Magellan Rx MANAGEMENT

Clinical Alert

April 2017

Hot Topic:

FDA Approves First Drug for Primary Progressive Multiple Sclerosis

Multiple sclerosis (MS) affects approximately 90 per 100,000 people in the United States (U.S.), about 15% of whom have primary progressive MS (PPMS). Relapsing MS (RMS) is characterized by exacerbations of neurologic symptoms, followed by periods of remission. PPMS is usually seen as a steady worsening of neurologic function without distinct relapses or remission.

On March 28, 2017, Genentech's breakthrough therapy, ocrelizumab (Ocrevus™), was the first drug to be approved by the Food and Drug Administration (FDA) for both PPMS and RMS. Ocrelizumab is a humanized monoclonal antibody that targets CD20+ B cells and affects myelin and axonal damage evident in MS.

In two 96-week clinical trials (OPERA I and OPERA II) in patients with RMS, ocrelizumab reduced the relative annualized relapse rates by approximately 46%, relative disability progression by 40%, and decreased brain lesion volume as compared to interferon beta-1a (Rebif®). Efficacy for PPMS was supported by the ORATORIO clinical trial, which showed a 24% relative reduction in disability progression and a reduction in brain lesions after 120 weeks of ocrelizumab therapy, compared to placebo.

Ocrelizumab is given via an intravenous (IV) infusion by a healthcare professional (HCP); therapy is initiated as two 300 mg doses given 2 weeks apart, followed by 600 mg every 6 months thereafter. Overall, reports of adverse events were similar when comparing ocrelizumab to interferon beta-1a and placebo. The most common adverse events associated with ocrelizumab were infusion reactions and infection. Progressive multifocal leukoencephalopathy (PML), a rare life-threatening brain infection, has not been reported with ocrelizumab, as with some other MS therapies, although it could occur.

While ocrelizumab has the opportunity to fill an unmet need for treatment of PPMS and compete in the RMS domain as a disease-modifying agent, long-term safety and efficacy will influence its overall place in therapy.

FOURIER: Final Results for Evolocumab Outcomes Trial

The highly anticipated final results of the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial were simultaneously published in the *New England Journal of Medicine* and presented at the American College of Cardiology Scientific Sessions on March 17, 2017. This study evaluated the potential cardiovascular (CV) benefits of Amgen's cholesterol lowering drug, evolocumab (Repatha®), a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. In the double-blind FOURIER trial, 27,564 patients with atherosclerotic CV disease (ASCVD) and low-density lipoprotein cholesterol (LDL-C) ≥ 70 mg/dL or non-high density lipoprotein cholesterol ≥ 100 mg/dL were randomly assigned to evolocumab (140 mg every 2 weeks or 420 mg monthly) or placebo subcutaneous (SC) injections. Background optimal statin therapy was continued. Ezetimibe use was allowed but infrequent. Median follow-up was 26 months. When added to statin therapy, evolocumab significantly reduced the risk of CV events compared to placebo. The primary endpoint, a composite of CV death, myocardial infarction (MI), stroke, hospitalization for unstable angina, or coronary revascularization, occurred 15% less often with evolocumab

Drug Information Highlights

- Mylan has announced a global voluntary recall, including the U.S., of 13 lots of Epipen® (epinephrine auto-injector) 0.15 mg and 0.3 mg devices. The recall was initiated after 2 reports of device failure; patients affected were able to be treated with an alternative Epipen device. The devices involved in the U.S. recall carry expiry dates in April, May, September, and October of 2017. Mylan's authorized generic product is not affected by this recall. Mylan will replace recalled devices with either brand Epipen or its authorized generic version at no cost to the patient. For more information visit https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm550170.htm.
- 2016-2017 Flu Season Update: During the week of March 19-25, 2017, influenza activity decreased but remained elevated in the U.S. Ten states reported high influenza-like activity; most were located in the Southeast. Eight states experienced moderate activity, and the remaining states, New York City, and Puerto Rico experienced low or minimal activity. Adequate supplies of the antiviral agents to treat influenza, oseltamivir (Tamiflu®) and zanamivir (Relenza®) remain.
- Merck's human programmed death receptor-1 (PD-1) inhibitor, pembrolizumab (Keytruda®), received approval for the treatment of pediatric and adult patients with refractory classical Hodgkin lymphoma (cHL), who have relapsed after ≥ 3 prior lines of therapy. For cHL, pembrolizumab is administered IV over 30 minutes by an HCP. The approved dosage is 200 mg for adults and 2 mg/kg (up to 200 mg) for pediatrics, given every 3 weeks until disease progression or unacceptable toxicity occur, or up to 24 months in patients without disease progression. The cHL indication is approved based on tumor response and durability under an accelerated approval; continued approval may depend on confirmatory trial results. Pembrolizumab is also approved for a number of other oncology indications.
- The FDA issued a Drug Safety Communication for eluxadoline (Viberzi®), warning that it may increase the risk of serious pancreatitis, including cases leading to hospitalization and death, in patients without a gallbladder. The product is indicated to treat irritable bowel syndrome with diarrhea and works by decreasing bowel contractions. Eluxadoline should not be prescribed in patients who do not have a gallbladder or in patients with a history of pancreatitis.

