in women of reproductive potential who are not using effective contraception because of the potential for fetal harm. Teratogenicity and embryofetal lethality occurred in animals at plasma teriflunomide exposures lower than that in humans. Exclude pregnancy before the start of treatment with AUBAGIO in females of reproductive potential. Advise females of reproductive potential to use effective contraception during treatment with AUBAGIO and during an accelerated drug elimination procedure after AUBAGIO treatment. Stop AUBAGIO and use an accelerated elimination procedure if the patient becomes pregnant. See Contraindications (4), Warnings and Precautions (5.2, 5.3), Use in Specific Populations (8.1), and Clinical Pharmacology (12.3) in the full prescribing information.

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)].

• Exclude pregnancy prior to initiation of treatment with AUBAGIO in females of reproductive potential.[see Warnings and Precautions (5.1)].

• Check blood pressure and screen for serious skin reactions.[see Contraindications (4), Warnings and Precautions (5.3)].

4 CONTRAINDICATIONS

AUBAGIO is contraindicated in:

• Patients with severe hepatic impairment.[see Warnings and Precautions (5.1)].

• Pregnant women and females of reproductive potential not using effective contraception. AUBAGIO may cause fetal harm.[see Warnings and Precautions (5.2 and 5.3) and Use in Specific Populations (8.1)].

• Patients with a history of a hypersensitivity reaction to teriflunomide, leflunomide, or to any of the inactive ingredients in AUBAGIO. Reactions have included anaphylaxis, angioedema, and serious skin reactions.[see Warnings and Precautions (5.3)].

• Co-administration with teriflunomide.[see Clinical Pharmacology (12.3) in the full prescribing information].

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Severe liver injury including fatal liver failure and dysfunction has been reported in some patients treated with leflunomide, which is indicated for rheumatoid arthritis. A similar risk would be expected for teriflunomide because recommended doses of teriflunomide and leflunomide result in a similar range of plasma concentrations of teriflunomide. Patients with pre-existing liver disease may be at increased risk of developing elevated serum transaminases when taking AUBAGIO. Patients with pre-existing acute or chronic liver disease, or those with serum alanine aminotransferase (ALT) greater than two times the upper limit of normal (ULN) before initiating treatment, should not normally be treated with AUBAGIO. AUBAGIO is contraindicated in patients with severe hepatic impairment.[see Contraindications (4)].

In placebo-controlled trials, ALT greater than three times the ULN occurred in 61/1045 (5.8%) and 62/1007 (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 elimina-
Vaccination

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

Malignancy

The risk of malignancy, particularly lymphoproliferative disorders, is increased with the use of some immunomodulatory therapies. 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 that a fever associated with signs of other organ system involvement (e.g., rash, lymphadenopathy, or hepatic dysfunction) may be drug-related. Instruct patients to discontinue AUBAGIO and seek immediate medical care should these signs and symptoms occur. Discontinue AUBAGIO, unless the reactions are clearly not drug-related, and begin an accelerated elimination procedure immediately [see Warnings and Precautions (5.3)]. In such cases, patients should not be re-exposed to teriflunomide [see Contraindications (4)].

5.6 Peripheral Neuropathy

In placebo-controlled studies, peripheral neuropathy, including both 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 (6 patients). Treatment was discontinued in 0.7% (6 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. 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 (5.2)].

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 1.6% 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 intestinal pneumatosis, 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

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

6 ADVERSE REACTIONS

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

- Respiratory Effects [see Warnings and Precautions (5.8)]
- Bone Marrow Effects/Immunosuppression Potential/Infestations [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)]
8.5 Geriatric Use

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

8.6 Hepatic Impairment

Effects of AUBAGIO on fertility in humans have not been evaluated.

Administration of teriflunomide to male rats resulted in no adverse effects on fertility. However, reduced epididymal sperm count was observed (see Nonclinical Toxicology (13.1) in the full prescribing information). Effects of AUBAGIO on fertility in humans have not been evaluated.

8.7 Renal Impairment

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

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

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
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November 2016

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**New Continuum Examines Cerebrovascular Disease**

Cerebrovascular disease in the focus of the latest issue of *Continuum: Lifelong Learning in Neurology®*. Participants can earn up to 14 hours of AMA PRA Category 1 Credit™ (12 of which apply to MOC Self-Assessment credit).

