PracticalNeurology NEWS
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Once-Monthly Self-Administered Multiple Sclerosis Treatment Zinbryta Wins FDA Approval

The FDA has approved Zinbryta (daclizumab, Biogen/AbbVie), a once-monthly, self-administered, subcutaneous treatment for relapsing forms of multiple sclerosis (RMS). The approval was based primarily on results from two clinical trials, including DECIDE, the largest and longest head-to-head Phase 3 clinical trial ever conducted in MS. The Phase 2b SELECT and Phase 3 DECIDE studies were global, randomized, double-blind, controlled studies that involved approximately 2,400 people living with RMS. Some patients in DECIDE were treated for up to three years. In both studies, Zinbryta significantly reduced the annualized relapse rate (ARR), the primary endpoint of the studies, by 45 percent compared to Avonex up to 144 weeks and by 54 percent compared to placebo at 52 weeks, respectively.

The precise mechanism of action of Zinbryta is unknown, but it is thought to work differently from other disease-modifying therapies by binding to CD25, a subunit of the interleukin-2 (IL-2) receptor found on activated lymphocytes, cells believed to underlie the biology of MS.

The Zinbryta label includes a boxed warning for the risk of hepatic injury, including autoimmune hepatitis, and other immune-mediated disorders. Because of these risks, access to Zinbryta in the US is restricted to prescribers, pharmacies, and patients enrolled in the Zinbryta Risk Evaluation and Mitigation Strategy (REMS) Program, which includes required monthly liver function tests.

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 therapies indicated for the treatment of MS.

Zecuity Withdrawn Due to Reports of Burning and Scarring

Teva Pharmaceutical Industries has voluntarily suspended marketing and initiated a pharmacy-level recall for the Zecuity (sumatriptan iontophoretic transdermal system) Patch for migraine headaches in the US. The decision comes after the recent publication of post-marketing reports of application site reactions such as burns and scars in patients treated with Zecuity. According to *Practical Neurology*® Chief Medical Editor Paul G. Mathew, MD, FAAN, FAHS, Assistant Professor of Neurology at Harvard Medical School, the withdrawal reflects the difficulties of treating migraines safely and effectively. "As neurologists, the treatment of a patient with migraines can be challenging, and the development of new medications and novel delivery systems is always promising," says Dr. Mathew. "The Zecuity Patch offered a niche abortive treatment for patients with early nausea—which limited oral medications—who were intolerant to intranasal and injectable triptan formulations."

Earlier this month, the FDA revealed that it was investigating the risk of serious burns and potential permanent scarring. Teva has indicated that it is working with the FDA to better understand the adverse events. "It is unfortunate that patients have experienced burns and scars as a result of using Zecuity, but patient safety concerns should always be paramount when making decisions about product recalls," Dr. Mathew observes. "Investigation of these adverse events may provide clues as to whether these unfortunate outcomes were due to the iontophoretic transdermal delivery system, the use of sumatriptan as the delivery drug of choice, and/or a predisposition that a certain patient subpopulation may have to develop reactions of this nature."

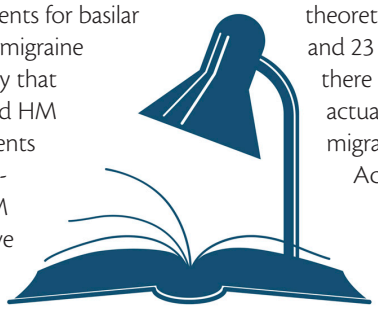
Novel SOD1 Pathology Found in Regions of Parkinson's Disease Brain

While it is already known that superoxide dismutase 1 (SOD1) protein aggregation in the brain is primarily associated with neuronal loss in amyotrophic lateral sclerosis (ALS), new data presented at the 20th International Congress of Parkinson's Disease and Movement Disorders suggest that SOD1 protein aggregation may also be associ-

STUDY SPOTLIGHT

Triptans and Dihydroergotamine Found Safe for the Treatment of Basilar and Hemiplegic Migraine

Triptans and Dihydroergotamine (DHE) can be used as abortive treatments for basilar migraine (BM) and hemiplegic migraine (HM), according to a new study that found no evidence that BM and HM carry an actual elevated risk for vascular events compared with migraine with aura. In a retrospective chart review of patients with BM features or HM who received acute abortive treatment with either triptans or DHE conducted at four headache centers to assess the frequency of ischemic vascular events after administration, headache specialists evaluated 67 patients with BM features and 13 patients with HM.



Among those receiving triptans, 40 were in the BM group and five were in the HM group. Among those receiving DHE, 27 were included in the BM group and eight were in the HM group. No side effects of stroke or myocardial infarction were reported. Although the small sample sizes generated theoretical statistical event rates of 4.5 percent for BM and 23 percent for HM, the researchers concluded that there is no clear evidence that BM and HM carry an actual elevated risk for vascular events compared with migraine with aura.