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than with placebo (9.8% versus 11.3%). The key secondary composite endpoint of CV death, MI, or stroke occurred 20% less often with evolocumab versus placebo (5.9% versus 7.4%). The degree of risk reduction of the key secondary endpoint improved from 16% during the first year to 25% beyond the first year; this may mean the benefit of LDL-C lowering translates to better CV outcomes over time. There was no significant difference in CV death or all-cause mortality in the study.

Furthermore, the double-blind EBBINGHAUS (Evaluating PCSK9 Binding antiBody Influence oN coGnitive HeAlth in high cardiovascUlar risk Subjects) trial evaluated cognitive effects of evolocumab when added to statin therapy in 1,974 FOURIER enrolled patients. Executive function (spatial working memory strategy index), working memory, memory function, and psychomotor speed were assessed at the beginning, at points during, and at the end of the study. Evolocumab was non-inferior to placebo in all measures. In addition, the achievement of very low LDL-C levels (< 25 mg/dL) did not impact cognitive function compared to higher LDL-C levels.

The results of ODYSSEY, Sanofi's CV outcomes trial for their PCSK9 inhibitor, alirocumab (Praluent®), are expected to be available in about a year.

American Society of Interventional Pain Physicians (ASIPP) Guidelines

Numerous organizations have released guidelines for responsible opioid prescribing in an effort to combat the ever-increasing problem of opioid abuse. The ASIPP has released their guidelines for "Responsible, Safe, and Effective Prescription of Opioids for Chronic Non-Cancer Pain" with the goal of decreasing the abuse and harms of opioids without jeopardizing their appropriate use in non-cancer pain management.

The ASIPP advises that initial steps of opioid therapy include a comprehensive assessment before starting opioids. Some of the elements to assess include the patient's general medical condition, psychosocial history, psychiatric status, and substance use history. Establishment of appropriate physical and psychological diagnoses is important and may require appropriate imaging tests. Prescription drug monitoring programs (PDMPs) should be utilized to identify patterns of prescription usage or doctor shopping. Medical necessity of opioid therapy is determined based on average moderate-to-severe pain, failure of non-opioid medications, and/or level of disability. Patients should be stratified based on risk for abuse (low, medium, high). Clinicians must understand the effectiveness and adverse consequences of opioids.

It is appropriate to initiate opioid therapy with low dose short-acting drugs, with appropriate monitoring. Per ASIPP, consider up to 40 morphine milligram equivalent (MME) to be low dose, 41 to 90 MME as moderate dose, and greater than 91 MME as high dose. Continued medical necessity is based on periodic assessment for pain relief and/or functional status improvement of ≥ 30% (without adverse consequences). Long-acting or high dose opioids should only be used in specific circumstances with severe, intractable pain. Avoid long-acting opioids for the initiation of opioid therapy. Prescribers should monitor for adherence, abuse, diversion, and noncompliance using urine drug testing (UDT) and PDMPs. Side effects (e.g., constipation) should be monitored and managed appropriately. Prescribing of methadone is advised only after failure of other opioid therapy and by clinicians with specific training in its risks and appropriate use. Electrocardiogram testing is recommended prior to and periodically during methadone treatment.

If medical necessity is ongoing, opioid therapy may continue with appropriate outcomes; patient monitoring should continue throughout therapy. Opioids should be discontinued if there is a lack of response, adverse consequences, or abuse. If drug abuse or diversion appear to be routine, a rehabilitation center referral should be considered.

The complete guidelines are available at https://asipp.org.