“This issue of *Continuum* represents an in-depth overview of the current state of cerebrovascular disease written by experts in the field,” said guest editor Kevin M. Barrett, MD, MSc, associate professor and vice chair of the department of neurology at Mayo Clinic Florida in Jacksonville.

“The content will be of practical value to neurologists in the diagnosis, management, and selection of evidence-based treatment for patients with cerebrovascular disorders.”

Articles in this issue include:

- Stroke Epidemiology and Risk Factor Management, by Amy Guzik, MD, and Cheryl Bushnell, MD, MHS
- Clinical Evaluation of the Patient with Acute Stroke, by Andrew M. Southerland, MD, MSc
- Treatment of Acute Ischemic Stroke, by Alejandro A. Rabinstein, MD, FAAN
- Diagnosis and Management of Transient Ischemic Attack, by Shelagh B. Coutts, MD, MSc, FRCP C
- Prevention and Management of Poststroke Complications, by Josephine F. Huang, MD
- Cardioembolic Stroke, by Cumara B. O’Carroll, MD, MPH, and Kevin M. Barrett, MD, MSc
- Large Artery Atherosclerotic Occlusive Disease, by John W. Cole, MD, MS
- Arterial Ischemic Stroke in Children and Young Adults, by Warren D. Lo, MD, and Riten Kumar, MD, MSc
- Management of Unruptured Intracranial Aneurysms and Cerebrovascular Malformations, by Kelly D. Flemming, MD, and Giuseppe Lanzino, MD
- Inherited and Uncommon Causes of Stroke, by Jennifer Juhl Majersik, MD, MS
- Stroke Rehabilitation, by Samir R. Belagaje, MD
- Discussing Life-sustaining Therapy with Surrogate Decision Makers, by David Y. Hwang, MD
- Remote Evaluation of the Patient with Acute Stroke, by Bart M. Demaerschalk, MD, MSc, FAHA, FRCP C
- Coding in Stroke and Other Cerebrovascular Diseases, by Pearce J. Korb, MD, and William Jones, MD

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**ESPAÑOL**

**Directrices Selectas Ahora Disponible en Español**

The American Academy of Neurology has collaborated with the Mexican Academy of Neurology to produce translations of select AAN clinical guidelines from English into Spanish.

Access these translations at [AAN.com/view/MultipleLanguages](AAN.com/view/MultipleLanguages).
SEIZURE CONTROL* DAY & NIGHT

Equetro® (carbamazepine) Extended-Release Capsules
Approved for Use in Treating Epilepsy*

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

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

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

*PLEASE SEE SPECIFIC INDICATIONS ON BACK.
PLEASE SEE IMPORTANT SAFETY INFORMATION ON BACK INCLUDING BOXED WARNING, CONTRAINDICATIONS, AND WARNINGS AND PRECAUTIONS.
SUMMARY OF IMPORTANT SAFETY INFORMATION WITH BOXED WARNING FOR EQUETRO® (CARBAMAZEPINE) EXTENDED-RELEASE CAPSULES

WARNING: SERIOUS DERMATOLOGIC REACTIONS AND APLASTIC ANEMIA AND AGRANULOCYTOSIS

Serious Dermalogic Reactions and HLA-B*1502 Allele

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and erythema multiforme (EM), have occurred in patients treated with carbamazepine. These syndromes may be accompanied by mucocutaneous ulcers, fever, or painful rash. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations, but the risk in patients of Asian descent is estimated to be about 10 times higher. There is a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. Test for HLA-B*1502, prior to initiating EQUETRO in patients with an increased likelihood of carrying this allele. Avoid use of EQUETRO in patients testing positive for the allele unless the benefit clearly outweighs the risk. Discontinue EQUETRO if you suspect the patient has a serious dermalogic reaction [see Warnings and Precautions, Laboratory Tests].