According to study co-author and *Practical Neurology®* Chief Medical Editor Paul G. Mathew, MD, FAAN, FAHS, the findings suggest that the use of triptans and DHE may be safe for the treatment of basilar and hemiplegic migraine. "Withholding these abortive medications from these patients can really limit treatment options, and lead to undue suffering," Dr. Mathew observes. "In addition, without the availability of these medications, providers may offer butalbital containing compounds and/or narcotics, which can contribute to medication overuse headache (rebound headaches)."

ated with neuronal loss in PD. Testing post-mortem tissues from PD and age-matched control brains, researchers found that protein aggregates that tested positive for SOD1 were significantly more abundant in degenerating regions of the PD brain (greater than five-fold increase in the substantia nigra and greater than 2.5-fold increase in the locus coeruleus). These findings establish a new role of SOD1 pathology in neuronal vulnerability in Parkinson's disease, according to the researchers.

World Stroke Organization and Medtronic Collaborate to Increase Stroke Awareness

The World Stroke Organization (WSO) is partnering with Medtronic to increase stroke awareness through several initiatives. The partnership, unveiled at the 2016 Annual Scientific Session of the Chinese Stroke Association (CSA) and Tiantan International Stroke Conference (TISC) in Beijing, will focus on continued growth of stroke awareness through the Stroke is Treatable World Stroke Day campaign; implementation of the WSO's new global stroke services guidelines: The Roadmap to Delivering Quality Stroke Care; and, supporting WSO's global clinical educational programs including the World Stroke Academy and teaching courses tailored to individual countries' needs. This year's programs will address evidence-based approaches to stroke prevention, treatment and rehabilitation, and improving stroke services, specifically in Beijing, the Philippines, and Hyderabad, India. In addition, the World Stroke Academy provides a digital teaching option to reach all member countries with educational programming on stroke.

New Findings Highlight Racial Disparities in Painful Diabetic Peripheral Neuropathy Diagnosis and Symptoms

New data suggest a need to broaden educational initiatives to promote discussion of painful diabetic peripheral neuropathy (pDPN), particularly among multicultural populations. According to results from the Community Health Perspectives survey presented at the recent American

THE FDA FILE

Orphan Drug Designation Granted to Investigational Huntington's Disease Agent

An investigational agent for the treatment of Huntington's disease (HD) recently received Orphan Drug Designation. Developed by WAVE Life Sciences, WVE-120101 is a single Nucleotide Polymorphism (SNP) that is associated with the disease-causing mutation in the huntington (HTT) gene. WAVE's approach enables selective silencing of the disease-causing HTT allele, while leaving the healthy HTT allele to produce normally functioning protein, according to the company.

"We are pleased to receive Orphan Drug Designation for our first Huntington's disease therapy and to advance what may be the first allele-targeted therapy into clinical trials, particularly as there are no approved disease-modifying treatments for HD," said Paul Bolno, MD, MBA, President and Chief Executive Officer of WAVE Life Sciences, in a statement.

Ocrevus Given Priority Review Status

The FDA has accepted Genentech's Biologics License Application (BLA) for Ocrevus (ocrelizumab) for the treatment of relapsing multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS) and granted the application Priority Review Designation with a targeted action date of December 28, 2016.

The Ocrevus Marketing Authorization Application (MAA) has also been validated by the European Medicines Agency (EMA). If approved by the FDA and EMA for both indications, Ocrevus would be the first and only treatment indicated for both forms of MS, which affect approximately 95 percent of people at diagnosis.

Diabetes Association (ADA) Annual Meeting (1478-P / 1478), significantly fewer African Americans and Hispanic Americans reported receiving a pDPN diagnosis compared to Non-Hispanic Whites. In addition, African Americans and Hispanic Americans reported fewer symptoms than Non-Hispanic Whites, while African Americans and Hispanic Americans were less likely to rate pain as moderate or severe than Non-Hispanic Whites. Community Health Perspectives was developed and sponsored by Pfizer Inc. in collaboration with the American Diabetes Association.

Michael J. Fox Foundation to Fund Studies Investigating Engineered Stem Cells

Two projects that will explore the potential of engineered stem cells for therapeutic development in Parkinson's disease have gained the support of the Michael J. Fox Foundation. The first project, which also has the support of the National Stem Cell Foundation (NSCF), will further study implantation of dopamine neurons made from induced pluripotent stem cells (iPSCs) in the brains of non-human primates. In 2015, Dr. Ole Isacson, MD showed that implanted iPSC-derived dopamine neurons survived and that the therapy was associated with motor improvement. In 2010, Dr. Isacson and colleagues published the first evidence of iPSC protocols, showing the function of human midbrain dopamine neurons.

