Pharmaceutical Approval Update

Mary Choy, PharmD, CGP, FASHP

Defibrotide Sodium (Defitelio)

Manufacturer: Jazz Pharmaceuticals, Inc., Palo Alto, California

Date of Approval: March 30, 2016

Indication: Defitelio is indicated for the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome, with renal or pulmonary dysfunction following hematopoietic stem-cell transplantation (HSCT).

Drug Class: Deoxyribonucleic acid derivative anticoagulant

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Uniqueness of Drug: Defitelio is the first therapy approved by the Food and Drug Administration (FDA) for treatment of severe hepatic VOD, a rare and life-threatening liver condition. It also has been granted orphan drug designation by the FDA. Fewer than 2% of patients develop severe hepatic VOD after HSCT, but as many as 80% of patients who develop it do not survive.

Warnings and Precautions:

Hemorrhage. Defitelio increased the activity of fibrinolytic enzymes *in vitro,* and it may increase the risk of bleeding in patients with VOD after HSCT. Do not initiate Defitelio in patients with active bleeding, and monitor for signs of bleeding. If patients develop bleeding, discontinue Defitelio, treat the underlying cause, and provide supportive care until bleeding stops. Concomitant use of Defitelio and a systemic anticoagulant or fibrinolytic therapy (not including use for routine maintenance or reopening of central venous lines) may increase the risk of bleeding. Discontinue anticoagulants and fibrinolytic agents prior to Defitelio treatment, and consider delaying the start of administration until the effects of the anticoagulant have abated.

Hypersensitivity reactions. Hypersensitivity reactions have occurred in less than 2% of patients and include rash, urticaria, and angioedema. If a severe hypersensitivity reaction occurs, discontinue Defitelio, treat according to the standard of care, and monitor until symptoms resolve.

Dosage and Administration: Defitelio is administered at 6.25 mg/kg every six hours as a two-hour intravenous (IV) infusion. The dose should be based on the patient's baseline body weight, defined as the patient's weight prior to the preparative regimen for HSCT. Treatment should be maintained for a minimum of 21 days. If after 21 days the signs and symptoms of VOD have not resolved, continue treatment until resolution or up to a maximum of 60 days.

Defitelio must be diluted prior to infusion. Before administration, confirm that the patient is not experiencing clinically significant bleeding and is hemodynamically stable on no more than one vasopressor. Administer by constant IV over a two-hour period using an infusion set equipped with a 0.2-micron inline filter. Flush the IV administration line (peripheral or central) with 5% dextrose injection, USP, or 0.9% sodium chloride injection, USP, immediately before and after administration. Do not coadminister Defitelio and other IV drugs within the same IV line.

Commentary: The efficacy of Defitelio was evaluated in three studies that enrolled 528 patients with hepatic VOD with liver or kidney abnormalities after HSCT. In clinical trials, 38% to 45% of patients treated with the drug were alive 100 days after HSCT. Data analysis from published reports indicates 100-day survival rates post HSCT for patients receiving only supportive care or interventions other than Defitelio are 21% to 31%. The most common side effects include hypotension, diarrhea, vomiting, nausea, and nosebleeds.

Sources: Jazz Pharmaceuticals, Inc.; Defitelio prescribing information

Emtricitabine 200 mg/Tenofovir Alafenamide 25 mg (Descovy)

Manufacturer: Gilead Sciences, Inc., Foster City, California

Date of Approval: April 4, 2016

Indication: Descovy is a two-drug combination used with other antiretrovirals for treating human immunodeficiency virus (HIV)-1 infection in adults and pediatric patients 12 years of age and older. It is not indicated for use as pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 in adults at high risk.

Drug Class: Nucleoside and nucleotide reverse transcriptase inhibitors

Uniqueness of Drug: Descovy consists of emtricitabine and tenofovir alafenamide (TAF). TAF is a novel targeted prodrug of tenofovir that has shown high antiviral efficacy similar to and at a dose less than one-tenth that of Gilead's Viread (tenofovir disoproxil fumarate, or TDF). Because TAF enters cells more efficiently than TDF, it can be given at a much lower dose, and it has also shown an improvement in renal and bone safety in clinical trials in combination with other antiretroviral agents. This is the first approval of new core therapy for HIV in more than 10 years.

Warnings and Precautions:

Boxed warning. Occurrences of lactic acidosis/severe hepatomegaly with steatosis and post-treatment acute exacerbation of hepatitis B have been reported with the use of nucleoside analogues, such as Descovy, in combination with other antiretrovirals.

Fat redistribution. Redistribution or accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance," has been observed in patients receiving antiretroviral therapy.

Immune reconstitution syndrome. Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy including emtricitabine, a

Dr. Choy is an Associate Professor at Touro College of Pharmacy and a Clinical Pharmacist at Metropolitan Hospital in New York, New York.

Descovy component, that may necessitate further evaluation and treatment.

New onset or worsening renal impairment. Serum phosphorus should be monitored in patients with chronic kidney disease.

Bone loss and mineralization defects. Assessment of bone mineral density should be considered for patients treated with Descovy who have a history of pathological bone fracture or other risk factors for osteoporosis or bone loss. Calcium and vitamin D supplementation may be beneficial for all patients.

Dosage and Administration: Before starting treatment, patients should be tested for hepatitis B virus infection and estimated creatinine clearance; urine glucose and urine protein levels should be obtained. The recommended dose of Descovy is one tablet taken once daily with or without food in patients 12 years of age and older with a body weight of at least 35 kg and a creatinine clearance of 30 mL or more per minute. Descovy is not recommended in patients with estimated creatinine clearance below 30 mL per minute.

