Pharmaceutical Approval Update

Kunj Gohil, PharmD, RPh

Eluxadoline (Viberzi)

Manufacturer: Patheon Pharmaceuticals Inc., Cincinnati, Ohio; and Forest Pharmaceuticals, Inc., Cincinnati, Ohio

Date of Approval: May 27, 2015

Indication: Eluxadoline is indicated in adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D).

It is contraindicated in patients with:

- Known or suspected biliary duct obstruction, or sphincter of Oddi disease or dysfunction.
- Alcoholism, alcohol abuse, or alcohol addiction, or in patients who drink more than three alcoholic beverages per day.
- A history of pancreatitis or structural diseases of the pancreas, including known or suspected pancreatic duct obstruction.
- Severe hepatic impairment (Child-Pugh Class C).
- A history of chronic or severe constipation or sequelae from constipation, or known or suspected mechanical gastrointestinal obstruction.

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Drug Class: Mu-opioid receptor agonist

Uniqueness of Drug: In addition to being a mu-opioid receptor agonist, eluxadoline is also a delta-opioid receptor antagonist and a kappa-opioid receptor agonist. It activates the nervous system and decreases bowel contractions.

Warnings and Precautions:

Sphincter of Oddi spasm. Instruct patients to stop taking eluxadoline and seek medical attention if they experience symptoms suggestive of sphincter of Oddi spasm, such as acute worsening of abdominal pain (e.g., acute epigastric or biliary [i.e., right upper quadrant] pain), which may radiate to the back or shoulder with or without nausea and vomiting, associated with elevations of pancreatic enzymes or liver transaminases. Do not restart eluxadoline in patients who developed biliary duct obstruction or sphincter of Oddi spasm while taking the medication.

Pancreatitis. Instruct patients to avoid chronic or acute excessive alcohol use while taking eluxadoline. Monitor for new or worsening abdominal pain that may radiate to the back or shoulder, with or without nausea and vomiting. Instruct patients to stop taking eluxadoline and seek medical attention if they experience symptoms suggestive of pancreatitis, such as acute abdominal or epigastric pain radiating to the back associated with elevations of pancreatic enzymes.

Dosage and Administration: The recommended dosage of eluxadoline is 100 mg taken orally twice daily with food.

Commentary: Irritable bowel syndrome affects approximately 10% to 15% of adults in the U.S., and IBS-D is a subtype characterized by loose and/or watery stools at least 25% of the time. Viberzi is a novel agent that activates receptors in the nervous system that can lessen bowel contractions. Approval was based on data from two clinical trials in which Viberzi was more effective in reducing symptoms than placebo during 26 weeks of treatment.

Sources: www.fda.gov, Viberzi prescribing information

Tiotropium Bromide/Olodaterol Inhalation Spray (Stiolto Respimat)

Manufacturer: Boehringer Ingelheim, Ridgefield, Connecticut

Date of Approval: May 26, 2015

Indication: Tiotropium bromide/olodaterol inhalation spray is indicated for long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

It is not indicated to treat acute deteriorations of COPD. It is also not indicated to treat asthma; the safety and effectiveness of the medication in asthma have not been established.

Drug Class: Tiotropium is an anticholinergic, and olodaterol is a long-acting $beta_2$-adrenergic agonist (LABA).

Uniqueness of Drug: Tiotropium is a long-acting muscarinic antagonist (often referred to as an anticholinergic). It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of M3 receptors at the smooth muscle, leading to bronchodilation. Olodaterol, a LABA, exerts its pharmacological effects by binding and activating $beta_2$ adrenoceptors after topical administration by inhalation. Activation of these receptors in the airways stimulates intracellular adenyl cyclase, an enzyme that mediates the synthesis of cyclic adenosine monophosphate (cAMP). Elevated levels of cAMP induce bronchodilation by relaxation of airway smooth muscle cells.

Warnings and Precautions:

Asthma-related death. LABAs may increase the risk of asthma-related death. Tiotropium bromide/olodaterol inhalation spray is not indicated for the treatment of asthma.

Deterioration of disease and acute episodes. If tiotropium bromide/olodaterol inhalation spray no longer controls symptoms of bronchoconstriction, if the patient's inhaled, short-acting $beta_2$ agonist becomes less effective, or if the patient needs to inhale more short-acting $beta_2$ agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once.

Excessive use of tiotropium bromide/olodaterol inhalation spray and use with other LABAs. Tiotropium bromide/olodaterol inhalation spray should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABAs, as an overdose may result.

Immediate hypersensitivity reactions. Such reactions, including urticaria, angioedema (including swelling of the lips, tongue, or throat), rash, bronchospasm, anaphylaxis, or itching may occur after administration. If such a reaction occurs,

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therapy should be stopped at once and alternative treatments should be considered.

Paradoxical bronchospasm. Tiotropium bromide/olodaterol inhalation spray should be stopped immediately if paradoxical bronchospasm occurs; alternative therapy should be instituted.

Cardiovascular effects. LABAs should be administered with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, and hypertension.

Coexisting conditions. Olodaterol, like other sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis, in patients with known or suspected prolongation of the QT interval, and in patients who are unusually responsive to sympathomimetic amines. Doses of the related $beta_2$ agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

Worsening of narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos, or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Worsening of urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination), especially in patients with existing prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Renal impairment. Patients with moderate-to-severe renal impairment (creatinine clearance of 60 mL/min or less) treated with tiotropium bromide/olodaterol inhalation spray should be monitored closely for anticholinergic side effects.

