Pharmaceutical Approval Update

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Idarucizumab (Praxbind)

Manufacturer: Boehringer Ingelheim, Ridgefield, Connecticut

Date of Approval: October 16, 2015

Indication: Praxbind is indicated for patients treated with dabigatran (Pradaxa, Boehringer Ingelheim) when reversal of the anticoagulant effects of dabigatran is needed for emergency surgery or urgent procedures or in life-threatening or uncontrolled bleeding.

Drug Class: Idarucizumab is a humanized monoclonal antibody fragment (Fab) derived from an immunoglobulin G_1 isotype molecule; its target is the direct thrombin inhibitor dabigatran.

Uniqueness of Drug: The Food and Drug Administration (FDA) approved dabigatran in 2010 to prevent stroke and systemic blood clots in patients with atrial fibrillation, as well as for the treatment and prevention of deep venous thrombosis and pulmonary embolism. Praxbind is the first reversal agent approved specifically for dabigatran. It binds to dabigatran and to dabigatran's acyl glucuronide metabolites with higher affinity than the binding affinity of dabigatran to thrombin, thereby neutralizing their anticoagulant effect. As a specific reversal agent for dabigatran, idarucizumab does not alter the effect of other anticoagulant or antithrombotic therapies.

Warnings and Precautions:

Thromboembolic risk. Patients being treated with dabigatran have underlying disease states that predispose them to thromboembolic events. Reversing dabigatran therapy with idarucizumab may expose patients to the thrombotic risk of their underlying disease.

Re-elevation of coagulation parameters. In the clinical development program for idarucizumab, elevated coagulation parameters (e.g., activated partial thromboplastin time or ecarin clotting time) were observed between 12 and 24 hours after the administration of a 5-g dose in some patients.

Hypersensitivity reactions. There is insufficient clinical experience with idarucizumab to evaluate the risk of hypersensitivity to the medication.

Risk to patients with hereditary fructose intolerance (HFI). Serious adverse events, including hypoglycemia, hypophosphatemia, metabolic acidosis, and acute liver failure, have been reported in HFI patients who have received parenteral sorbitol. The recommended dose of idarucizumab contains 4 g of sorbitol as an excipient.

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

Dosage and Administration: The recommended dose of idarucizumab is 5 g provided as two separate vials, each containing 2.5 g/50 mL idarucizumab. There are limited data to support the administration of an additional 5 g of idarucizumab. The initial 5-mg dose (two vials, each containing 2.5 g) should be administered 1) as two consecutive infusions, or 2) as a bolus injection by injecting both vials consecutively one after another via syringe.

Commentary: The FDA granted Praxbind a breakthrough therapy designation, and the new drug application received priority review. The application included data from healthy volunteers as well as results from an interim analysis of the RE-VERSE AD trial. In these studies, the reversal effects of Praxbind were evident within minutes after the administration of a 5-g dose. No procoagulant effect was observed.

Although idarucizumab will rarely be used in clinical practice, a specific reversal agent for dabigatran may provide an important therapeutic option for physicians and patients.

Sources: FDA, Praxbind prescribing information, Boehringer Ingelheim

Aripiprazole Lauroxil (Aristada)

Manufacturer: Alkermes Inc., Waltham, Massachusetts

Date of Approval: October 5, 2015

Indication: Aristada is indicated for the treatment of schizophrenia.

Drug Class: Aripiprazole lauroxil is a long-acting second-generation antipsychotic (a prodrug of aripiprazole).

Uniqueness of Drug: After injection, Aristada dissolves slowly over four to six weeks, negating the need for a daily pill. This may help improve treatment efficacy in schizophrenia patients who have difficulty taking their medications regularly.

Warnings and Precautions:

Boxed warning. Aristada and other second-generation antipsychotic drugs used to treat schizophrenia have a boxed warning alerting health care professionals about an increased risk of death associated with the off-label use of these drugs to treat behavioral problems in older people with dementia-related psychosis. No drug in this class is approved to treat patients with dementia-related psychosis. Aristada must be dispensed with a patient medication guide that describes important information about the drug's uses and risks.

Cerebrovascular adverse reactions. Among elderly patients with dementia-related psychosis, the incidence of strokes and transient ischemia attacks increases.

Neuroleptic malignant syndrome. Discontinue the medication at once and monitor the patient closely.

Tardive dyskinesia. Discontinue if clinically appropriate.

Metabolic changes. Monitor for hyperglycemia, dyslipidemia, and weight gain.

Orthostatic hypotension. Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease and a risk of dehydration or syncope.

Leukopenia, neutropenia, and agranulocytosis. Perform complete blood counts in patients with a history of a clinically significant low white blood cell (WBC) count. Consider discontinuation if a clinically significant decline in WBCs occurs in the absence of other causes.

Seizures. Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.

Potential for cognitive and motor impairment. Use caution when operating machinery.

Body temperature regulation. Disruption of the body's

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ability to reduce its core temperature has been reported with antipsychotic agents.