- Endo Pharmaceuticals, announced a class II recall of 1 lot of Edex® (alprostadil for injection) 10 mcg, used for male erectile dysfunction. The recall is due to a defect in the crimp cap of the affected lot, which could affect sterility and lead to adverse events such as infection. Consumers in possession of any unused Edex 10 mcg product bearing lot number 207386 should immediately discontinue its use and return any unused product.
- The FDA approved the addition of a new warning to all antipsychotic medications. The new warning states that these medications can cause somnolence, postural hypotension, and motor instability that could increase the risk of falls leading to fractures and other injuries.
- The FDA issued a Drug Safety Communication regarding rare, serious allergic reactions, including anaphylaxis, to the skin antiseptic chlorhexidine gluconate. At least 43 cases of anaphylaxis have been reported since 1969. Of these, 24 were reported after 2010; all were serious cases. As a result, the agency is requesting manufacturers of over-the-counter (OTC) antiseptics containing chlorhexidine to revise their labeling to include this warning.
- Bio Products Laboratory received approval for a new concentration of human immune globulin, Gammaplex® 10%, to treat primary immunodeficiency and chronic idiopathic thrombocytopenia (ITP) in adults. The product is approved as a 1 g/10 mL solution, stabilized with glycine, for IV administration in 50 mL, 100 mL, and 200 mL single-use bottles. Gammaplex is also available as a 5% solution.

Pipeline News: Upcoming Prescription Drug User Fee Acts (PDUFA) Dates

- **April, 2017:** MK-1293; insulin glargine (biosimilar to Sanofi's Lantus®); SC long-acting insulin; types 1 and 2 diabetes; Merck/Samsung Bioepis.
- **April 5, 2017:** Remune; intramuscular HIV vaccine; HIV infection; Immune Response/Biopharma.
- **April 11, 2017:** Ingrezza; valbenazine; oral VMT2 inhibitor; tardive dyskinesia; Neurocrine.
- **April 27, 2017:** Brineura; cerliponase alfa; IV enzyme replacement therapy; classic late infantile neuronal ceroid lipofuscinosis 2 (CLN2) disease; Biomarin.
- **April 29, 2017:** brigatinib; oral anaplastic lymphoma kinase (ALK) inhibitor; non-small cell lung cancer; Ariad/Takeda.
- **April 29, 2017:** Ravicti®; glycerol phenylbutyrate; oral nitrogen-binding agent; urea cycle disorders (ages 2 months to 2 years); Horizon.
- **April 30, 2017:** Tecentriq®; atezolizumab; IV programmed death-ligand 1 (PD-L1) inhibitor; advanced/metastatic urothelial carcinoma; Genentech/Roche.
- **Quarter 2, 2017:** durvalumab; IV PD-L1 inhibitor; advanced/metastatic urothelial carcinoma; AstraZeneca/Medimmune.
- **Quarter 2, 2017:** nonacog beta pegol; IV long-acting factor IX; Hemophilia B; Novo Nordisk.
- **First Half, 2017:** baricitinib; oral Janus kinase inhibitor; rheumatoid arthritis, psoriasis; Eli Lilly/Incyte.

Likelihood of Long-Term Opioid Use

The 2016 Centers for Disease Control and Prevention (CDC) Guidelines for Prescribing Opioids for Chronic Pain included recommendations for opioid product selection and duration of use; however, there are few data on the transition from acute to chronic opioid use. Early opioid prescribing patterns may predict the likelihood of long-term use, which, research suggests, is associated with increased risk for harm.

A random 10% sample of patient records was drawn from the IMS Lifelink+ database, representing the U.S. commercially-insured population. Patients included in the sample were aged ≥ 18 years and had at least 1 opioid prescription claim between June 1, 2006 and September 1, 2015. They were also required to have at least 6 months of continuous enrollment prior to their first opioid prescription. Researchers excluded patients with cancer, a substance abuse disorder diagnosis within 6 months prior to their first opioid prescription, or buprenorphine prescriptions indicated for a substance abuse disorder. Sampled patients were followed from the date of their first prescription until loss of enrollment, study end date, or discontinuation of opioids (defined as ≥ 180 days without opioid use).

The researchers found 33,548 of 1,294,247 (2.6%) patients sampled continued opioid therapy for 1 year or longer. In this sample of adults who received a prescription for an opioid pain reliever, the likelihood of chronic opioid use increased with each additional day of medication supplied, starting with the third day. The sharpest increases in chronic opioid use were observed after the fifth and thirty-first day of therapy, in patients with a second prescription or refill, an initial fill of over 10- or 30-day supply, and a 700 MME cumulative dose. Continued use at 1 and 3 years was seen most often in patients who were started on a long-acting opioid, followed by patients who were prescribed tramadol.