Commentary: The approval of Descovy is supported by 48-week data from two pivotal phase 3 studies in which the F/TAF-based regimen (administered as elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg, E/C/F/TAF [Genvoya, Gilead]) met its primary objective of noninferiority compared to an F/TDF-based regimen (administered as elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg, E/C/F/TDF [Stribild, Gilead]) among treatment-naïve adult patients. Tests of certain renal and bone laboratory parameters favored the F/TAF-based regimen over the F/TDF-based regimen. The approval is also supported by a phase 3 study evaluating the F/TAF-based regimen (administered as Genvoya) among virologically suppressed adult patients who switched from F/TDF-based regimens. In the study, the F/TAF-based regimen was found to be statistically noninferior to the F/TDF-based regimens and demonstrated improvements in certain bone and renal laboratory parameters compared to the F/TDF-based regimens. In addition, the approval is supported by data from phase 3 studies evaluating the F/TAF-based regimen (administered as Genvoya) among virologically suppressed adults with mild-to-moderate renal impairment and among treatment-naïve adolescents. Finally, bioequivalence studies demonstrated that Descovy achieved the same drug levels of TAF and emtricitabine in the blood as Genvoya.

Sources: Gilead Sciences, Inc.; Descovy prescribing information

Infliximab-dyyb (Inflectra)

Manufacturer: Celltrion, Inc., Incheon, Republic of Korea

Date of Approval: April 5, 2016

Indication: Inflectra is approved for the treatment of adult and pediatric patients (ages 6 years and older) with moderately to severely active Crohn's disease (CD) who have had an inadequate response to conventional therapy; adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy; patients with moderately to severely active rheumatoid arthritis (RA) in combination with methotrexate; patients with active ankylosing spondylitis (AS); patients with active psoriatic arthritis (PsA); and adult patients with chronic severe plaque psoriasis.

Drug Class: Tumor necrosis factor-alpha inhibitors

Uniqueness of Drug: Inflectra is the second biosimilar in the U.S. approved by the Food and Drug Administration. It is a biosimilar to Janssen Biotech, Inc.'s Remicade (infliximab).

Warnings and Precautions:

Boxed warning. Inflectra has a boxed warning for an increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and others. It is also noted that lymphoma and other malignancies, some fatal, have been reported in children and adolescents treated with tumor necrosis factor blockers, including infliximab products such as Inflectra. Other serious side effects may include liver injury, blood problems, lupus-like syndrome, psoriasis, and, in rare cases, nervous system disorders. The drug must be dispensed with a patient medication guide that describes important information about its uses and risks.

Serious infections. Do not give Inflectra during an active infection. If an infection develops, monitor carefully and stop Inflectra if the infection becomes serious. For patients who reside or travel in regions where mycoses are endemic, invasive fungal infections should be suspected if they develop a serious systemic illness. Empiric antifungal therapy should be considered for those patients. Perform a test for latent TB; if positive, start TB treatment before starting Inflectra. Monitor all patients for active TB during treatment, even if the initial latent TB test is negative.

Malignancies. The incidence of malignancies including lymphoma was greater in TNF-blocker–treated patients than in controls. Due to the risk of hepatosplenic T-cell lymphoma, carefully assess the risk–benefit, especially if the patient has CD or UC, is male, and is receiving azathioprine or 6-mercaptopurine treatment.

Hepatitis B virus (HBV) reactivation. Test for HBV infection before starting Inflectra. Monitor HBV carriers during and for several months after therapy. If reactivation occurs, stop Inflectra and begin antiviral therapy.

Hepatotoxicity. Rare severe hepatic reactions may occur, some fatal or necessitating liver transplantation. Discontinue Inflectra in cases of jaundice and/or marked liver enzyme elevations.

Heart failure. New onset or worsening symptoms may occur.

Cytopenias. Advise patients to seek immediate medical attention if signs and symptoms develop, and consider stopping Inflectra.

Hypersensitivity. Serious infusion reactions, including anaphylaxis or serum sickness-like reactions, may occur.

Live vaccines or therapeutic infectious agents. Live vaccines or therapeutic infectious agents should not be given with Inflectra. Bring pediatric patients up to date with all vaccinations before initiating Inflectra. A waiting period of at least six months following birth is recommended before the administration of live vaccines to infants exposed *in utero* to infliximab products.

continued on page 441

Pharmaceutical Approval Update

continued from page 417

Dosage and Administration: Inflectra is administered by intravenous infusion over a period of at least two hours. Dosing varies with indication and patient weight:

CD: 5 mg/kg at zero, two, and six weeks, then every eight weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response.

Pediatric CD, UC, PsA, and plaque psoriasis: 5 mg/kg at zero, two, and six weeks, then every eight weeks.

RA: In conjunction with methotrexate, 3 mg/kg at zero, two, and six weeks, then every eight weeks. Some patients may benefit from increasing the dose to 10 mg/kg or treating as often as every four weeks.

AS: 5 mg/kg at zero, two, and six weeks, then every six weeks.

Commentary: The approval of Inflectra was based on the review of evidence that included structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamics data, clinical immunogenicity data, and other clinical safety and effectiveness data that demonstrates Inflectra is biosimilar to Remicade. The most common side effects of Inflectra include respiratory infections, headache, coughing, and stomach pain. Infusion reactions can occur up to two hours postinfusion, with symptoms including fever, chills, chest pain, hypotension or hypertension, shortness of breath, rash, and/or itching.

Sources: Celltrion, Inc.; Inflectra prescribing information ■