Dosage and Administration: Aripiprazole lauroxil is to be administered only as an intramuscular injection by a health care professional. Depending on individual patients' needs, treatment can be initiated at a dose of 441 mg, 662 mg, or 882 mg administered monthly, which corresponds to 300 mg, 450 mg, and 600 mg of aripiprazole, respectively. Treatment may also be initiated with the 882-mg dose every six weeks.

Aripiprazole lauroxil should be administered either in the deltoid muscle (441-mg dose only) or the gluteal muscle (441 mg, 662 mg, or 882 mg).

Commentary: Aripiprazole lauroxil is a chemical entity that, once injected into the body, undergoes steps to yield aripiprazole, which is marketed by Otsuka as Abilify. Otsuka lost patent protection for its popular schizophrenia treatment in April 2015. The manufacturer of Aristada, Alkermes Inc., specializes in making extended-release versions of generically available drugs.

Although the mechanism of action of aripiprazole is unknown, its efficacy could be mediated through a combination of partial agonist activity at D2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Actions at other receptors could explain some of the adverse events associated with aripiprazole. For example, the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic alpha-1 receptors.

Sources: FDA, Aristada prescribing information, *Boston Globe*

Insulin Degludec Injection (Tresiba)

Manufacturer: Novo Nordisk, Plainsboro, New Jersey

Date of Approval: September 25, 2015

Indication: Tresiba is indicated to improve glycemic control in adults with diabetes mellitus. It is not recommended for treating diabetic ketoacidosis.

Drug Class: Tresiba is a long-acting basal human insulin analog.

Uniqueness of Drug: Tresiba is the first new basal insulin molecule to be approved by the FDA in 10 years. Once injected into subcutaneous tissue, Tresiba forms long molecular chains (multihexamers), resulting in a subcutaneous insulin degludec depot. This process provides an extended duration of action.

Warnings and Precautions:

Hypoglycemia or hyperglycemia. Changes in insulin, manufacturer, type, or method of administration may affect glycemic control and predispose patients to hypoglycemia or hyperglycemia. Hypoglycemia is the most common adverse reaction of insulin, including Tresiba. Increase monitoring with changes to insulin dosage, coadministered glucose-lowering medications, meal pattern, and physical activity, and in patients with renal or hepatic impairment or hypoglycemia unawareness.

Hypersensitivity reactions. Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including Tresiba.

Hypokalemia. All insulin products, including Tresiba, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death.

Fluid retention and congestive heart failure (CHF). Thiazolidinediones, which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate CHF. Patients treated with insulin, including Tresiba, and a PPAR-gamma agonist should be observed for signs and symptoms of CHF.

Sharing Tresiba pens. Patients should never share a pen, even if the needle is changed.

Immunogenicity. As with all therapeutic proteins, insulin administration may cause anti-insulin antibodies to form.

Dosage and Administration: The recommended starting dose of Tresiba in insulin-naïve patients with type-1 diabetes is approximately one-third to one-half of the total daily insulin dose. The remainder of the total daily insulin dose should be administered as a short-acting insulin and divided between each daily meal. The recommended starting dose of Tresiba in insulin-naïve patients with type-2 diabetes mellitus is 10 units once daily. Tresiba should be started at the same unit dose as the total daily long- or intermediate-acting insulin unit dose in patients with type-1 or type-2 diabetes who are already receiving insulin therapy.

Tresiba is injected subcutaneously once daily at any time of day. The recommended intervals between dose increases are three to four days. Tresiba doses should be individualized based on the patient's type of diabetes, metabolic needs, blood-glucose monitoring results, and glycemic control goal.

Commentary: The efficacy and safety of Tresiba used in combination with mealtime insulin for the treatment of patients with type-1 diabetes were evaluated in a total of 1,102 study participants exposed to Tresiba. In addition, the efficacy and safety of Tresiba used in combination with mealtime insulin or used as an add-on to common background oral antidiabetic drugs for the treatment of patients with type-2 diabetes were evaluated in a total of 2,702 study participants exposed to Tresiba. In subjects with type-1 or type-2 diabetes who had inadequate blood sugar control at trial entry, treatment with Tresiba provided reductions in hemoglobin A1c or glycosylated hemoglobin (a measure of blood sugar control) in line with reductions achieved with other, previously approved long-acting insulin.

Sources: FDA, Tresiba prescribing information, Novo Nordisk ■

Correction

A Drug Forecast article in the October 2015 issue of *P&T* ("Edoxaban [Savaysa]: a Factor Xa Inhibitor," pages 651–655, 696) incorrectly characterized a boxed warning for edoxaban. The article should have said that edoxaban's efficacy is reduced in nonvalvular atrial fibrillation patients with a creatinine clearance (CrCl) greater than 95 mL/min. Edoxaban should not be initiated in patients with an estimated CrCl of greater than 95 mL/min due to high-dose edoxaban's association with an increased risk of ischemic stroke compared to patients treated with warfarin.