Aplastic Anemia and Agranulocytosis

Aplastic anemia and agranulocytosis can occur during treatment with EQUETRO. The risk of developing these reactions with EQUETRO is 5-8 times greater than in the general population. However, the overall risk in the general population is low (6 cases in a population of one million per year for agranulocytosis and two cases in a population of one million per year for aplastic anemia), Aplastic anemia and agranulocytosis have occurred in patients treated with carbamazepine. These syndromes may be accompanied by mucocutaneous ulcers, fever, or painful rash. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations, but the risk in patients of Asian descent is estimated to be about 10 times higher. There is a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. Test for HLA-B*1502, prior to initiating EQUETRO in patients with an increased likelihood of carrying this allele. Avoid use of EQUETRO in patients testing positive for the allele unless the benefit clearly outweighs the risk. Discontinue EQUETRO if you suspect the patient has aplastic anemia or agranulocytosis [see Warnings and Precautions, Laboratory Tests].

INDICATION: EQUETRO is indicated for the treatment of:

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

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

Prior to initiating treatment with EQUETRO, test patients in genetically at-risk populations for the presence of the HLA-B*1502 allele. Complete pretreatment blood counts, baseline and periodic liver, eye, urinalysis and BUN testing should be obtained for patients and their immediate family members and if present, benefits outweigh the risks.

CONTRAINDICATIONS: EQUETRO is CONTRAINDICATED in PATIENTS WITH BONE MARROW DEPRESSION, KNOWN HYPERSENSITIVITY TO CARBAMAZEPINE, SUCH AS ANAPHYLAXIS OR SERIOUS HYPERSENSITIVITY REACTIONS, OR KNOWN HYPERSENSITIVITY TO ANY OF THE TRICYCLIC COMPOUNDS, SUCH AS AMITRIPTYLINE, DESIPRAMINE, IMIPRAMINE, PROTRIPYLINE, AND NORTRIPTYLINE. HYPERSENSITIVITY REACTIONS INCLUDE ANAPHYLAXIS AND SERIOUS RASH. CONCOMITANT USE OF CARBAMAZEPINE AND OTHER DRUGS THAT INDUCE CYTOCHROME P450 ISOENZYMES SHOULD BE AVOIDED DUE TO POSSIBLE INTERACTIONS. CONTRAINDICATED in patients with a history of cardiac, hepatic, or renal damage; adverse hematologic reactions have occurred in patients treated with carbamazepine. These syndromes may be accompanied by mucocutaneous ulcers, fever, or painful rash. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations, but the risk in patients of Asian descent is estimated to be about 10 times higher. There is a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. Test for HLA-B*1502, prior to initiating EQUETRO in patients with an increased likelihood of carrying this allele. Avoid use of EQUETRO in patients testing positive for the allele unless the benefit clearly outweighs the risk. Discontinue EQUETRO if you suspect the patient has aplastic anemia or agranulocytosis [see Warnings and Precautions, Laboratory Tests].

WARNINGS: SERIOUS DERMATOLOGIC REACTIONS

Discontinue EQUETRO if you suspect that a patient has a serious dermalogic reaction. If signs or symptoms suggest SJS/TEN, do not resume treatment with EQUETRO. Drug Reaction with Eosinophilia and Systemic Symptoms/Multorgan Sensitivity

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

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

Suicidal Behavior and Ideation. Antiepileptic drugs (AEDs), including EQUETRO, may rarely result in serious suicidal thoughts or behavior in patients taking these drugs for any indication. Anyone considering prescribing EQUETRO must balance the risk of suicidal thought or behavior with the risk of untreated illness. Treatment of serious illness in the setting of a known or suspected psychiatric condition may require careful consideration of the use of an AED. Carbamazepine is not approved for use in treating bipolar depression.

Usage in Pregnancy. EQUETRO is associated with an increased risk of congenital disorders and other adverse maternal and fetal outcomes when used during pregnancy. A drug associated with an increased risk of congenital disorders and other adverse maternal and fetal outcomes is not FDA approved for use in pregnant women for this indication. EQUETRO should not be used in pregnant women for this indication.

Usage in Pregnancy: Carbamazepine is transferred to the breast milk of nursing mothers. It is not known whether EQUETRO is excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.

Usage in Pediatric Patients: The safety and effectiveness of EQUETRO have not been established in pediatric patients for indications other than Epilepsy. See Full Prescribing Information for potential drug interactions.

ADVERSE REACTIONS. The most serious adverse reactions previously observed with carbamazepine were reported in the hemopoietic system and skin and in the cardiovas- cular system during lactation. Because of the potential for serious adverse reactions in nursing infants from carbamazepine, 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.