This analysis suggests that transitions from acute to chronic therapy can occur rapidly, as early as after the third day supply, and supports the recommendations that treatment of acute pain with opioids should be for the shortest duration possible. Limitations of this analysis include lack of data regarding pain intensity or duration, pain etiology, and whether chronic opioid use was intentional or an extension of acute pain.

Continued Use of Benzodiazepine in Older Adults Despite Safety Concerns

Benzodiazepine use in older adults is common and of particular concern due to associations between benzodiazepines and adverse outcomes such as falls, fractures, motor vehicle accidents, impaired cognition, and dementia. The American Geriatrics Society's (AGS) Beers Criteria include a strong recommendation to avoid any type of benzodiazepine for the treatment of insomnia or agitation in older adults.

A recent cross-sectional analysis of adults, including 32,544 patients ≥ 65 years of age, evaluated the rate of new and continuous use of benzodiazepines in this population. The investigators limited the analysis to non-psychiatrist physician visits since studies reveal that these providers prescribe nearly 95% of the benzodiazepines in this population.

The authors found that in approximately 6% of the visits, patients 65 years and older were prescribed a benzodiazepine; most were written as continuation of therapy, while a small percentage of benzodiazepines were considered new starts. The rate of per-population benzodiazepine visits (office visit in which a benzodiazepine was newly prescribed or continued) increased with age and was lowest with young adults. Notably, in the older population, the investigators found that < 1% of patients received or were referred to psychotherapy, 16% of continuation users had any mental health diagnosis, and 10% were using concomitant opioids (which increases risk of falls and fractures, respiratory depression, and overdose deaths).

There are more appropriate treatment options for anxiety disorders for older adults, such as psychotherapy and selective-serotonin reuptake inhibitors, both of which are considered first-line treatment. Nonetheless, among all visits that resulted in a benzodiazepine prescription, approximately one-quarter of individuals were taking an antidepressant. Results of this study suggest that older adults continue to receive treatment with benzodiazepines despite more appropriate and safer alternative therapies.

American Academy of Sleep Medicine (AASM) Guidance for Chronic Insomnia

The AASM published guidelines on the pharmacologic treatment of chronic insomnia to be used in conjunction with their previous guidelines on evaluation and treatment of insomnia. Chronic insomnia is defined as insomnia that occurs at least 3 times per week for at least 3 months. The new document focuses on use of insomnia agents once the decision has been made to use pharmacotherapy, as based on specific treatment goals, comorbidities, prior treatment responses, availability, safety, patient preference, and cost. Treatment of comorbid conditions, adjustment of medications and substances that interfere with sleep, and improvement of sleep environment are general treatment measures. Similar to the American College of Physicians (ACP), AASM maintains that cognitive behavioral therapies for insomnia (CBT-I) is first-line therapy for chronic insomnia due to its favorable benefit-to-risk ratio. Drug therapy may be considered for patients who cannot participate in or do not respond to CBT-I or who need temporary adjunct to CBT-I. AASM recommends the following for sleep onset: eszopiclone, ramelteon, temazepam, triazolam, zaleplon, and zolpidem (weak recommendation); doxepin, eszopiclone, suvorexant, temazepam, and zolpidem are recommended to maintain sleep (weak recommendation). AASM advises against use of diphenhydramine, melatonin, tiagabine, trazodone, tryptophan, and valerian. An AASM 2006 paper indicates that there is little evidence that support the use of OTC agents for insomnia. In addition, a 2005 National Institutes of Health (NIH) consensus conference found moderate-to-high grade evidence for CBT-I and benzodiazepines for short-term management, but little evidence for their long-term use. Furthermore, ACP states that evidence is lacking to determine the efficacy of benzodiazepines, trazodone, and melatonin for chronic insomnia. The entire guideline is available at www.aasmnet.org.