The second project is led by Lorenz Studer, MD and will investigate transplantation of dopamine neurons derived from embryonic stem cells drawn from existing cell lines. Dr. Studer has received multiple grants from the Foundation to study the potential of embryonic stem cells to treat Parkinson's. He was also part of the team that first successfully developed dopamine neurons from human embryonic stem cells.

Briviact Now Available for Patients with Partial-Onset Seizures

UCB's recently approved Briviact (brivaracetam) CV, an adjunctive therapy for the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy, is now available in the US. Briviact is available in three formulations: film-coated tablets, oral solution, and injection. The molecular entity was approved by the FDA in February. While the recommended starting dosage is 50mg twice daily, the dosage may be adjusted down to 25mg twice daily or up to 100mg twice daily, based on individual patient tolerability and therapeutic response.

National Parkinson Foundation Updates Enrollment on Parkinson's Outcomes Project

More than 8,000 individuals have enrolled in the National Parkinson Foundation's (NPF) Parkinson's Outcomes Project, the largest-ever clinical study of Parkinson's disease. The study, which is in its seventh year and now includes 20 clinics in four countries, aims to identify and explain how expert care delivers better outcomes for people with PD. New findings presented by NPF researchers at the 20th International Congress of Parkinson's Disease and Movement Disorders in Berlin confirm how this study is working to meet its objective of improved patient care.

In the latest analysis, researchers examined medication use patterns across expert PD clinics. With over 346 different combinations of the ten different classes of medication used to manage PD, half of the participants were treated using just nine combinations. More importantly, different centers employed different approaches to medication. In other words, the very best Parkinson's care is not systematic; it instead reflects the preferences of the neurologist as well as the patient, according to the Foundation.

NPF plans to enroll 10,000 participants with PD in the study at NPF Centers of Excellence across the world. The goal of the study is to continue to identify best care practices for Parkinson's and to widely disseminate models of excellent care to benefit more patients. For more information about the study, visit www.parkinson.org/outcomes.

IN THE PIPELINE

Encouraging Early Results for Inhaled Zolmitriptan

Findings from a recent Phase 1 study of an inhaled formulation of zolmitriptan (CVT-427) for migraines have compelled manufacturer Acorda Therapeutics to move forward with additional clinical work. Presented at the Annual Scientific Meeting of the American Headache Society, the data showed increased bioavailability and faster absorption of CVT-427 vs. oral and nasal administration of zolmitriptan in healthy adults. Additionally, CVT-427 had better bioavailability than the reference formulations with less variability in plasma concentration.

The company also noted that there were no serious adverse events, dose-limiting toxicities, or study discontinuations due to adverse events. Other than cough, single-dose CVT-427 tolerability was generally consistent with the known safety profile of zolmitriptan.

More Headlines from NeurologyWire

Investigational Agent for Relapsing MS Fails to Meet Primary Endpoint in Phase 2 Trial

Opicinumab (anti-LINGO-1), Biogen's investigational monoclonal antibody for the treatment of relapsing multiple sclerosis (MS), missed its primary endpoint in a recently released top-line results form its Phase 2 SYNERGY trial. The study was designed to assess the biological activity and clinical potential of opicinumab and evaluated improvement of physical and cognitive function, as well as disability. The company has indicated that it will continue to analyze the data to inform the next steps of its clinical development program.

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CMSC: New Studies Show Benefit of Alemtuzumab in Relapsing MS

Two studies presented at the Consortium of Multiple Sclerosis Centers (CMSC) suggest long-term benefits associated with alemtuzumab (Lemtrada) for the treatment of relapsing multiple sclerosis (MS).

In the first study, investigators found that five-year efficacy of alemtuzumab in patients with highlight active relapsing MS despite prior therapy was superior to that of subcutaneous interferon beta 1a (SC IFNB-1a) in the core study (CARE-MS II) and was durable in the extension through year despite the majority not receiving treatment since month 12. These results suggest that alemtuzumab may provide a unique treatment approach with durable efficacy in the absence of continued treatment for highly active RRMS, according to the researchers.

The second study evaluated long-term treatment response in alemtuzumab patients who had no evidence of disease activity (NEDA) during year two of the core CARE-MS II study and entered the ongoing extension study. The findings revealed that most patients who achieved NEDA in year two received no further treatment following the initial two courses of alemtuzumab. Of these patients who did not receive further treatment, nearly half had sustained NEDA through year five. The investigators concluded that alemtuzumab may provide durable efficacy in the absence of continued treatment for RRMS patients.

Both studies were sponsored by Sanofi-Genzyme. ■