Pharmaceutical Approval Update

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Sarilumab (Kevzara)

Manufacturer: Sanofi-Aventis, Bridgewater, New Jersey

Date of Approval: May 22, 2017

Indication: Sarilumab is an interleukin (IL)-6 receptor antagonist indicated for treating adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to or are intolerant of one or more disease-modifying antirheumatic drugs (DMARDs). It is approved for use as monotherapy or in combination with methotrexate or other DMARDs.

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Drug Class: IL-6 inhibitor

Uniqueness of Drug: Sarilumab is the first IL-6-receptor–targeting monoclonal antibody approved by the Food and Drug Administration (FDA) to treat adults with moderately to severely active RA who are intolerant of or who do not respond adequately to one or more DMARDs.

Warnings and Precautions:

Boxed warning: serious infections. Bacterial, viral, invasive fungal, and other opportunistic infections leading to hospitalization or death have occurred in patients receiving sarilumab. If a serious infection occurs, discontinue sarilumab until the infection is controlled. Prior to starting sarilumab, test for latent tuberculosis (TB), and if positive, TB treatment should be initiated; cases of TB have been reported during sarilumab treatment. Patients should be closely monitored for signs and symptoms of infection while taking sarilumab, and the drug should be avoided during an active infection.

Cytopenia. Cytopenia has occurred during treatment with sarilumab. A higher incidence of absolute neutrophil count decrease, including neutropenia and thrombocytopenia, was associated with sarilumab in clinical trials. Assess neutrophil and platelet counts prior to starting sarilumab, then four to eight weeks after starting therapy and every three months thereafter during therapy. Dose modifications based on platelet and neutrophil counts can be found in the full prescribing information.

Elevated liver enzymes. A higher incidence of transaminase elevations was noted with sarilumab treatment; this increased when potential hepatotoxins were used in combination with sarilumab. No clinical hepatic injury occurred in clinical studies. Assess alanine transaminase (ALT)/aspartate transaminase (AST) levels prior to sarilumab initiation, and monitor ALT/AST levels four to eight weeks after starting therapy and every three months thereafter during therapy. Dose modifications based on AST/ALT levels can be found in the full prescribing information. Sarilumab treatment is not recommended in patients with active hepatic disease or hepatic impairment.

Lipid parameter increases. Increases in low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and triglycerides have been associated with sarilumab treatment. Lipid parameters should be assessed every four to eight weeks following sarilumab initiation, then at approximate six-month intervals.

Gastrointestinal (GI) perforations. GI perforations have been reported primarily as diverticulitis complications. GI perforation risk may be increased with concurrent diverticulitis or concomitant use of nonsteroidal anti-inflammatory drugs or corticosteroids. Patients should be evaluated promptly if they present with new-onset abdominal symptoms.

Hypersensitivity reactions. Hypersensitivity reactions requiring drug discontinuation occurred in 0.3% of patients in controlled RA clinical trials. Injection-site rash, rash, and urticaria were the most frequent hypersensitivity reactions. Patients should be advised to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. Sarilumab should not be given to anyone with known hypersensitivity to the drug or its ingredients.

Live vaccines. Live vaccines should be avoided in combination with sarilumab due to the risk of infection. Clinical safety of live vaccines during sarilumab treatment has not been established. Follow current vaccination guidelines for immunosuppressed patients.

Embryo-fetal effects. There are limited human data regarding sarilumab use in pregnant women; these data are not sufficient to inform drug-associated risk for major birth defects and miscarriage. A pregnancy exposure registry that monitors outcomes in women exposed to sarilumab during pregnancy has been established. Patients who are pregnant are encouraged to register by calling (877) 311-8972.

Dosage and Administration: Sarilumab may be used as monotherapy or in combination with methotrexate or other conventional DMARDs. The recommended sarilumab dose is 200 mg once every two weeks given as a subcutaneous injection. The dose should be reduced to 150 mg once every two weeks when management of neutropenia, thrombocytopenia, or elevated liver enzymes is required. Sarilumab is intended for use under the guidance of a health care professional but can be self-administered by the patient or administered by a caregiver. Patients and/or caregivers should be properly trained in the preparation and administration of sarilumab prior to use according to the manufacturer's instructions. The prefilled syringe should be administered after sitting for at least 30 minutes at room temperature.