Recent FDA Approvals

Generic Name	Trade Name	Description	Applicant	FDA Status
telotristat ethyl	Xermelo™	Telotristat ethyl (Xermelo), a tryptophan hydroxylase inhibitor, has been approved for use in combination with somatostatin analog (SSA) therapy to treat carcinoid syndrome diarrhea in adults who are inadequately controlled by SSA monotherapy. Telotristat ethyl is the only oral product approved for this indication. It was awarded FDA fast track and orphan drug designations. Approved as a 250 mg tablet, the recommended dose is 1 tablet 3 times daily with food. Discontinue telotristat ethyl if severe diarrhea develops. If prescribed, administer short-acting octreotide ≥ 30 minutes after telotristat ethyl.	Lexicon	FDA NDA priority approval 02/28/2017
house dust mite allergen extract	Odactra™	House dust mite (HDM) allergen extract (Odactra) has been approved to treat HDM-induced allergic rhinitis, with or without conjunctivitis, in patients 18 to 65 years old. Diagnosis should be confirmed by *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* HDMs, or skin testing to licensed HDM allergen extracts. One sublingual tablet, containing 12 SQ-HDM, is taken once daily, year round. The first dose is administered by an HCP, after which the patient is observed for 30 minutes for potential severe allergic reactions (boxed warning); if tolerated, subsequent doses may be self-administered. Noticeable benefit may take 8 to 14 weeks to appear. Patients should also be prescribed auto-injectable epinephrine. Contraindications include history of any severe system or local reaction to sublingual allergen immunotherapy (SLIT), history of eosinophilic esophagitis, and hypersensitivity to any inactive ingredients.	Merck	FDA BLA approval 03/01/2017
desmopressin acetate	Noctiva™	The FDA approved desmopressin acetate nasal spray (Noctiva), a vasopressin analog, for the treatment of nocturia due to nocturnal polyuria in adults who awaken ≥ 2 times per night to void. The preservative-free nasal spray delivers 0.83 mcg or 1.66 mcg of desmopressin acetate per 0.1 mL spray. Noctiva is self-administered as 1 spray in either nostril nightly, approximately 30 minutes before bedtime. Patients < 65 years old who are not at increased risk for hyponatremia should use the 1.66 mcg dosage, while patients ≥ 65 years and any patient at risk for hyponatremia should start therapy with the 0.83 mcg dosage; after 7 days, the dose can be increased to 1.66 mcg if serum sodium is normal. Do not substitute 1 spray of 1.66 mcg with 2 sprays of 0.83 mcg. Noctiva carries several contraindications and a boxed warning regarding hyponatremia.	Serenity	FDA 505(b)(2) NDA approval 03/03/2017
ribociclib	Kisqali®	The kinase inhibitor, ribociclib (Kisqali), was approved for use, in combination with an aromatase inhibitor (AI), as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. Ribociclib is approved as a 200 mg oral tablet that can be taken at the same time each day without regard to food. The starting dose of ribociclib is 600 mg (3 tablets) once daily for 21 consecutive days followed by 7 days off treatment. Refer to the package insert for dosing recommendations for specific AI products. Treatment is continued until disease progression or unacceptable toxicity occurs. Ribociclib was granted a breakthrough therapy designation.	Novartis	FDA NDA priority approval 03/13/2017
safinamide	Xadago®	The monoamine oxidase type B (MAO-B) inhibitor safinamide (Xadago) received approval as adjunct to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes. It has not been shown to be effective as monotherapy for PD. Approved as 50 mg and 100 mg oral tablets, the starting dose is 50 mg once daily at the same time each day; the dose may be increased after 2 weeks.	Newron	FDA NDA approval 03/21/2017
avelumab	Bavencio®	The FDA approved, under accelerated approval, avelumab (Bavencio) a PD-L1 inhibitor for the treatment of adults and pediatric patients ≥ 12 years of age with metastatic Merkel cell carcinoma (MCC). Avelumab is approved as a 20 mg/mL solution in a 10 mL single-dose vial. The recommended dose is 10 mg/kg infused IV over 60 minutes by an HCP every 2 weeks. Premedicate with acetaminophen and an antihistamine for the first 4 doses, and as needed thereafter, for infusion reaction. Withhold the dose for moderate pneumonitis; discontinue if pneumonitis is severe or recurrent.	EMD Serono	FDA BLA approval 03/23/2017
naldemedine	Symproic®	Naldemedine (Symproic) is an opioid antagonist FDA approved to treat opioid-induced constipation (OIC) in adults with chronic non-cancer pain. It is a Schedule II controlled substance. The recommended dose is one 0.2 mg tablet taken once daily with or without food. Patients who have been treated with opioids for < 4 weeks may be less responsive to naldemedine. Stop naldemedine if opioid therapy is discontinued. Patients with a known or suspected gastrointestinal obstruction should not take naldemedine.	Shionogi	FDA NDA approval 03/23/2017

ANDA = Abbreviated New Drug Application; BLA = Biologics License Application; NDA = New Drug Application; sBLA = Supplemental Biologics License Application; sNDA = Supplemental New Drug Application

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