Pharmaceutical Approval Update

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Benznidazole

Manufacturer: Exeltis USA, Inc., Florham Park, New Jersey

Date of Approval: August 29, 2017

Indication: Benznidazole (brand name not yet announced) is indicated for the treatment of pediatric patients 2 to 12 years of age with Chagas disease (American trypanosomiasis) caused by *Trypanosoma cruzi*.

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Drug Class: Nitroimidazole antimicrobial

Uniqueness of Drug: Benznidazole tablets are the first approved treatment in the United States for Chagas disease, a parasitic infection caused by *Trypanosoma cruzi*. The primary route of infection is through vectorborne transmission (triatomine bug feces) in Chagas disease-endemic locations, mainly rural areas of Latin America. The disease can also be transmitted through blood transfusions and organ transplants, or from mother to child during pregnancy. Recent estimates suggest there may be approximately 300,000 people in the United States with Chagas disease. After years of infection, the disease can cause serious cardiac illness, and can also affect swallowing and digestion. The Food and Drug Administration (FDA) granted benznidazole priority review, accelerated approval, and orphan drug designation.

Warnings and Precautions:

Concomitant disulfiram. Psychotic reactions have been reported in patients who concomitantly took disulfiram and nitroimidazole agents (structurally related to benznidazole, but not with benznidazole). Therefore, benznidazole should not be administered to patients who have taken disulfiram within the prior two weeks.

Consumption of alcohol and products containing propylene glycol. Abdominal cramps, nausea, vomiting, headaches, and flushing may occur if alcoholic beverages or products containing propylene glycol are consumed during or following therapy with nitroimidazole agents, which are structurally related to benznidazole. No similar reactions have been reported with benznidazole. However, due to this structural similarity, alcoholic beverages or products containing propylene glycol should be discontinued during and for at least three days after therapy with benznidazole.

Genotoxicity and carcinogenicity. The genotoxicity of benznidazole was demonstrated *in vitro* in several bacterial species and mammalian cell systems, and *in vivo* in mammals. Nitroimidazoles, similar in chemical structure to benznidazole, have been reported to be carcinogenic in mice and rats.

Hypersensitivity reactions. Hypersensitivity skin reactions have been reported. In case of skin reactions presenting with additional systemic symptoms (e.g., fever, lymphadenopathy, purpura), benznidazole therapy should be discontinued.

Paresthesia or peripheral neuropathy. If these symptoms occur, benznidazole should be discontinued immediately.

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Hematologic effects. Bone marrow depression, including anemia, leukopenia, neutropenia, and thrombocytopenia, have occurred with benznidazole therapy.

Dosing and Administration: Benznidazole 12.5-mg and 100-mg tablets are for oral use and may be taken with or without food. The total daily pediatric dose for patients 2 to 12 years of age is 5–8 mg/kg administered orally in two divided doses separated by approximately 12 hours for a duration of 60 days. The 100-mg tablets are scored so they can be split in half or into quarters. The tablets can also be made into slurry as an alternative method of administration. Refer to the full prescribing information for exact dosing and administration recommendations.

Commentary: The efficacy and safety of benznidazole were established in two placebo-controlled clinical trials in patients 6 to 12 years of age. In one trial, approximately 60% of benznidazole-treated children had an antibody test change from positive to negative versus approximately 14% of placebo-treated children. In the second trial, approximately 55% of benznidazole-treated children had an antibody test change from positive to negative versus 5% of placebo-treated children. In a safety and pharmacokinetics study, the dosing recommendations for patients as young as 2 years of age were determined. The most common adverse reactions in benznidazole-treated patients were anorexia, pruritus, stomach pain, rash, weight loss, headache, nausea, vomiting, leukopenia, and urticaria.

Sources: Exeltis USA, Inc., Benznidazole prescribing information, Centers for Disease Control and Prevention

Vestronidase Alfa-vjbk (Mepsevii)

Manufacturer: Ultragenyx Pharmaceutical, Inc., Novato, California

Date of Approval: November 15, 2017

Indication: Vestronidase alfa-vjbk injection for intravenous (IV) use is indicated for the treatment of pediatric and adult patients with the inherited metabolic condition mucopolysaccharidosis type VII (MPS VII).

Drug Class: Enzyme replacement therapy

Uniqueness of Drug: Vestronidase alfa-vjbk is the first agent approved to treat patients with MPS VII, a lysosomal storage disorder caused by deficiency of the enzyme beta-glucuronidase. MPS VII, also known as Sly syndrome, is an extremely rare, progressive condition that affects most tissues and organs, and impacts fewer than 150 patients worldwide. The features of MPS VII vary, but most patients have skeletal abnormalities that become more pronounced with age. Individuals can also develop heart valve abnormalities, hepatosplenomegaly, and narrowed airways, which can lead to lung infections and difficulty breathing. The life expectancy of individuals with MPS VII depends on symptom severity. Some affected individuals do not survive infancy, while others may live into adolescence or adulthood. Heart disease and airway obstruction are major causes of death in these patients. Affected individuals may have developmental delays and progressive

intellectual disability. This treatment was granted fast-track and orphan drug designations and was approved under priority review by the Food and Drug Administration (FDA).