Usage in Pregnancy: Carbamazepine is metabolized mainly by cytochrome P450 3A4 to the active carbamazepine-10,11-epoxide, which is further metabolized to the transdiol by epoxide hydrolase; the potential exists for interaction between EQUETRO and any agent that inhibits CYP3A4 and/or epoxide hydrolase and/or induce CYP3A4.

Usage in Pregnancy: Pregnancy Category D (see WARNINGS).

Nursing Mothers: Carbamazepine and its epoxide metabolite are transferred to the breast milk of nursing mothers. It is not known whether EQUETRO is excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.

Usage in Pediatric Patients: The safety and effectiveness of EQUETRO have not been established in pediatric patients for indications other than Epilepsy. See Full Prescribing Information for potential drug interactions.

ANYONE CONSIDERING PRESCRIBING EQUETRO MUST BALANCE THE RISK OF SUICIDAL THOUGHT OR BEHAVIOR WITH THE RISK OF UNTREATED ILLNESS. TREATMENT OF SERIOUS ILLNESS IN THE SETTING OF A KNOWN OR SUSPECTED PSYCHIATRIC CONDITION MAY REQUIRE CAREFUL CONSIDERATION OF THE USE OF AN AED. CARBAMAZEPINE IS NOT APPROVED FOR USE IN TREATING BIPOLAR DEPRESSION.

Carbamazepine and its epoxide metabolite are transferred to the breast milk of nursing mothers. It is not known whether EQUETRO is excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.

**Please see Full Prescribing Information available at Equetro.com.**
AAN Partners in TRANSCENDS Program for Underrepresented Minority or Disabled Physician-Scientists

The AAN is collaborating with the Medical University of South Carolina to offer TRANSCENDS (Training in Research for Academic Neurologists to Sustain Careers and Enhance the Numbers of Diverse Scholars), a new program that is funded by a grant from the National Institutes of Health. TRANSCENDS seeks to train and inspire underrepresented minority physician-scientists and persons with disabilities who are post-residency fellows and junior faculty to conduct high-quality neurologic research and develop successful academic careers.

The program will accept applications until February 15, 2017. Up to six individuals will be selected to participate in 2017, with more positions available in subsequent years. Eligibility is limited to junior fellows or neurologists and physician scientists three years or less from first appointment, or five years or less from completion of residency, who are disabled and/or belong to an underrepresented minority in neurology including Black/African American, Hispanic, Latino, Native American, Pacific Islander, Native Alaskan, or Hawaiian.

Experts cite a serious and significant underrepresentation of certain populations in the biomedical, clinical, behavioral, and social sciences in the US. A well-trained workforce of underrepresented minority faculty is considered essential in neurology, because these faculty members are more likely to engage in research to reduce disparities in neurologic outcomes that affect underserved and/or low-income communities, and help improve the paucity of race-ethnic minority participation in clinical trials.

Selected program participants will receive:
- A master of science degree in clinical research through the Medical University of South Carolina by completing a primarily online two-year course curriculum (38 credit hours)
- Mentoring and support in the development of their current research portfolio
- Support in the creation of a real or mock K application
- AAN member benefits
- Opportunities to present research and network with leadership at the AAN Annual Meeting

Learn more and apply online by February 15 at AAN.com/view/TRANSCENDS.

Residents & Fellows

Resident Sought to Join Continuum Editorial Board

AAN member residents are encouraged to apply to serve on the Continuum® Editorial Board. This board provides oversight of Continuum: Lifelong Learning in Neurology®, the official CME journal of the AAN, and the companion product, Continuum® Audio. The Editorial Board is responsible for topic and guest editor selection and review and evaluation of issues in accordance with the ACCME.

One resident will be selected to serve a one-year term on the editorial board during the 2018 calendar year representing the perspective of Junior members of the Academy for Continuum, which is complimentary to all Junior members. The resident member would be included as a guest at the fall Continuum Editorial Board meeting in September 2017, and expected to attend the spring and fall meetings in 2018. Residents should be in their PGY3 or PGY4 year of training at the time of application.

“Having a neurology resident on our Editorial Board provides an important voice to our trainees in the direction of Continuum, while at the same time providing a unique opportunity for a resident to learn the ‘ins and outs’ of production of a major clinical journal,” said Continuum Editor-in-Chief Steven L. Lewis, MD, FAAN.

