Pharmaceutical Approval Update

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Inbrija (levodopa inhalation powder) for oral inhalation

Manufacturer: Acorda Therapeutics Inc., Ardsley, New York

Date of Approval: December 21, 2018

Indication: Levodopa inhalation powder is an aromatic amino acid for the intermittent treatment of "off" episodes in Parkinson's disease patients treated with carbidopa/levodopa.

Drug Class: Inhaled aromatic amino acid

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Uniqueness of Drug: Levodopa inhalation powder is the first and only inhaled levodopa product for intermittent treatment of "off" episodes in patients with Parkinson's disease who are treated with carbidopa/levodopa. Levodopa uses Acorda Therapeutic's innovative ARCUS® inhaled platform. A marketing authorization application for levodopa inhalation powder was submitted to the European Medicines Agency in March 2018 and was formally validated in May 2018.

Warnings and Precautions:

Falling asleep. Patients have reported falling asleep while performing activities of daily living (ADLs) including driving, which sometimes resulted in accidents. Although many patients reported somnolence, some reported no warning signs (sleep attack) and believed that they were alert immediately prior to the event. Some of these events have been reported as long as one year after starting treatment. Prescribers should reassess patients for drowsiness or sleepiness. Before starting levodopa treatment, patients should be advised about the potential for developing drowsiness. Other factors that may increase the risk of somnolence should be assessed, such as combined use with sedating medications and the presence of sleep disorders.

Development of a symptom complex that looks like neuroleptic malignant syndrome (e.g., elevated temperature, muscular rigidity, altered consciousness, and autonomic instability) has been reported in association with rapid dose reduction, withdrawal of, or changes in dopaminergic therapy. Therefore, patients should avoid sudden discontinuation or rapid dose reduction.

Hallucinations and/or exacerbation of psychosis may occur. Therefore, patients with major psychotic disorders should not be treated with levodopa.

Impulse Control Disorders. If patients develop an impulse control disorder, levodopa should be dose-reduced or stopped.

Dyskinesia. Dyskinesia can occur with or be exacerbated by levodopa. Levodopa therapy dose adjustments, or discontinuation, may be considered.

Pulmonary diseases. Levodopa is not recommended in patients with asthma, chronic obstructive pulmonary disorder (COPD), or other chronic underlying lung disease.

Drug Interactions. Patients taking monoamine oxidase-B (MAO-B) inhibitors should be monitored for the occurrence of orthostatic hypotension. Patients receiving dopamine D2 antagonists, isoniazid, and iron salts may have reduced effectiveness with levodopa inhalation powder.

Contraindications: Levodopa inhalation powder is contraindicated in patients currently taking a nonselective MAO inhibitor or who have recently (within the last two weeks) taken a nonselective MAO inhibitor.

Availability, Dosage, and Administration: Levodopa capsules for inhalation are 42 mg each and come in two package sizes: 60 capsules (15 blister cards containing 4 capsules each) plus an inhaler, and 92 capsules (23 blister cards containing 4 capsules each) plus an inhaler. Levodopa should only be used with the levodopa inhaler. For dosing, inhale the contents of two levodopa capsules (84 mg) as needed for "OFF" symptoms, up to five times daily, with a maximum dose per OFF period of 84 mg. The maximum recommended daily dosage is 420 mg.

Commentary: The efficacy of levodopa inhalation powder was evaluated in the phase 3 SPAN-PD trials. This was a 12-week, randomized, placebo-controlled, double-blind study in patients with mild-to-moderate Parkinson's disease experiencing OFF periods. The SPAN-PD trial met its primary endpoint of patients showing a statistically significant improvement in motor function at the week 12 visit. This was measured by a reduction in the Unified Parkinson's Disease Rating Scale (UPDRS) Part III score for levodopa 84 mg-treated patients (n = 114) compared to placebo-treated patients (n = 112) at 30 minutes post-dose. The onset of action was seen by as early as 10 minutes. A long-term, phase 3, active-controlled, randomized, open-label study assessed safety and tolerability on pulmonary function over one year (n = 398). For levodopa-treated patients and observational cohorts, the average reduction in forced expiratory volume in one second (FEV_{1}) from baseline was the same. Patients with pulmonary disease within the last five years were excluded from this study. The most common adverse reactions (incidence ≥ 5% and higher than placebo) were cough (15% vs. 2%), discolored sputum (5% vs. 0%), nausea (5% vs. 3%), and upper respiratory tract infection (6% vs. 3%).