Commentary: The FDA approval of sarilumab was based on two randomized, double-blind, placebo-controlled, multicenter phase 3 studies in approximately 2,900 adults with moderately to severely active RA, who had an inadequate response to previous treatment regimens. Sarilumab plus background DMARDs demonstrated statistically significant and clinically meaningful improvements in these patients, as assessed by American College of Rheumatology 20% improvement criteria (ACR20) for RA signs and symptoms, modified total Sharp score (radiographic progression of structural damage), and the Health

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Assessment Questionnaire–Disability Index. ACR20 responses at week 24 were 56% to 66% for sarilumab-treated patients compared with 33% to 34% for placebo-treated patients. The most common adverse reactions were neutropenia, increased ALT, injection-site erythema, upper respiratory infections, and urinary tract infections.

Sources: Sanofi-Aventis, Kevzara prescribing information

Valbenazine Tosylate (Ingrezza)

Manufacturer: Neurocrine Biosciences, Inc., San Diego, California

Date of Approval: April 11, 2017

Indication: Valbenazine is indicated for the treatment of adults with tardive dyskinesia (TD).

Drug Class: Vesicular monoamine transporter 2 inhibitor

Uniqueness of Drug: Valbenazine is the first drug approved by the Food and Drug Administration (FDA) for the treatment of adults with TD, a neurological disorder characterized by involuntary movements of the face, tongue, or other body parts that cannot be controlled. TD is a serious side effect most often seen in patients treated with older antipsychotic agents for long periods of time for schizophrenia, bipolar disorder, depression, or related disorders. TD can also occur from the use of some medications to treat gastrointestinal and other conditions. Prior to its approval, valbenazine received FDA fast-track, priority review, and breakthrough therapy designations.

Warnings and Precautions:

Somnolence. Valbenazine may impair a patient's ability to drive or operate hazardous machinery. Patients should not perform activities requiring mental alertness until they know how the drug affects them.

QT prolongation. Valbenazine may cause an increase in the QT interval. In patients taking strong cytochrome P450 (CYP) 2D6 or CYP3A4 inhibitors or in those who are CYP2D6 poor metabolizers, valbenazine concentrations may be higher and QT prolongation may be clinically significant. Dose reduction may be necessary for patients who are CYP2D6 poor metabolizers or are taking strong CYP2D6 inhibitors. In patients taking strong CYP3A4 inhibitors, the valbenazine dose should be reduced to 40 mg once daily. The drug should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, the QT interval should be assessed before dosage increases.

Drug or drug-class interactions. Clinically significant drug interactions have occurred with valbenazine. Concomitant use with monoamine oxidase inhibitors and strong CYP3A4 inducers should be avoided. For patients taking strong CYP2D6 inhibitors, a reduction in the valbenazine dose should be considered based on tolerability. Valbenazine may increase the concentration of digoxin; therefore, patient digoxin concentrations should be monitored and digoxin doses adjusted as needed.

Hepatic/renal impairment. A reduction in valbenazine dosage is recommended for patients with moderate-to-severe hepatic impairment (Child–Pugh score 7–15). These patients demonstrated higher valbenazine exposures in clinical trials. Dosage adjustment is not necessary for patients with mild-to-moderate renal impairment (creatinine clearance [CrCl] of 30–90 mL/min). Valbenazine is not recommended in patients with severe renal impairment (CrCl less than 30 mL/min).

Dosage and Administration: Valbenazine is available as 40-mg capsules. The initial dose is 40 mg orally, once daily, with or without food. After one week, the dose can be increased to the recommended dose of 80 mg once daily. Continuation of 40 mg once daily may be considered for some patients, such as those with moderate-to-severe hepatic impairment (Child–Pugh score 7–15).

Commentary: The FDA approval of valbenazine was based on a randomized, double-blind, placebo-controlled clinical trial that included 234 patients. After six weeks, participants who received valbenazine showed improvements in the severity of abnormal involuntary movements compared with those individuals who received placebo. This was determined by response to the abnormal involuntary movement scale and was continued through 48 weeks of treatment. Valbenazine was not associated with the worsening of safety scale scores for depression, or suicidal ideation or behaviors. The most common adverse reactions were somnolence and QT interval prolongation.