To apply, candidates should submit a one-page letter of interest, CV, and a letter of recommendation from their program director or department chair. For more information or to apply, contact Amanda Doering, Continuum Senior Program Manager, at adoering@aan.com by March 15, 2017.
American Brain Foundation to Launch New Crowdfunding Platform

The American Brain Foundation is developing a new online neuroscience research crowdfunding platform that will allow members of the public to search for and give money to research projects addressing brain diseases.

The foundation plans to launch the platform this year as part of its new strategic plan to reach out to the public for support.

“This inventive, new initiative has the potential to unlock significant new funds for our cause, and we all understand the urgency of attracting new money to brain disease research,” said Robert C. Griggs, MD, FAAN, chair of the foundation’s Research Advisory Committee, which is developing guidelines for researcher applications and for the scientific review of applications to determine which projects meet the criteria to be posted on the crowdfunding site.

The foundation has been working with the Diabetes Research Connection, which launched a crowdfunding site for diabetes research in 2012.

The American Brain Foundation, which was founded in 1992 as the charitable arm of the AAN, has invested more than $20 million in funding for clinical research in its quest to find cures for brain and nervous system diseases affecting nearly 50 million Americans.

Look for more information about the new crowdfunding platform, including how to submit a project for funding, at the American Brain Foundation booth at the AAN Annual Meeting in Boston in April.

Robert C. Griggs, MD, FAAN

The American Brain Foundation has consulted with the Diabetes Research Connection on its successful crowdfunding platform.
Indication

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

Important Safety Information

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

Hepatic Injury Including Autoimmune Hepatitis

- ZINBRYTA can cause severe liver injury including life-threatening events, liver failure, and autoimmune hepatitis. Obtain transaminase and bilirubin levels before initiation of ZINBRYTA. Monitor and evaluate transaminase and bilirubin levels monthly and for 6 months after the last dose.

- ZINBRYTA is contraindicated in patients with pre-existing hepatic disease or hepatic impairment.

Other Immune-Mediated Disorders

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

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

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

Contraindications

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

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

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

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

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

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

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

SELECT was a randomized, double-blind, placebo-controlled study that compared ZINBRYTA 150 mg subcutaneous (n=208) every 4 weeks to placebo (n=204). Treatment duration was 52 weeks. The primary outcome measure was ARR at Week 52. Additional outcome measures included new T1 Gd-enhancing lesions between Weeks 8 to 24, the proportion of patients relapsed, the proportion of patients who experienced 12-week CDP, and the number of new or newly enlarging T2 hyperintense lesions. The study included RMS patients with an EDSS score of 0.0-5.0 who had experienced ≥1 relapse in the year prior to randomization or who had ≥1 T1 Gd-enhancing MRI lesions within 6 weeks of randomization. Patients with progressive forms of MS were excluded.

**Important Safety Information (Continued)**

**Hepatic Injury**

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

**Immune-Mediated Disorders**

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

Immune-Mediated Disorders (Continued)

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

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

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

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

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

ZINBRYTA REMS Program

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

Acute Hypersensitivity

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

Infections

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

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

Depression and Suicide

In controlled trials, depression-related events occurred in 10% of ZINBRYTA-treated patients compared with 8% of AVONEX-treated patients (Study 1) and in 7% of ZINBRYTA-treated patients compared with 2% of patients taking placebo (Study 2). Administer ZINBRYTA with caution to patients with previous or current depressive disorders. Advise patients and/or caregivers to immediately report any symptoms of new or worsening depression and/or suicidal ideation. If a patient develops severe depression and/or suicidal ideation, consider discontinuation of ZINBRYTA.

Adverse Reactions

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

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

**Brief Summary for ZINBRYTA (daclizumab) injection, for subcutaneous use**

**Consult Full Prescribing Information**

**WARNING: HEPATIC INJURY INCLUDING AUTOIMMUNE HEPATITIS and OTHER IMMUNE-MEDIATED DISORDERS**
- Hepatic Injury Including Autoimmune Hepatitis

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

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

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

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

- Other Immune-Mediated Disorders

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

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

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

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

**1 INDICATIONS AND USAGE**

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

**2 DOSAGE AND ADMINISTRATION**

**2.1 Dosing Information**

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

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

**2.2 Important Administration Instructions**

ZINBRYTA is for subcutaneous use only.

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

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

Sites for injection include the thigh, abdomen, and back of the upper arm.

