Pharmaceutical Approval Update

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Bedaquiline (Sirturo) Tablets

Manufacturer: Janssen/Johnson & Johnson, Titusville, N.J.

Indication: Bedaquiline has been approved for adults 18 years of age and older with multidrug-resistant strains of pulmonary tuberculosis (MDR–TB). The medication is intended to be part of combination therapy when an effective alternative treatment is not available. This indication was based on an analysis of time to sputum culture conversion from two controlled phase 2 trials. The safety and efficacy of bedaquiline in treating latent infection caused by *Mycobacterium tuberculosis* have not been established.

Drug Class: Bedaquiline is a diaryl-quinoline antimycobacterial agent.

Uniqueness of Drug: Bedaquiline inhibits an enzyme needed by *M. tuberculosis* to replicate and spread throughout the body.

Boxed Warning: In one placebo-controlled trial, an increased risk of death was seen in 11.4% of bedaquiline-treated patients compared with 2.5% of placebo patients. This drug should be used only when an effective treatment regimen cannot otherwise be provided. QT interval prolongation can occur with treatment, and the use of bedaquiline with drugs that prolong the QT interval may cause additional QT prolongation.

Warnings and Precautions:

Increased mortality. An increased risk of death was seen with bedaquiline.

QT interval prolongation. Bedaquiline prolongs the QT interval. An electrocardiogram (ECG) should be obtained before treatment begins and at least 2, 12, and 24 weeks after treatment starts. Baseline serum potassium, calcium, and magnesium levels should be obtained and corrected if they are abnormal. All other drugs that prolong the QT interval should be discontinued if ventricular arrhythmia or a corrected Fridericia interval (QTcF) of more than 500 milliseconds (msec) occurs and is confirmed by another ECG. The risk of QT interval prolongation during treatment may be increased by:

- the use of bedaquiline with other QT interval–prolonging drugs, including fluoroquinolones, macrolides, and the antimycobacterial agent clofazimine (Lamprene, Novartis).
- a patient's history of torsades de pointes, congenital long-QT syndrome, hypothyroidism, bradyarrhythmias, or uncompensated heart failure.
- serum calcium, magnesium, or potassium levels below the lower limits of normal.

Bedaquiline has not been studied in patients with ventricular arrhythmias or recent myocardial infarction. ECGs should be monitored closely.

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Hepatic drug reactions. More liver-related adverse drug reactions were reported with bedaquiline when it was used with other TB drugs compared with other TB drugs used without the addition of bedaquiline. Alcohol and other hepatotoxic drugs should be avoided during bedaquiline therapy, especially in patients with diminished hepatic reserve. Liver function and related laboratory tests should be monitored closely. Treatment should be stopped if liver enzyme (aminotransferase) elevations are accompanied by a total bilirubin elevation of more than two times the upper limit of normal (ULN), if these elevations are more than eight times the ULN, and if these elevations persist beyond 2 weeks.

Dosage and Administration: Bedaquiline tablets are taken in combination with other medications that are used to treat TB. The tablets should be taken with food and should be swallowed whole with water for a total of 24 weeks. During weeks 1 and 2, the dose is 400 mg (four tablets) one time each day. During weeks 3 to 24, the dose is 200 mg (two tablets) each day three times weekly (e.g., on a Monday, Wednesday and Friday every week).

Patients should not take more than 600 mg (six tablets) during a 7-day period. Other TB medications might need to be taken for longer than 24 weeks. Bedaquiline doses should not be skipped. If doses are skipped or if the 24-week treatment is not completed, TB might be more difficult to treat.

If a dose is missed during week 1 or 2, patients should not take a double dose; the next dose should be taken as usual. If a dose is missed during weeks 3 to 24, the missed dose should be taken as soon as possible and the three-times-weekly schedule should be resumed.

Patients are observed by a health care professional when they receive and take the drug as a way to reduce the risk of interrupted treatment and noncompliance.

Commentary: According to the Centers for Disease Control and Prevention, nearly 9 million people around the world and 10,528 people in the U.S. contracted TB in 2011. Multidrug-resistant TB (MDR–TB) occurs when *M. tuberculosis* does not respond to isoniazid and rifampin, two potent, commonly used TB drugs. Bedaquiline is the first drug approved to treat MDR–TB, and it is used in combination with other TB medications.