Warnings and Precautions:

Boxed warning: anaphylaxis. Anaphylaxis has occurred with vestronidase alfa-vjbk administration as early as the first dose. Appropriate medical support should be readily available when the agent is administered. Patients should be observed closely for at least 60 minutes following infusion. If anaphylaxis occurs, vestronidase alfa-vjbk should be discontinued immediately.

Immunogenicity. As with all therapeutic proteins, there is immunogenicity potential with use of this treatment.

Limitations of use. The effect of vestronidase alfa-vjbk on the central nervous system manifestations of MPS VII has not been determined.

Dosage and Administration: Vestronidase alfa-vjbk should be administered via IV infusion under the supervision of a health care professional with the capability to manage anaphylaxis. Premedication with a nonsedating antihistamine with or without an antipyretic medication is recommended 30 to 60 minutes before the start of the infusion. Using aseptic technique, vestronidase alfa-vjbk should be diluted 1:1 with 0.9% sodium chloride injection, USP, as indicated in the instructions provided in the full prescribing information. The recommended dosage is 4 mg/kg administered every two weeks. It should be administered over approximately four hours. The first 2.5% of the total volume of the infusion should be administered over the first hour. After the first hour, the infusion rate can be increased as tolerated to give the infusion over the following three hours according to the manufacturer's rate guidelines. If immediate use is not possible, the diluted solution may be stored up to 36 hours under refrigeration at 36–46° F followed by up to six hours at room temperature.

Commentary: The safety and efficacy of vestronidase alfa-vjbk were established in clinical trial and expanded access protocols enrolling 23 patients ranging from 5 months to 25 years of age. Patients received treatment at doses of up to 4 mg/kg once every two weeks for up to 164 weeks. Efficacy was primarily assessed via the six-minute walk test in 10 patients who could perform the test. After 24 weeks of treatment, the mean difference in distance walked relative to placebo was 18 meters. Additional follow-up for up to 120 weeks suggested continued improvement in three patients and stabilization in the other patients. Two patients in the vestronidase alfa-vjbk development program experienced marked improvement in pulmonary function. The most common side effects following treatment were anaphylaxis, diarrhea, infusion-site reactions, peripheral edema, and rash.

Sources: Ultragenyx Pharmaceutical, Inc., Mepsevii prescribing information, FDA

Hepatitis B Vaccine (Recombinant), Adjuvanted (Heplisav-B)

Manufacturer: Dynavax Technologies Corporation, Berkeley, California

Date of Approval: November 9, 2017

Indication: Heplisav-B is indicated for the prevention of infection caused by all known subtypes of hepatitis B virus (HBV) in adults 18 years of age and older.

Drug Class: HBV vaccine

Uniqueness of Drug: This is the first new HBV vaccine approved in the United States in more than 25 years. It is also the only two-dose HBV vaccine for adults.

Warnings and Precautions:

Contraindications. Heplisav-B is contraindicated in patients who have had a severe allergic reaction (e.g., anaphylaxis) after a previous dose of any HBV vaccine or to any component of Heplisav-B, including yeast.

Managing allergic reactions. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of this vaccine.

Immunocompromised patients. A diminished immune response to Heplisav-B may be experienced by immunocompromised patients, including those on immunosuppressant therapy.

Limitations of vaccine effectiveness. HBV has a long incubation period. Heplisav-B may not prevent HBV infection in individuals who have an unrecognized HBV infection at the time of vaccination.

Pregnancy. There are no human data regarding the effects of the vaccine on pregnant women or the fetus. Pregnant women who are administered Heplisav-B are encouraged to enroll in the pregnancy registry by calling (844) 443-7734.

Use with immune globulin. There are no data to assess the concomitant use of Heplisav-B with immune globulin. When concomitant administration of Heplisav-B and immune globulin is needed, they should be given with different syringes at different injection sites.

Interference with laboratory tests. Hepatitis B surface antigen (HBsAg) derived from hepatitis B vaccines has been transiently detected in blood samples following vaccination. Serum HBsAg detection may not have diagnostic value within 28 days of immunization.

Dosage and Administration: Two doses of Heplisav-B (0.5 mL each) should be administered intramuscularly, one month apart.

Commentary: The approval of Heplisav-B was based on data from three phase 3 noninferiority trials of approximately 10,000 adults who received the vaccine. The studies compared Heplisav-B administered in two doses over one month with Engerix-B (hepatitis B vaccine recombinant, GlaxoSmithKline) administered in three doses over six months. In results from the largest phase 3 trial (N = 6,665), Heplisav-B demonstrated a statistically significant higher rate of protection compared with Engerix-B (95% versus 81%). Heplisav-B also demonstrated a statistically significant higher rate of protection (90%) versus Engerix-B (65%) in a subgroup analysis of participants with type-2 diabetes (n = 961). The most common local reaction in clinical trials was injection-site pain (23% to 39%). The most common systemic reactions were fatigue (11% to 17%) and headache (8% to 17%).

Sources: Dynavax Technologies Corporation, Heplisav-B prescribing information ■