Pharmaceutical Approval Update

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Cablivi (caplacizumab-yhdp) for injection, for intravenous or subcutaneous use

Manufacturer: Genzyme Corporation, Cambridge, Massachusetts

Date of Approval: February 6, 2019

Indication: Caplacizumab-yhdp is a von Willebrand factor (vWF)-directed antibody fragment indicated for the treatment of adults with acquired thrombotic thrombocytopenic purpura (aTTP), in combination with plasma exchange and immunosuppressive therapy.

Drug Class: Targets the A1-domain of vWF, and is a platelet inhibitor

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Uniqueness of Drug: This is the first therapy specifically designed to treat adults with aTTP. A rare and life-threatening blood-clotting disorder, aTTP has a current occurrence rate of about 3.7 cases per million people each year, according to the National Organization for Rare Disorders. It usually affects people aged 20 to 50 years old, and two-thirds of affected patients are women. Patients can develop aTTP from cancer, human immunodeficiency virus, pregnancy, lupus, or infections, or after undergoing surgery, bone marrow transplant, or chemotherapy. The Food and Drug Administration (FDA) granted the drug application priority review and orphan drug designations.

Warnings and Precautions:

Bleeding. Severe bleeding can occur, with a higher risk in patients with underlying coagulopathies. If clinically significant bleeding occurs, therapy should be interrupted. Caplacizumab-yhdp therapy should be withheld seven days prior to elective surgery, dental procedures, or other invasive interventions. In clinical trials, severe-bleeding adverse reactions, including epistaxis, gingival bleeding, upper gastrointestinal hemorrhage, and metrorrhagia, were each reported in 1% of patients. Overall, bleeding events occurred in about 58% of patients treated with caplacizumab-yhdp compared to 43% of placebo-treated patients.

Use in Specific Populations:

Pregnancy. There is no available data for caplacizumab-yhdp in pregnant women. There are potential risks of hemorrhage in the mother and fetus associated with caplacizumab-yhdp use.

Fetal/neonatal adverse reactions. Caplacizumab-yhdp may increase the risk of bleeding in the fetus and neonate. These patients should be monitored for bleeding.

Maternal adverse reactions. All patients treated with Caplacizumab-yhdp, including pregnant women, are at risk for bleeding. Pregnant women should be carefully monitored for evidence of excessive bleeding.

Contraindications:

Hypersensitivity. Caplacizumab-yhdp is contraindicated in patients with a previous severe hypersensitivity reaction to caplacizumab-yhdp or to any of the excipients in the formulation.

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Availability and Storage: Caplacizumab-yhdp for injection is a sterile, white, preservative-free, lyophilized powder in a single-dose vial. Each carton contains one single-dose vial of 11 mg caplacizumab-yhdp; one 1-mL Sterile Water for Injection, USP, and one prefilled glass syringe (diluent); one sterile vial adapter; one sterile hypodermic needle (30 gauge); and two individually packaged alcohol swabs. The drug should be stored in a refrigerator at 2°C to 8°C (36°–46°F) in the original carton to protect it from light. It should not be frozen. Unopened vials may be stored in the original carton at room temperature up to 30°C (86°F) for a single period of up to two months. If stored at room temperature, caplacizumab-yhdp should not be returned to the refrigerator.

Dosing and Administration: The first dose of caplacizumab-yhdp should be administered by a health care provider as an intravenous (IV) bolus injection. Subsequent doses should be administered subcutaneously in the abdomen. Caplacizumab-yhdp should be administered upon initiation of plasma exchange therapy. The recommended dose is as follows:

- First day of treatment: 1-mg IV bolus injection at least 15 minutes prior to plasma exchange, followed by an 11-mg subcutaneous injection after completion of plasma exchange on day 1;
- Subsequent treatment during daily plasma exchange: 11-mg subcutaneous injection once daily following plasma exchange;
- Treatment after plasma exchange period: 11-mg subcutaneous injection once daily for 30 days beyond the last plasma exchange;
- If signs of persistent underlying disease remain present after the initial treatment course, such as suppressed ADAMTS13 activity levels, treatment may be extended for a maximum of 28 days;
- Caplacizumab-yhdp should be discontinued if the patient experiences more than two aTTP recurrences during treatment.

Commentary: The efficacy of caplacizumab-yhdp was evaluated in the multicenter, randomized, double-blind, placebo-controlled HERCULES trial. Patients (N = 145) in both groups received plasma exchange and immunosuppressive therapy. Patients received a single 11-mg caplacizumab-yhdp IV bolus injection or placebo prior to the first plasma exchange on the study, followed by a daily subcutaneous injection of 11 mg caplacizumab-yhdp or placebo after plasma exchange completion, for the duration of the daily plasma-exchange period and for 30 days thereafter. If, after the initial treatment course, there were signs of persistent underlying disease (e.g., presence of suppressed ADAMTS13 activity), treatment was extended for seven-day intervals for a maximum of 28 days. The median caplacizumab-yhdp treatment duration was 35 days. The study results demonstrated that platelet counts improved

faster in patients treated with caplacizumab-yhdp compared to placebo-treated patients. Treatment with caplacizumab-yhdp also resulted in a lower total number of patients with either aTTP-related death and recurrence of aTTP during the treatment period, or at least one treatment-emergent major thrombotic event. The proportion of patients with a recurrence of aTTP in the overall study period was lower in patients treated with caplacizumab-yhdp (13%) compared to placebo-treated patients (38%), which was statistically significant. Common side effects reported by patients in clinical trials were epistaxis and bleeding gums, as well as headache.