Use each prefilled syringe one time and then place in a sharps disposal container for disposal according to community guidelines [see How Supplied/Storage and Handling (16.3)].

**2.3 Assessment Prior to Initiating ZINBRYTA**

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

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

Prior to initiation of ZINBRYTA, screen patients for Hepatitis B and C.

ZINBRYTA is contraindicated in patients with pre-existing hepatic disease [see Contraindications (4)].

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

**2.4 Laboratory Testing and Monitoring to Assess Safety After Initiating ZINBRYTA**

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

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

**Table 1: ZINBRYTA Treatment Modification for Liver Test Abnormalities**

<table>
<thead>
<tr>
<th>Lab Value(s) Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT or AST greater than 5 times ULN OR total bilirubin greater than 2 times ULN</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>
</tr>
</tbody>
</table>

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

ULN = upper limit of normal

**3 DOSAGE FORMS AND STRENGTHS**

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

**4 CONTRAINDICATIONS**

ZINBRYTA is contraindicated in patients with:
- Pre-existing hepatic disease or hepatic impairment, including ALT or AST at least 2 times the ULN, because ZINBRYTA could exacerbate existing liver dysfunction [see Dosage and Administration (2.3) and Warnings and Precautions (5.1)].
- A history of autoimmune hepatitis or other autoimmune condition involving the liver [see Warnings and Precautions (5.1)].
- A history of hypersensitivity to daclizumab or any other components of the formulation. Use in such patients may result in anaphylaxis or life-threatening multi-organ hypersensitivity [see Warnings and Precautions (5.4)].
5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Injury

ZINBRYTA can cause life-threatening severe liver injury, including liver failure and autoimmune hepatitis. In controlled studies, serious drug-related hepatic injury occurred in 0.7% of ZINBRYTA-treated patients compared with 0.4% of AVONEX-treated patients (Study 1) and in 1.0% of ZINBRYTA-treated patients compared with no injury in placebo patients (Study 2). Across all clinical studies (controlled and open-label), serious drug-related hepatic injury occurred in 1% of ZINBRYTA-treated patients, with monthly monitoring of transaminases and total bilirubin. The incidence of discontinuation due to drug-related hepatic injury was 3% in ZINBRYTA-treated patients and 4% in AVONEX-treated patients.

Autoimmune Hepatitis: Across all clinical studies (controlled and open-label), 0.3% of ZINBRYTA-treated patients developed autoimmune hepatitis. One fatal case of primary immune hepatitis occurred in a patient re-initiating ZINBRYTA after a planned 6 month treatment interruption period. This patient subsequently received two doses of ZINBRYTA in the presence of persisting alanine aminotransferase levels (ALT) more than 5 times the upper limit of normal (ULN).

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

Monitoring: Prior to starting treatment with ZINBRYTA, obtain serum 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 discontinue treatment with ZINBRYTA, as appropriate. Patients with prolonged elevations of serum transaminases should be evaluated for other possible causes, such as infection, and a specialist should evaluate the patient (see Table 1). Discontinue ZINBRYTA if autoimmune hepatitis is suspected. Treatment of autoimmune hepatitis with systemic corticosteroids and other immunosuppressant drugs may be required. Some patients may need long-term immunosuppression.

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

5.2 Immune-Mediated Disorders

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

Some patients required invasive procedures for diagnosis (e.g., colonoscopy, liver biopsy, kidney biopsy, lung biopsy), hospitalization for fluid replacement or blood transfusion, or prolonged treatment with systemic corticosteroids or immunosuppressant drugs. Some of these patients 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 3% 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. Rashess 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 or eczema occurred more frequently in ZINBRYTA-treated patients compared to AVONEX-treated patients or to patients on placebo, and eczema was observed more frequently in ZINBRYTA-treated patients compared to AVONEX-treated patients [see Adverse Reactions (6.1)]. Psoriatic conditions occurred in 2% of ZINBRYTA-treated patients compared with 0.3% of AVONEX-treated patients. 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 lymphedectis occurred in 6% of ZINBRYTA-treated patients compared with 1% of AVONEX-treated patients (Study 1) and in 2% of ZINBRYTA-treated patients compared with 1% of placebo-treated patients (Study 2). Onset of lymphadenopathy or lymphedectis occurred throughout the treatment period. Serious events related to lymphadenopathy or lymphedectis included infections, benign salivary neoplasm, 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. Dermatitis occurred in one patient, and 1% of the relationship to ZINBRYTA is unknown [see Adverse Reactions (6.1)]. Some required treatment with systemic corticosteroids. Some required several months for resolution after the last dose of ZINBRYTA.