Hypokalemia and hyperglycemia. Beta-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Inhaling high doses of $beta_2$-adrenergic agonists may produce increases in plasma glucose.

Dosage and Administration: The recommended dose is two inhalations once daily at the same time of day.

Commentary: COPD, a treatable lung disease affecting 210 million people worldwide, includes chronic bronchitis and emphysema. It is expected to become the third leading cause of death within the next 15 years. Approval of Stiolto Respimat was based on the TONADO clinical program, which included two pivotal phase 3 trials. Statistically significant improvements in lung function were seen with Stiolto Respimat over tiotropium and olodaterol alone.

Sources: www.boehringer-ingelheim.com, Stiolto Respimat prescribing information

Sirolimus (Rapamune)

Manufacturer: Wyeth Pharmaceuticals, Inc., Philadelphia, Pennsylvania

Date of Approval of New Indication: May 28, 2015

Indication: Sirolimus is now indicated for the treatment of patients with lymphangioleiomyomatosis (LAM).

Drug Class: Immunosuppressive agent

Uniqueness of Drug: Sirolimus inhibits T-lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism that is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production.

Warnings and Precautions:

Increased susceptibility to infection and the possible development of lymphoma. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information needed for the follow-up of the patient.

Liver transplantation—excess mortality, graft loss, and hepatic artery thrombosis (HAT). The safety and efficacy of sirolimus as immunosuppressive therapy have not been established in liver-transplant patients; therefore, such use is not recommended. The use of sirolimus has been associated with adverse outcomes in patients following liver transplantation, including excess mortality, graft loss, and HAT.

Lung transplantation—bronchial anastomotic dehiscence. The safety and efficacy of sirolimus as immunosuppressive therapy have not been established in lung-transplant patients; therefore, such use is not recommended.

Hypersensitivity reactions. Such reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis, have been associated with the administration of sirolimus.

Angioedema. Sirolimus has been associated with the development of angioedema. The concomitant use of this medication with other drugs known to cause angioedema, such as angiotensin-converting enzyme inhibitors, may increase the risk of developing angioedema.

Fluid accumulation and abnormal wound healing. Appropriate measures should be considered to minimize such complications. Patients with a body mass index greater than 30 kg/m^2 may be at increased risk of abnormal wound healing based on data from the medical literature.

Hyperlipidemia. During sirolimus therapy with or without cyclosporine, patients should be monitored for elevated lipids, and patients administered a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor and/or fibrate should be monitored for possible development of rhabdomyolysis and other adverse effects, as described in the respective labeling for these agents.

Renal function. Appropriate adjustment of the immunosuppressive regimen, including discontinuation of sirolimus and/or cyclosporine, should be considered in patients with elevated or increasing serum creatinine levels. Caution should be exercised when using agents (e.g., aminoglycosides and amphotericin B) that are known to have a deleterious effect on renal function.

Proteinuria. Periodic quantitative monitoring of urinary protein excretion is recommended. The safety and efficacy of conversion from calcineurin inhibitors to sirolimus in maintenance renal transplant patients have not been established.

Latent viral infections. In immunosuppressed patients, physicians should consider progressive multifocal leukoen-

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cephalopathy (PML) in the differential diagnosis of patients reporting neurological symptoms; consultation with a neurologist should be considered as clinically indicated. Consideration should be given to reducing the amount of immunosuppression in patients who develop PML. In transplant patients, physicians should also consider the risk that reduced immunosuppression represents to the graft.

Interstitial lung disease (ILD). Cases of ILD (including pneumonitis, bronchiolitis obliterans organizing pneumonia, and pulmonary fibrosis), some fatal, have occurred with no identified infectious etiology in patients receiving immunosuppressive regimens. In some cases, the ILD has resolved upon discontinuation or dose reduction.

De novo *use without cyclosporine.* The safety and efficacy of *de novo* use of sirolimus without cyclosporine is not established in renal transplant patients.

Increased risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA). The concomitant use of sirolimus with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced HUS/TTP/TMA.

Antimicrobial prophylaxis. Antimicrobial prophylaxis for *Pneumocystis carinii* pneumonia should be administered for one year following transplantation. Cytomegalovirus (CMV) prophylaxis is recommended for three months after transplantation, particularly for patients at increased risk for CMV disease.

Different sirolimus trough concentration reported between chromatographic and immunoassay methodologies. Currently in clinical practice, sirolimus whole blood concentrations are being measured by various chromatographic and immunoassay methodologies. Patient sample concentration values from different assays may not be interchangeable.

Skin cancer. Patients on immunosuppressive therapy are at increased risk for skin cancer. Exposure to sunlight and ultraviolet light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Interaction with strong inhibitors and inducers of CYP3A4 and/or P-gp. Coadministration of sirolimus with strong inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin) is not recommended.

Dosage and Administration: The initial sirolimus dose should be 2 mg per day orally, with or without food. Sirolimus whole blood trough concentrations should be measured in 10 to 20 days, with dosage adjustment to maintain concentrations between 5 and 15 ng/mL.

Commentary: LAM is a very rare disease, affecting only two to five women per million women worldwide. It can be characterized by an abnormal growth of smooth muscle cells that invade lung tissues, causing destruction of the lung. This destruction can occur in the airways and in blood/lymph vessels, resulting in airflow obstruction and limited delivery of oxygen to the body. Rapamune (which was approved in 1999 to help prevent rejection of transplanted kidneys) received breakthrough therapy, priority review, and orphan product designations for this use.

Sources: www.fda.gov, Rapamune prescribing information ■