MDR–TB is considered an orphan disease. The FDA's accelerated approval was based on studies showing that the drug eradicated bacteria more quickly compared with a standard regimen; however, it is not known whether patients actually fared better with bedaquiline. Janssen plans to conduct larger clinical trials to investigate whether the drug performs as predicted.

Bedaquiline provides a benefit for patients without other therapeutic options. Because the drug also carries significant risks, physicians should ensure that it is used appropriately. Therapy for MDR–TB may be necessary for 18 to 24 months or longer; therefore, treatment can cost 200 times as much as that used for the ordinary form of TB.

Sources: www.janssentherapeutics.com/sites/default/files/pdf/sirturo-pi.pdf; www.fda.com; www.jnj.com

Flublok Influenza Vaccine

Manufacturer: Protein Sciences, Meriden, Conn.

Indication: Flublok is a trivalent recombinant hemagglutinin (HA) seasonal flu vaccine for people 18 through 49 years of age.

Biological Class: The vaccine is a sterile, clear, colorless solution of recombinant HA proteins from three influenza viruses for intramuscular (IM) injection.

Uniqueness of Biological Product: Flublok contains purified HA proteins produced in a continuous insect cell line (*expres*Sf+) that is derived from Sf9 cells of the fall armyworm, *Spodoptera frugiperda*. The cell line is grown in a serum-free medium composed of chemically defined lipids, vitamins, amino acids, and mineral salts. The three HAs are expressed in this cell line using a baculovirus vector (*Autographa californica* nuclear polyhedrosis virus), extracted from the cells with Triton X-100 surfactant and then purified by column chromatography. The purified HAs are blended and poured into single-dose vials.

Live virus does not need to be grown in chicken eggs; theoretically, therefore, the vaccine could be ready weeks earlier in the event of a pandemic.

Flublok contains the HA proteins of the three strains of influenza virus included in the annual seasonal vaccine. These proteins function as antigens, which induce a humoral immune response, and are measured by HA inhibition antibody.

Warnings and Precautions:

Guillain-Barré syndrome. The 1976 swine influenza vaccine was associated with an increased incidence of Guillain-Barré syndrome (GBS). It is not clear whether a causal relationship to GBS exists with other influenza vaccines. If an excess risk exists, it is probably slightly more than one additional case per 1 million persons vaccinated. If GBS occurs within 6 weeks after a person has received a prior influenza vaccine, the decision as to whether to give Flublok should be based on careful consideration of the potential benefits and risks.

Allergic reactions. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following inoculation.

Altered immunocompetence. If Flublok is administered to immunocompromised individuals or those receiving immunosuppressive therapy, the immune response may be diminished.

Dosage and Administration: Flublok is a sterile solution supplied in single-dose 0.5-mL vials and is approved for IM injection only. The vial should be shaken gently before the vaccine dose is withdrawn. If particulate matter or discoloration is visible, the vaccine should not be administered. The preferred site for injection is the deltoid muscle. A sterile needle and syringe are used. Flublok should not be mixed with any other vaccine in the same syringe or vial.

Commentary: Unlike other vaccines, Flublok consists of only a protein (HA) from the virus. The protein is made by inserting the gene for HA into a virus that infects insect cells. Those cells, from the fall armyworm, are grown in culture and churn out the protein. Neither eggs nor the live virus is used, although it is necessary to obtain genetic information about the virus. In a clinical trial, Flublok was about 44.6% effective against all influenza strains, not only the strains that matched the strains contained in the vaccine.

As with current vaccines, Flublok composition must be changed each year to match the flu strains in circulation. Antibodies against one influenza virus type or subtype confer limited or no protection against another virus, and antibodies to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virological basis for seasonal epidemics and the reason for the usual replacement of one or more influenza virus strains in each year's vaccine. Therefore, the vaccines are standardized to contain the HAs of influenza virus strains (typically two type A and one type B), representing those viruses likely to be circulating in the U.S. during the next winter.

