Molecular and Cellular Pharmacology
www.mcpharmacology.com

Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibodies for Treatment of COVID-19

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for bamlanivimab and etesevimab administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age or older weighing at least 40 kilograms [about 88 pounds]) who test positive for SARS-CoV-2 and who are at high risk for progressing to severe COVID-19. The authorized use includes treatment for those who are 65 years of age or older or who have certain chronic medical conditions.

In a clinical trial of patients with COVID-19 at high risk for disease progression, a single intravenous infusion of bamlanivimab and etesevimab administered together significantly reduced COVID-19-related hospitalization and death during 29 days of follow-up compared to placebo. The safety and effectiveness of this investigational therapy for use in the treatment of COVID-19 continue to be evaluated.

Bamlanivimab and etesevimab are not authorized for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19. Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

"Today's action, which provides another treatment for COVID-19, reflects the FDA's strong commitment to working with sponsors to expand potential treatment options health care providers can use to fight this pandemic," said Patrizia Cavazzoni, M.D., acting director of the FDA's Center for Drug Evaluation and Research. "The data supporting this emergency authorization add to emerging evidence that points to the clinical utility of neutralizing antibodies for the treatment of COVID-19 in certain patients. As part of our Coronavirus Treatment Acceleration Program, the FDA uses every resource at our disposal to make treatments such as these monoclonal antibodies available while continuing to study their safety and effectiveness."

Monoclonal antibodies are laboratory-made proteins that mimic the immune system's ability to fight off harmful pathogens such as viruses. Bamlanivimab and etesevimab are monoclonal antibodies that are specifically directed against the spike protein of SARS-CoV-2, designed to block the virus' attachment and entry into human cells. Bamlanivimab and etesevimab bind to different but overlapping sites on the spike protein of the virus.

The issuance of an EUA is different than an FDA approval. In determining whether to issue an EUA, the FDA evaluates the totality of available scientific evidence and carefully balances any known or potential risks with any known or potential benefits of the product for use during an emergency. Based on the FDA's review of the totality of the scientific evidence available, the agency has determined that it is reasonable to believe that bamlanivimab and etesevimab administered together may be effective in treating certain patients with mild or moderate COVID-19. When used to treat COVID-19 for the authorized population, the known and potential benefits of these antibodies outweigh the known and potential risks. There are no adequate, approved and available alternative treatments to bamlanivimab and etesevimab administered together for the authorized population.

The data supporting this EUA for bamlanivimab and etesevimab are based on a randomized, double-blind, placebo-controlled clinical trial in 1,035 non-hospitalized adults with mild to moderate COVID-19 symptoms who were at high risk for progressing to severe COVID-19. Of these patients, 518 received a single infusion of bamlanivimab 2,800 milligrams and etesevimab 2,800 milligrams together, and 517 received placebo. The primary endpoint was COVID-19 related hospitalizations or death by any cause during 29 days of follow-up. Hospitalization or death occurred in 36 (7%) patients who received placebo compared to 11 (2%) patients treated with bamlanivimab 2,800 milligrams and etesevimab 2,800 milligrams administered together, a 70% reduction. All 10 deaths (2%) deaths occurred in the placebo group. Thus, all-cause death was significantly lower in the bamlanivimab 2,800-milligram and etesevimab 2,800-milligram group than the placebo group.

The authorized dosage of 700 milligrams bamlanivimab and 1400 milligrams etesevimab administered together is based on analyses of available preclinical, clinical, and virologic data, as well as pharmacokinetic and pharmacodynamic modeling, which, in totality, support that the authorized dosage is expected to have a similar clinical and virologic effect to 2,800 milligrams

bamlanivimab and 2,800 milligrams etesevimab administered together.

On Nov. 9, 2020, the FDA issued an EUA for a single infusion of 700 mg bamlanivimab for the treatment of mild-to-moderate COVID-19 in adult and certain pediatric patients. While bamlanivimab and etesevimab administered together resulted in a lower risk of resistant viruses developing during treatment compared with bamlanivimab administered alone, both treatments are expected to benefit patients at high risk of disease progression. At present, both 700 milligrams bamlanivimab alone as well as 700 milligrams bamlanivimab and 1,400 milligrams etesevimab administered together will be available under an EUA.

Under the EUA, fact sheets that provide important information about using bamlanivimab and etesevimab administered together in treating COVID-19 as authorized must be made available to health care providers and to patients and caregivers. These fact sheets include dosing instructions, potential side effects and drug interactions. Serious and unexpected adverse events including hypersensitivity, anaphylaxis, and infusion-related reactions have been observed with bamlanivimab with and without coadministration of etesevimab. In addition, clinical worsening following bamlanivimab administration has been reported, although it is not known if these events were related to bamlanivimab use or were due to progression of COVID-19. Possible side effects of bamlanivimab and etesevimab administered together include nausea, dizziness, pruritus, and rash.

The EUA was issued to Eli Lilly and Co.

FDA News released Feb 9, 2021. www.fda.gov.

FDA Approves Targeted Treatment for Rare Duchenne Muscular Dystrophy Mutation

Today, the U.S. Food and Drug Administration granted approval for Amondys 45 (casimersen) injection for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping (Exons are pieces of DNA that provide information for making proteins in a person's genome). The agency approved Amondys 45 based on an increase in dystrophin (a protein that helps keep muscle cells intact) production in skeletal muscle observed in patients treated with the therapy. This is the first FDA-approved targeted treatment for patients with this type of mutation. Approximately 8% of patients with DMD have a mutation that is amenable to exon 45 skipping.