Source: Acorda Therapeutics, Inc., Inbrija® prescribing information.

Ultomiris (ravulizumab) injection

Manufacturer: Alexion Pharmaceuticals, Boston, Massachusetts

Date of Drug Approval: December 21, 2018

Indication: For treating adults with paroxysmal nocturnal hemoglobinuria (PNH)

Drug Class: Long-acting, intravenous, C5 complement inhibitor

Uniqueness of Drug: PNH is a rare acquired disorder that leads to hemolysis. Patients are missing a certain protein that normally protects red blood cells from being destroyed by the immune system. Patients with PNH have sudden, recurring episodes where red blood cells are prematurely hemolyzed.

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During these episodes, the patient may develop severe anemia, profound fatigue, shortness of breath, intermittent hematuria, renal disease, or recurrent pain. PNH can occur at any age, although it is most often diagnosed in young adulthood. PNH can cause a wide range of debilitating symptoms and complications, including thrombosis, which can occur anywhere in the body and result in organ damage and premature death. Prior to the approval of ravulizumab, the only approved treatment required therapy every two weeks. Ravulizumab uses a novel formulation that allows the agent to be administered every eight weeks. Ravulizumab has received orphan drug designation for treating patients with PNH in the U.S. and the European Union, and for the subcutaneous treatment of atypical hemolytic uremic syndrome patients in the U.S.

Contraindications: Ravulizumab is contraindicated in patients with unresolved *Neisseria meningitidis* infection.

Boxed Warning:

Serious meningococcal infections. Life-threatening meningococcal infections/sepsis have occurred in patients treated with ravulizumab. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Comply with the most current Advisory Committee on Immunization Practices recommendations for meningococcal vaccination in patients with complement deficiencies. Immunize patients with meningococcal vaccines at least two weeks prior to administering the first ravulizumab dose, unless the risks of delaying ravulizumab therapy outweigh the risk of developing a meningococcal infection. Vaccination reduces, but does not eliminate, meningococcal infection risk. Patients should be monitored for early signs of meningococcal infections and be evaluated immediately if infection is suspected. Because of the risk of meningococcal infections, ravulizumab is available only through a restricted program under a risk evaluation and mitigation strategy (REMS). Under the ravulizumab REMS, prescribers must enroll in the program. Prescribers must counsel patients about the risk of meningococcal infection/sepsis, provide patients with REMS educational materials, and ensure that patients are vaccinated with meningococcal vaccines.

Additional Warnings and Precautions:

Other infections. Because ravulizumab blocks terminal complement activation, patients may have increased susceptibility to encapsulated bacteria infections, especially infections caused by *Neisseria meningitidis* but also by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and also possibly *Neisseria gonorrhoeae*. If ravulizumab is administered to patients with active systemic infections, they should be closely monitored for signs and symptoms of worsening infection.

Drug discontinuation. After discontinuing ravulizumab treatment, patients should be closely monitored for signs and symptoms of hemolysis, identified by elevated lactate dehydrogenase (LDH) along with a sudden decrease in PNH clone size or hemoglobin, or the re-appearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, dyspnea, thrombosis, dysphagia, or erectile dysfunction. All patients who discontinue ravulizumab should be monitored for at least 16 weeks to detect hemolysis and other reactions. If signs and symptoms of hemolysis occur following discontinuation, consider restarting ravulizumab treatment.

Thromboembolic event management. The effect of withdrawal of anticoagulant therapy during ravulizumab treatment has not been established. Therefore, ravulizumab treatment should not alter anticoagulant management.

Infusion reactions. Low back pain, hypotension, and infusion-related pain during administration may occur. In clinical trials, these reactions did not require ravulizumab discontinuation. However, interruption of ravulizumab infusion should occur and appropriate supportive measures should be instituted if signs of cardiovascular instability or respiratory compromise occur.

Immunogenicity. As with all therapeutic proteins, there is potential for immunogenicity.

Availability, Dosage, and Administration: Ravulizumab injection is available in a single-dose vial of 300 mg/30 mL (10 mg/mL). Ravulizumab requires dilution to a final concentration of 5 mg/mL, and is dosed based on body weight (following the guidelines in the package label). Starting two weeks after administration of a loading dose, maintenance doses are given at an interval of once every eight weeks. For patients switching from eculizumab to ravulizumab, the loading dose should be administered two weeks after the last eculizumab infusion, and then maintenance doses administered once every eight weeks, starting two weeks after the loading dose.