Sources: Genzyme Corporation, Cablivi® prescribing information; FDA, February 6, 2019.

Egaten (triclabendazole) tablets, for oral use

Manufacturer: Novartis Pharmaceuticals, Inc., East Hanover, New Jersey

Date of Approval: February 13, 2019

Indication: Triclabendazole is indicated for treating fascioliasis (liver fluke infestation) in patients 6 years of age and older.

Drug Class: An anthelmintic

Uniqueness of Drug: Fascioliasis, commonly known as liver fluke infestation, is estimated to infect 2.4 million people globally. Novartis has been donating triclabendazole to the World Health Organization (WHO) since 2005, to help treat around two million patients in more than 30 countries with this disease. Triclabendazole is the only drug approved in the United States for treating fascioliasis and is currently the only treatment recommended by WHO. It is on the WHO Model List of Essential Medicines. It is supplied by WHO during epidemic outbreaks and for periodic use in endemic countries. FDA approval of triclabendazole is expected to facilitate drug licensing and importation to these countries, helping ensure sufficient and prompt availability of the drug when needed. Fascioliasis is recognized by the FDA as a neglected tropical disease, triggering the award of a priority review designation based upon this approval.

Warning and Precautions:

QT prolongation. Triclabendazole may prolong the QT interval. The EKG should be monitored in patients with a history of QT prolongation or who are taking medications which prolong the QT interval.

Drug Interactions: When administering triclabendazole with CYP2C19 substrates, re-check the plasma concentration of concomitantly administered CYP2C19 substrates after cessation of triclabendazole therapy, if the plasma concentrations of the CYP2C19 substrates are elevated during its administration.

Contraindications: Triclabendazole is contraindicated in patients with known hypersensitivity to triclabendazole, other benzimidazole derivatives, or any of the excipients in the formulation.

Availability, Dosage, and Administration: Triclabendazole is available as 250-mg tablets.

The recommended dosage is to take 10 mg/kg every 12 hours for two doses in patients 6 years of age and older. The medication should be taken with food. Tablets should be swallowed whole or divided in half and taken with water, or crushed and administered with applesauce. If the exact dose cannot be given, it should be rounded upwards.

Commentary: The efficacy of triclabendazole was evaluated in 100 patients aged 9 to 74 years old with acute symptomatic fascioliasis in an open-label, randomized trial in Vietnam. The study compared triclabendazole (two 10-mg/kg doses given 12 hours apart with food) to oral artesunate (4 mg/kg, given once daily for 10 days). Fifty patients were randomized to each group. At month 3 after treatment, 92% of triclabendazole-treated patients and 76% of artesunate-treated patients reported no clinical symptoms. In addition, six non-randomized, open-label studies were performed in Cuba, Bolivia, Peru, Chile, and Iran, in 245 adult and pediatric patients with stool-confirmed fascioliasis in the triclabendazole clinical program. Triclabendazole doses ranged from 5 to 20 mg/kg, administered on days 1 through 3. Across these studies, there was a dose-response finding. The day-60 cure rate was highest (95.5%) for the 20 mg/kg dose, which was given in two divided doses (the FDA-approved dose), followed by cure rates of 88% (15 mg/kg dose), 80% (10 mg/kg dose), and 50% (5 mg/kg dose). The 5 mg/kg, 10 mg/kg, and 15 mg/kg dosing regimens are not approved. These rates were significantly higher than those estimated from patients receiving an inadequate, non-triclabendazole treatment in a separate study (22%). The most common adverse reactions in clinical studies were abdominal pain, hyper-hidrosis, vertigo, nausea, urticaria, vomiting, and headache.

Sources: Novartis Pharmaceuticals, Inc., Egaten prescribing information; Novartis, February 13, 2019.

Spravato (esketamine) nasal spray

Manufacturer: Janssen Pharmaceuticals, Inc., Titusville, New Jersey

Date of Approval: March 5, 2019

Indication: Esketamine is indicated for adults in conjunction with an oral antidepressant, for treatment-resistant depression. This is defined as having tried at least two other antidepressant medicines without any benefit.