Sources: FDA, January 16, 2013; *The New York Times*, January 17, 2013; GlobalData, January 18, 2013

Octaplas Solution for Infusion

Manufacturer: OctaPharma, Vienna, Austria

Indication: Octaplas is approved to manage or prevent bleeding in patients who need replacement of multiple plasma coagulation factors, patients with coagulation deficiencies caused by hepatic disease, and those undergoing cardiac surgery or liver transplantation. The product is also intended for transfusion or plasma exchange in patients with congenital or acquired thrombotic thrombocytopenic purpura (TTP), a rare blood disorder. Both acquired and congenital forms of TTP are associated with a severe deficiency of an enzyme required to regulate the activity of a large protein. A coagulation factor deficiency can contribute to excessive bleeding or clot formation in small blood vessels, especially those of the heart, brain, and kidneys.

Biological Class: Octaplas is a pooled plasma product, derived from several human donors, in a solvent/detergent procedure.

Uniqueness of Biological Product: Solvent/detergent treatment is a well-recognized method of reducing highly infectious enveloped viruses. Octaplas is designed to protect against viral transmission, to prevent transfusion-related acute lung injury and nonhemolytic allergic reactions, and to provide coagulation factor levels that would be equivalent to single-donor fresh frozen plasma. Pooling human plasma from multiple donors of the same specific blood group (ABO) reduces variations in essential coagulation factors and in immune-neutralizing antibodies that could occur with a single donor.

Warnings and Precautions: Transfusion reactions can occur with ABO blood group mismatches. High infusion rates of Octaplas (e.g., 25–50 mL/kg) can induce hypervolemia, resulting in pulmonary edema or cardiac failure. Excessive bleeding caused by hyperfibrinolysis can occur if alpha$_2$-antiplasmin levels are low, and thrombosis can occur if protein S levels are low. Citrate toxicity can occur with Octaplas volumes that exceed 1 mL/kg per minute.

Because Octaplas is made from human plasma, it may carry a risk of transmission of viruses; the variant Creutzfeldt–Jakob disease (vCJD) agent; and, theoretically, the CJD agent. Octaplas is contraindicated in patients with immunoglobulin A deficiency; severe protein S deficiency; a history of hypersensitivity to fresh frozen plasma, plasma-derived products, or plasma protein; or a history of a hypersensitivity reaction to the product.

Dosage and Administration: The dosage of Octaplas depends upon the patient's underlying disorder, but 12 to 15 mL/kg is the generally accepted starting dose. This dose

should increase the patient's plasma coagulation factor levels by approximately 25%. It is important to monitor the response by measuring prothrombin time, partial thromboplastin time, and coagulation factor.

An adequate hemostatic effect is typically achieved after an infusion of 5 to 20 mL/kg in patients with coagulation factor deficiency, in those experiencing minor and moderate hemorrhages, and in those who are having surgery. This dose should increase plasma coagulation factor levels by approximately 10% to 33%. If the patient is experiencing a major hemorrhage or is undergoing surgery, a hematologist should be consulted. In patients with TTP, the whole plasma volume that is exchanged should be replaced with Octaplas.

Administration must be based on ABO blood group compatibility. In emergencies, blood group AB can be regarded as universal plasma for all patients. Octaplas must be administered by intravenous (IV) infusion immediately after it is thawed via an infusion set with a filter. An aseptic technique must be used. Because of the risk of citrate toxicity, the infusion rate should not exceed 0.020 to 0.025 mmoL/kg of citrate/kg per minute (or 1 mL/kg or less per minute of Octaplas). Toxic effects of citrate can be minimized if IV calcium gluconate is injected into another vein.

Commentary: The solvent/detergent process used to produce Octaplas inactivates enveloped viruses by irreversibly disrupting their lipid coats, thereby reducing the risk of infectivity. With plasma pooling, the risk of transmitting enveloped viruses (e.g., herpes simplex virus-1) and non-enveloped viruses (e.g., hepatitis A virus, hepatitis E virus, and parvovirus B19) is reduced. Plasma pooling, cell filtration, and solvent/detergent treatment may neutralize antibodies against white blood cell antigens and reduce bioactive lipids, which mediate the development of transfusion-related acute lung injury, a severe yet underreported cause of morbidity and mortality.

Like fresh frozen plasma, Octaplas should be matched to the recipient's blood group to reduce the chance of transfusion reactions. An additional benefit of Octaplas is that each lot is always tested for composition of key clotting factors and is released only if the levels are within acceptable ranges.

Sources: www.octaplasus.com; FDA, January 17, 2013, www.fda.gov**;** Reuters, January 22, 2013, www.reuters.com ■