"Developing drugs designed for patients with specific mutations is a critical part of personalized medicine," said Eric Bastings, M.D., deputy director of the Office of Neuroscience in the FDA's Center for Drug Evaluation and Research. "Today's approval of Amondys 45 provides a targeted treatment option for Duchenne muscular dystrophy patients with this confirmed mutation."

DMD is a rare genetic disorder characterized by progressive muscle deterioration and weakness. It is the most common type of muscular dystrophy. DMD is caused by mutations in the DMD gene that results in an absence of dystrophin, a protein found in muscle fiber. The first symptoms are usually seen between three and five years of age and worsen over time. DMD occurs in approximately one out of every 3,600 male infants worldwide; in rare cases, it can affect females.

Amondys 45 was evaluated in a double-blind, placebo-controlled study in which 43 patients were randomized 2:1 to receive either intravenous Amondys 45 (30 mg/kg) or placebo. All patients were male, between 7 and 20 years of age, and had a genetically confirmed mutation of the DMD gene that is amenable to exon 45 skipping.

In the study, patients who received Amondys 45 showed a significantly greater increase in dystrophin protein levels from baseline to week 48 of treatment compared to those who received placebo.

The FDA has concluded that the data submitted by the applicant demonstrated an increase in dystrophin production that is reasonably likely to predict clinical benefit in patients with DMD who have a confirmed mutation of the dystrophin gene amenable to exon 45 skipping. A clinical benefit of the drug, including improved motor function, has not been established. In making this decision, the FDA considered the potential risks associated with the drug, the life-threatening and debilitating nature of the disease, and the lack of available therapy.

The most common side effects observed in DMD patients treated with Amondys 45 were upper respiratory tract infections, cough, fever, headache, joint pain and throat pain.

Although kidney toxicity was not observed in the Amondys 45 clinical studies, kidney toxicity was observed in the nonclinical studies. Kidney toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense

oligonucleotides. Kidney function should be monitored in patients taking Amondys 45.

Amondys 45 was approved using the Accelerated Approval pathway, under which the FDA may approve drugs for serious conditions where there is unmet medical need and a drug is shown to have certain effects that are reasonably likely to predict a clinical benefit to patients. Further study is required to verify and describe anticipated clinical benefits of Amondys 45, and the sponsor is currently conducting an ongoing, double-blind, placebo-controlled, multicenter study designed to evaluate the safety and efficacy of Amondys 45 in ambulatory DMD patients.

The FDA granted this application Fast Track and Priority Review designations. Amondys 45 also received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases.

The FDA is granting the approval to Sarepta Therapeutics, Inc.

FDA News released Feb 25, 2021. www.fda.gov.

FDA Approves Treatment for Chronic Kidney Disease

Approval is First to Cover Many Causes of Disease

Today, the U.S. Food and Drug Administration approved Farxiga (dapagliflozin) oral tablets to reduce the risk of kidney function decline, kidney failure, cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease who are at risk of disease progression.

"Chronic kidney disease is an important public health issue, and there is a significant unmet need for therapies that slow disease progression and improve outcomes," said Aliza Thompson, M.D., M.S., deputy director of the Division of Cardiology and Nephrology in the FDA's Center for Drug Evaluation and Research. "Today's approval of Farxiga for the treatment of chronic kidney disease is an important step forward in helping people living with kidney disease."

Chronic kidney disease occurs when the kidneys are damaged and cannot filter blood normally. Due to this defective filtering, patients can have complications related to fluid, electrolytes (minerals required for many bodily processes), and waste build-up in the body. Chronic kidney disease sometimes can progress to kidney failure. Patients also are at high risk of cardiovascular disease, including heart disease and stroke.

The efficacy of Farxiga to improve kidney outcomes and reduce cardiovascular death in patients with chronic kidney disease was evaluated in a multicenter, double-blind study. In this study, 4,304 patients were randomly assigned to receive either Farxiga or a placebo. The study compared the two groups for the number of patients whose disease progressed to a composite (or combined) endpoint that included at least a 50% reduction in kidney function, progression to kidney failure, or cardiovascular or kidney death. Results showed that 197 of the 2,152 patients who received Farxiga had at least one of the composite endpoint events compared to 312 of the 2,152 patients who received a placebo. The study also compared the two groups for the number of patients who were hospitalized for heart failure or died from cardiovascular disease. A total of 100 patients who received Farxiga were hospitalized or died compared to 138 patients who received a placebo.

Farxiga was not studied, nor is expected to be effective, in treating chronic kidney disease among patients with autosomal dominant or recessive polycystic (characterized by multiple cysts) kidney disease or among patients who require or have recently used immunosuppressive therapy to treat kidney disease.

Patients should not use Farxiga if they have a history of serious hypersensitivity reactions to the medication or if they are on dialysis treatment. Serious, life-threatening cases of Fournier's Gangrene have occurred in patients with diabetes taking Farxiga. Patients should consider a lower dose of insulin or insulin secretagogue to reduce the risk of hypoglycemia (low blood sugar) if they are also taking Farxiga. Farxiga can cause dehydration, serious urinary tract infections, genital yeast infections, and metabolic acidosis or ketoacidosis (acid build-up in the blood). Patients should be assessed for their volume status and kidney function before starting Farxiga.

Farxiga was originally approved in 2014 to improve glycemic control in adults with type 2 diabetes in addition to diet and exercise.

Farxiga received Fast Track, Breakthrough Therapy and Priority Review designations for the indication being approved today. Fast track is designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. Breakthrough therapy designation is designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence

indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s). Priority review directs overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis or prevention of serious conditions when compared to standard applications.

The FDA granted the approval of Farxiga to AstraZeneca.

FDA News released April 30, 2021. www.fda.gov.

Source: FDA