Drug Class: N-methyl-D-aspartate (NMDA) receptor antagonist

Uniqueness of Drug: Esketamine is the s-enantiomer of ketamine, which was approved by the FDA (CIII) in 1970.This is the first FDA approval of esketamine for any use. Because of the risk of serious adverse outcomes resulting from sedation and dissociation caused by the administration of esketamine, and the potential for its abuse and misuse, it is only available through a restricted distribution system, under a risk evaluation and mitigation strategy (REMS). There is a need for additional, effective treatments for treatment-resistant depression, which is a serious and life-threatening condition. Controlled clinical trials that studied the safety and efficacy of this drug, along with a careful review through the FDA's drug approval process and discussions with the external advisory committees, were important in deciding to approve esketamine nasal spray. Because of safety concerns, it will only be available through a restricted distribution system and it must be administered in a certified medical office where the health care provider can monitor the patient. The FDA granted this application fast track and breakthrough therapy designations.

Boxed Warnings:

Risk for sedation and dissociation after administration. Patients should be monitored for at least two hours after

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each treatment administration. This assessment will be used to determine when the patient is considered clinically stable and ready to leave the health care setting. In clinical trials, 49 to 61% of esketamine-treated patients developed sedation and 0.3% had loss of consciousness. The most common psychological effects of esketamine were dissociative or perceptual changes (including distortion of time, space, and illusions), derealization, and depersonalization (61–75%). With its potential to cause dissociative effects, patients with psychosis should be carefully assessed prior to starting esketamine.

Potential for abuse and misuse. The risks and benefits of prescribing esketamine should be considered prior to using it in patients at higher abuse risk. Patients should be monitored for signs and symptoms of abuse and misuse. Esketamine is a CIII controlled substance. Esketamine nasal spray is only available through a restricted program called the SPRAVATO REMS.

Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. All antidepressant-treated patients should be closely monitored for clinical worsening and for emergence of suicidal thoughts and behaviors. Esketamine nasal spray is not approved for use in pediatric patients.

Warnings and Precautions:

Blood pressure increases. Patients with cardiovascular and cerebrovascular conditions and risk factors may be at an increased risk of associated adverse effects. Approximately 8 to 17% of esketamine-treated patients in clinical trials had systolic blood pressure increases of at least 40 mmHg and/or a 25-mmHg increase in diastolic blood pressure. In these patients, the benefits versus risks should be carefully assessed prior to treatment.

Cognitive impairment. Esketamine may impair attention, judgment, thinking, reaction speed, and motor skills. In healthy individuals, esketamine caused cognitive-performance decline 40 minutes post-dose. Compared to placebo-treated patients, esketamine-treated subjects took longer to complete cognitive tests 40 minutes post-dose. At two hours post-dose, mental effort and cognitive performance were comparable between esketamine-treated patients and placebo-treated patients. Sleepiness was comparable between both groups four hours post-dose.

Impaired ability to drive and operate machinery. Patients should not drive or operate machinery until the next day after a restful sleep. Patients should arrange for transportation home following esketamine treatment.

Embryo–fetal toxicity. Esketamine may cause fetal harm. Women should be advised of the potential risk to an infant exposed to esketamine *in utero*. Women of reproductive potential should consider pregnancy planning and prevention. Health care providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or online at *https://womensmentalhealth.org/clinical-and-researchprograms/pregnancyregistry/antidepressants/*.

Contraindications: Esketamine nasal spray is contraindicated for use in patients with aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation; intracerebral hemorrhage; or in patients with a hypersensitivity to esketamine, ketamine, or any of the excipients in the formulation.

Availability, Dosage, and Administration: Esketamine is available as a nasal spray device with 28 mg of esketamine per device. Each device delivers two sprays containing a total of 28 mg of esketamine. It should be administered intranasally under the supervision of a health care provider. Blood pressure should be assessed prior to and following administration. Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine the need for continued treatment.

Commentary: The efficacy of ekatamine nasal spray was evaluated in three four-week, short-term clinical trials, and one long-term maintenance-of-effect trial. In the three short-term studies, patients were randomized to receive esketamine nasal spray or a placebo nasal spray. Because of the serious nature of treatment-resistant depression (and the need for patients to receive some treatment), all study patients were started on a new oral antidepressant at the time of study randomization that was continued throughout the trial. Efficacy was measured as change from baseline of depressive symptoms. In one of the short-term studies, esketamine nasal spray-treated patients showed a statistically significant effect compared to placebo-treated patients on the severity of depression, and some effect was seen within a couple of days. In the two other short-term trials, esketamine-treated patients did not meet the pre-specified statistical tests for effectiveness. In the long-term maintenance-of-effect trial, patients in remission or with a steady response who continued treatment with esketamine nasal spray plus an oral antidepressant experienced a statistically significantly longer time to depressive-symptom relapse than did the placebo (nasal spray) plus oral antidepressant-treated patients. The most common side effects in esketamine-treated patients were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, increased blood pressure, vomiting, and feeling drunk.

Source: Janssen Pharmaceuticals Inc., Spravato prescribing information. ■