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

5.3 ZINBRYTA REMS Program

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

Notable requirements of the ZINBRYTA REMS Program include the following:

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

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

5.4 Acute Hypersensitivity

ZINBRYTA can cause anaphylaxis, angioedema, and urticaria after the first dose or at any time during treatment. Discontinue and do not restart ZINBRYTA if anaphylaxis or other allergic reactions occur [see Contraindications (4)].
5.5 Infections
ZINBRYTA increases the risk for infections. In controlled trials, infections occurred in 69% of ZINBRYTA-treated patients compared with 57% of AVONEX-treated patients (Study 1) and in 59% 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 ideation or suicide attempt, 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, 2716 patients were treated with ZINBRYTA for a total of 5214 person-years. Of these patients, 1576 received ZINBRYTA for at least 1 year, 1259 for at least 2 years, and 888 for at least 3 years. In the controlled studies, approximately 67% were female, 92% were Caucasian, and the mean age was 36 years at study entry.

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

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

The most common adverse reactions 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>14</td>
</tr>
<tr>
<td>Rash1</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Influenza</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Dermatitis1</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Eczema4</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Tonsillitis</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Acne</td>
<td>3</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZINBRYTA 150 mg SQ Every 4 Weeks N = 208 %</th>
<th>Placebo N = 204 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Depression1</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Rash1</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>5</td>
<td>2</td>
</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, rash, and vesicular rash
3 includes allergic dermatitis, atopic dermatitis, bullous dermatitis, dermatitis, exfoliative dermatitis, and seborrheic dermatitis

Other clinically relevant adverse reactions observed at <2% difference included abnormal liver function test, decreased lymphocyte count, diarrhea, dry skin, erythema, folliculitis, increased hepatic enzyme, laryngitis, lymphadenitis, pneumonia, pruritus, psoriasis, respiratory tract infection, skin exfoliation, toxic skin eruption, and viral infection.
Seizures: In Study 1, seizures occurred in 1% of ZINBRYTA-treated patients, compared with 0.3% of AVONEX-treated patients. In Study 2, no seizures occurred in either treatment group.

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

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

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. In Study 1, patients were tested for anti-drug (daclizumab) antibodies at Week 4 and approximately every 3 months thereafter. Anti-drug antibodies and neutralizing antibodies were observed in 19% (175/913) and 8% (71/913) of patients, respectively. Anti-drug antibody responses were transient in 12% (110/913) of patients. 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 non-prescription 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 (5.4)].

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 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.

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 (5.4, 5.5)].

8.5 Geriatric Use

Clinical studies of ZINBRYTA did not include a sufficient number of patients aged 65 years 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 significant 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 (5.4)].

17 PATIENT COUNSELING INFORMATION

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

Hepatic Injury: Inform the patient of the risk of severe hepatic injury associated with ZINBRYTA. Advise patients of the symptoms of hepatic dysfunction, and instruct patients to report such symptoms to their healthcare provider immediately [see Warnings and Precautions (5.4)].

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

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

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

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

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

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

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

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

APRIL 22–28, 2017
AAN Annual Meeting, Boston
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 angiograms, EEGs, Evoked Potentials, EKGs, and 24-72 Hour Ambulatory EEGs. We also have an active Teleneurology service that is affiliated with Massachusetts General Hospital. Central Maine Medical Center is the flagship hospital of Central Maine Healthcare. The medical center has 250 inpatient beds and offers a broad range of services that include, among many, neurosurgery, a Level II trauma center, cardiovascular medicine, vascular and cardiac surgery, and medical and radiation oncology. The Central Maine Medical Group comprises of approximately 350 providers, approximately half of which are in primary care. The group delivers care across almost 2,500 square miles at numerous outpatient sites and four hospitals. A competitive salary and attractive benefits package are enhanced by the scenic beauty and abundant outdoor adventure found in Maine. Interested candidates, please send CV to Gina Malluzzi, Central Maine Medical Center, 300 Main Street, Lewiston, ME 04240. Fax: (207) 795-5696, email: MalluzziG@cmhc.org, or call: (800) 445-7431. Not a J1 Opportunity.