Commentary: The efficacy of ravulizumab was evaluated in 246 PNH-treatment naive patients. This was a 26-week, multicenter, open-label, randomized, active-controlled, non-inferiority phase 3 study. Patients were randomized to treatment with ravulizumab or Soliris (eculizumab), which is the current standard of care for treating PNH. The results of the trial demonstrated that ravulizumab was non-inferior to eculizumab. Ravulizumab-treated patients did not receive a blood transfusion and had a similar incidence of hemolysis, measured by LDH normalization. Ravulizumab was also studied in 195 patients with PNH who were clinically stable after treatment with eculizumab for at least the prior six months. This was a 26-week, multicenter, open-label, randomized, active-controlled, non-inferiority phase 3 study. These patients were randomized to treatment with ravulizumab or for continuation of eculizumab treatment. Ravulizumab-treated patients showed non-inferiority to eculizumab-treated patients on several clinical measures, including hemolysis and avoiding blood transfusion. Common adverse reactions in clinical trials were headache and upper respiratory infection.

Sources: Alexion Pharmaceuticals, Ultomiris prescribing information; FDA. FDA approves new treatment for adult patients with rare, life-threatening blood disease. December 21, 2018.

Yupelri (revefenacin) inhalation solution

Manufacturer: Mylan Specialty L.P., Morgantown, West Virginia

Date of Approval: November 9, 2018

Indication: For the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD)

Drug Class: Long-acting muscarinic (anticholinergic) antagonist

Uniqueness of Drug: This is the first and only once-daily, nebulized bronchodilator approved for treating COPD in the

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U.S. COPD is the third leading cause of death and the fourth leading cause of hospital readmissions in the U.S., and it affects approximately 16 million Americans.

Contraindications: Revefenacin is contraindicated in patients with hypersensitivity to revefenacin or any component of this product.

Warnings and Precautions:

Revefenacin should not be started in acutely deteriorating COPD, or to treat acute symptoms.

Revefenacin should be discontinued if paradoxical bronchospasm occurs, and another treatment should then be started.

Narrow-angle glaucoma worsening may occur. Revefenacin should be used with caution in patients with narrow-angle glaucoma. Patients should contact a health care provider immediately if symptoms occur or if glaucoma symptoms worsen.

Urinary retention worsening may occur. Revefenacin should be used with caution in patients with prostatic hyperplasia or bladder-neck obstruction. Patients should contact a health care provider immediately if urinary symptoms worsen.

Immediate hypersensitivity reactions may occur with revefenacin. If this reaction occurs, therapy should be immediately stopped and another treatment should be considered.

Drug Interactions: *Anticholinergics*. An additive interaction may occur with concomitantly used anticholinergic medications. Avoid administration of revefenacin with other anticholinergic-containing agents. *Transporter-related drug interactions.* Coadministration of revefenacin with OATP1B1 and OATP1B3 inhibitors (e.g., rifampicin, cyclosporine, etc.) may lead to an increase in exposure of the active metabolite. Therefore, these combinations with revefenacin are not recommended.

Availability, Dosage, and Administration: Revefenacin is for oral inhalation use only. The inhalation solution is in a unit-dose vial for nebulization. Each vial contains a 175 mcg/3 mL solution for once-daily administration. It is to be used with a standard jet nebulizer with a mouthpiece connected to an air compressor.

Commentary: The safety and efficacy of revefenacin was replicated in two pivotal clinical trials demonstrating statistically significant and clinically meaningful improvements compared to placebo after 12 weeks, in trough FEV_1, as well as in overall treatment effect on trough FEV_1. Revefenacin had comparable adverse event (AE) rates compared to placebo, low rates of serious adverse events (SAEs), and no clinically meaningful differences in blood parameters or electrocardiogram (ECG) data across active and placebo-treated groups. The most commonly reported AEs were cough, nasopharyngitis, upper respiratory tract infection, headache, and back pain. In addition, a 12-month, phase 3, open-label safety study compared revefenacin to tiotropium. No new safety issues were identified. Rates of AEs and SAEs in the study were low, and comparable to those seen in the tiotropium-treated patients.

Source: Mylan Specialty L.P., Yupelri prescribing information. ■