Sources: Neurocrine Biosciences, Inc., Ingrezza prescribing information, FDA

Cerliponase Alpha (Brineura)

Manufacturer: BioMarin Pharmaceutical, Inc., Novato, California

Date of Approval: April 27, 2017

Indication: Cerliponase alpha is a hydrolytic lysosomal N-terminal tripeptidyl peptidase indicated to slow the loss of ambulation in symptomatic pediatric patients at least 3 years of age with late infantile neuronal ceroid lipofuscinosis type-2 (CLN2) disease, also known as tripeptidyl peptidase 1 deficiency.

Drug Class: Enzyme replacement therapy

Uniqueness of Drug: CLN2 disease is part of a group of neuronal ceroid lipofuscinoses (NCLs) known as Batten disease, a relatively rare but fatal disorder occurring in an estimated two to four of every 100,000 live births in the U.S. CLN2 disease is inherited and primarily affects the nervous system. In the late infantile form of the disease, signs and symptoms usually begin between 2 years and 4 years of age. The initial symptoms include language delay, epilepsy, and ataxia. These children also develop myoclonus and vision loss. CLN2 disease affects essential motor skills, such as sitting and walking, and by late childhood, these patients often require a wheelchair and typically do not survive past their teens. Cerliponase alpha is an enzyme replacement therapy administered to the intraventricular cerebrospinal fluid (CSF) through a surgically implanted device. Prior to its approval, the Food and Drug Administration (FDA) granted the treatment priority review, breakthrough therapy, and orphan drug designations.

Warnings and Precautions:

Intraventricular access device-related complications. The scalp should be inspected for skin integrity and for signs of intraventricular access device leakage. Cerliponase alpha should not be administered if there are signs of device leakage or infection. CSF samples should be sent routinely for testing to detect subclinical device-related infections.

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Cardiovascular adverse reactions. Patient vital signs should be monitored before, during, and after cerliponase alpha infusion. An electrocardiogram (ECG) should be monitored during the infusion in patients with a history of bradycardia or conduction disorder, or with structural heart disease. Patients without cardiac abnormalities should have a regular 12-lead ECG evaluation every six months.

Hypersensitivity reactions. Patients should be observed during and after infusion for severe hypersensitivity reactions. If one occurs, the infusion should be stopped immediately and appropriate treatment should be initiated.

Dosage and Administration: The recommended dosage of cerliponase alpha is 300 mg administered once every other week as an intraventricular infusion into the CSF via a surgically implanted reservoir and catheter. An infusion of intraventricular electrolytes immediately follows the administration of cerliponase alpha. The complete infusion takes approximately 4.5 hours. Aseptic technique must be strictly observed during preparation and administration. Cerliponase alpha should be administered by or under the direction of a physician knowledgeable in intraventricular administration. Patients should be pretreated with antihistamines with or without antipyretics or corticosteroids 30 to 60 minutes prior to the start of cerliponase alpha infusion. Cerliponase alpha injection is provided as a 150-mg/5-mL (30 mg/mL) solution in two single-dose vials per carton and is packaged along with the intraventricular electrolytes injection, 5 mL in a single-dose vial. See the full prescribing information for details on preparation, specific intraventricular access device for use, and administration.

Commentary: The efficacy of cerliponase alpha was determined in a nonrandomized, single-arm dose-escalation clinical study in symptomatic pediatric patients with CLN2 disease (n = 22). These patients were compared with untreated patients with CLN2 disease from a natural history cohort (an independent historical control group) who were at least 3 years of age and had motor or language symptoms (n = 42). Cerliponase alpha-treated patients (when age, baseline walking ability, and genotype were taken into account) had fewer walking ability declines versus the untreated (natural history cohort) patients. Cerliponase alpha safety was assessed in 3- to 8-year-olds (n = 24) with CLN2 disease who received at least one cerliponase alpha dose in clinical studies. The most common adverse reactions occurring at a rate of 8% or greater were bradycardia; decreased CSF protein; device-related infection; ECG abnormalities; fever; headache; hematoma; hypersensitivity; hypotension; increased CSF protein; irritability; jitteriness; pleocytosis; seizures; and vomiting.

Sources: BioMarin Pharmaceutical, Inc., Brineura prescribing information, FDA ■