Movement Disorders Neurologist
Help Build a Gateway for Better Health. At Northwest Permanente, P.C., we want every patient we see to receive the medical care they need to live long and thrive. You’ll benefit from a comprehensive network of support services and a talented team of colleagues who share your passion for medicine and patient care. We are a self-governed, physician-led, multi-specialty group with a patient-centered focus. Our practice model is designed to deliver primary care and medical subspecialties throughout the region. Our integrated delivery system offers care across almost 2,500 square miles at numerous outpatient sites and four hospitals. A competitive salary and attractive benefits package are enhanced by the scenic beauty and abundant outdoor adventure found in Maine. Interested candidates, please send CV to Gina Malluzzi, Central Maine Medical Center, 300 Main Street, Lewiston, ME 04240. Fax: (207) 795-5696, email: MalluzziG@cmhc.org, or call: (800) 445-7431. Not a J1 Opportunity.

Vascular Neurologists
The University of Toledo Department of Neurology is recruiting Vascular Neurologists to join their expanding department. The Stroke Program provides stroke and neuro-interventional services at the first comprehensive stroke center in NW Ohio, a primary stroke center and tele-stroke consultation at 17 hospitals throughout the region. Nationally recognized for excellence, the stroke program has been awarded Joint Commission certification since 2005, the GWTG “Gold Plus Performance Award” for the past 7 years, and been named by AHA to the “Target Stroke Honor Roll” for 3 consecutive years. The Stroke Program offers an ACGME accredited fellowship and includes teaching responsibilities for medical students, residents, and vascular fellows. Salary and rank will be commensurate with experience. Applicants should be BE/BC certified in Neurology, with vascular fellowship training. Submit a letter of interest, CV, and letters of reference to: Gretchen Tietjen, MD, Professor and Chair, Department of Neurology, University of Toledo, 3000 Arlington Avenue MS 1195, Toledo, Ohio 43614 or email ann.murphy@utoledo.edu

Clinical Neurophysiologist
The University of Toledo Department of Neurology is recruiting Clinical Neurophysiologists to join their expanding department. The Neurophysiology Program offers an ACGME accredited fellowship and includes teaching responsibilities for medical students, residents, and vascular fellows. Salary and rank will be commensurate with experience. Applicants should be BE/BC certified in Neurology, with vascular fellowship training. Submit a letter of interest, CV, and letters of reference to: Gretchen Tietjen, MD, Professor and Chair, Department of Neurology, University of Toledo, 3000 Arlington Avenue MS 1195, Toledo, Ohio 43614 or email ann.murphy@utoledo.edu

Clinical Neurophysiologist
The Department of Neurology of Memorial Sloan Kettering Cancer Center is presently seeking a full-time Clinical Neurophysiologist (CNP) with an emphasis in EMG. This position offers academically-oriented candidates an exciting opportunity to join an established neurophysiology program where opportunities for career development and clinical research are excellent. The position involves clinical care based at our Manhattan campus and MSK Westchester. Candidates must be BC/BE in Neurology, and CNP or American Board of Electrodiagnostic Medicine. Rank will be commensurate with experience and qualifications. Interested candidates should send a Curriculum Vitae and the names of three references to: Dr. Edward Axel, Vice-Chair, Department of Neurology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065; email: eaxel@mskcc.org

Fellowship in Neuroimaging
Winchester Neurological Consultants, Inc., in conjunction with Virginia Commonwealth University and Winchester Medical Center, is offering a clinical Neuroimaging Fellowship for BC/BE neurology graduates that can be completed in one or two years. Located approximately one hour from Washington, D.C., our United Council of Neurologic Subspecialties fully accredited fellowship offers extensive training in the performance and interpretation of diagnostic inpatient and outpatient MRR, 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 $50,000.00 per year plus benefits. CV should be emailed to gsteele@winchesterneurological.com

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Are you seeing the whole picture?

Migraine is a common and debilitating neurological disease. Uncover its true impact on the lives of patients, and see how the neuropeptide CGRP can play a key role in migraine’s complex pathophysiology.


Learn more about the impact of migraine and the science behind it at www.scienceofmigraine.com/learnmore

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