FDA Approves New Therapy for Rare Form of Blood Cancers Called Myelodysplastic Syndromes

Today, the U.S. Food and Drug Administration approved Tibsovo (ivosidenib) for the treatment of adult patients with relapsed or refractory (R/R) myelodysplastic syndromes (MDS) with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test. This is the first targeted therapy approved for this indication. The agency also approved the Abbott RealTime IDH1 Assay as a companion diagnostic for the selection of R/R MDS patients with an IDH1 mutation.

MDS are a rare form of blood cancers that can occur when the mutations in the bone marrow progenitor cells (cells that form blood) lead to insufficient numbers of healthy blood cells. Approximately 60,000 to 170,000 people live with MDS in the U.S., with an estimated 87,000 new cases each year worldwide. About 3.6 percent of patients with MDS have an IDH1 mutation.

"Today's approval represents an important treatment advancement for rare blood cancers, and more specifically, patients with relapsed or refractory MDS who have an IDH1 mutation," said Richard Pazdur, M.D., director of the FDA's Oncology Center of Excellence and acting director of the Office of Oncologic Diseases in the FDA's Center for Drug Evaluation and Research. "Through the FDA's Oncology Center of Excellence Rare Cancers Program, we remain committed to promoting scientific innovation and advancing the development of safe and effective novel therapies to treat patients with rare cancers."

Tibsovo was previously approved for certain adults with newly-diagnosed Acute Myeloid Leukemia (AML), relapsed or refractory AML and locally advanced or metastatic cholangiocarcinoma. The Abbott RealTime IDH1 Assay was also previously approved as a companion diagnostic to identify AML patients with an IDH1 mutation for treatment with Tibsovo or Rezlidhia (olutasidenib).

The effectiveness of Tibsovo for this new indication was evaluated in an open-label, single-arm, multicenter study of 18 adult patients with relapsed or refractory MDS with an IDH1 mutation. IDH1 mutations were detected in peripheral blood or bone marrow by a local or central diagnostic test and confirmed retrospectively using the Abbott RealTime IDH1 Assay. Tibsovo was given orally at a starting dose of 500 milligram daily continuous for 28-day cycles until disease progression, development of unacceptable toxicity or undergoing bone marrow transplantation.

The main efficacy outcome measures were the rate of complete remission or partial remission, the duration of complete remission or partial remission and the rate of conversion from transfusion dependence to transfusion independence. The complete remission or partial remission rate was 39% (7/18). All observed responses were complete remissions and the median duration of complete remission ranged from 1.9 to 80.8 months. For patients who achieved a complete remission, the median time to complete remission was 1.9 months. Among the nine patients who required transfusions of blood or platelets due to MDS at the start of the study, six (67%) no longer required transfusions after treatment with Tibsovo.

The most common side effects were similar to common side effects seen with ivosidenib monotherapy for patients with AML. This includes diarrhea, constipation, nausea, joint pain, fatigue, cough, muscle aches and rash. Tibsovo may also cause a condition which can lead to abnormal heart rhythms called QTc prolongation.

The prescribing information for Tibsovo includes a boxed warning that an adverse reaction known as differentiation syndrome can occur and can be fatal if not treated. Signs and symptoms of differentiation syndrome may include fever, difficulty breathing (dyspnea), low oxygen levels, inflammation in the lungs (radiographic pulmonary infiltrates), fluid around the lungs or heart (pleural or pericardial effusions), rapid weight gain, swelling (peripheral edema) or liver (hepatic), kidney (renal) or multi-organ dysfunction. At first suspicion of symptoms, health care providers should treat patients with corticosteroids and monitor patients closely until symptoms go away.

Tibsovo was granted Priority Review designation, under which the FDA's goal is to take action on an application within six months where the agency determines that the drug, if approved, would significantly improve the safety or effectiveness of treating, diagnosing or preventing a serious condition. Tibsovo also received FDA Breakthrough Therapy designation and Orphan Drug designation for the indication noted above. Orphan drug designation provides incentives to assist and encourage drug development for rare diseases.

The FDA granted the approval of Tibsovo to Servier Pharmaceuticals LLC.

The FDA granted the approval of the RealTime IDH1 Assay to Abbott Laboratories.

FDA News released Oct 24, 2023. www.fda.gov.

FDA Approves First Treatment for Patients with Rare Inherited Blood Clotting Disorder

Today, the U.S. Food and Drug Administration approved Adzynma, the first recombinant (genetically engineered) protein product indicated for prophylactic (preventive) or on demand enzyme replacement therapy (ERT) in adult and pediatric patients with congenital thrombotic thrombocytopenic purpura (cTTP), a rare and life-threatening blood clotting disorder.

"The FDA remains deeply committed in our efforts to help facilitate the development and approval of safe and effective therapies for patients with rare diseases," said Peter Marks, M.D., Ph.D., director of the FDA's Center for Biologics Evaluation and Research. "Without treatment, cTTP is ultimately fatal. Today's approval reflects important progress in the development of much-needed treatment options for patients affected by this life-threatening disorder."

The very rare, inherited blood clotting disorder called cTTP is caused by a disease-causing mutation in the ADAMTS13 gene, which is responsible for making an enzyme, also named ADAMTS13, that regulates blood clotting. A deficiency in this enzyme causes blood clots to form in the small blood vessels throughout the body. It is estimated that cTTP affects fewer than one thousand people in the United States. Symptoms typically develop in infancy or early childhood, but in some cases may develop in adulthood and may first manifest during pregnancy. Individuals with cTTP may experience severe bleeding episodes, strokes and damage to vital organs. If left untreated, the disease can be fatal. Treatment for cTTP typically involves prophylactic plasma-based therapy for individuals with chronic disease to reduce the risk of clotting/bleeding by replenishing the absent/low ADAMTS13 enzyme.

Adzynma is a purified recombinant form of the ADAMTS13 enzyme that works by providing a replacement for the low levels of the deficient enzyme in patients with cTTP. For prophylactic ERT, Adyznma is administered to help reduce the risk of disease symptoms. The product may also be administered as an on-demand ERT for treatment when the patient is experiencing an acute event. Adzynma is administered intravenously once every other week for prophylactic ERT, and once daily for on-demand ERT.

The safety and effectiveness of Adzynma were demonstrated in a global study evaluating prophylactic and on-demand ERT with Adzynma compared to plasma-based therapies in patients with cTTP.

The efficacy of Adzynma in the prophylactic treatment of patients with cTTP was evaluated in 46 patients who were randomized to receive 6 months of treatment with either Adzynma or plasma based therapies (Period 1), then crossed over to the other treatment for 6 months (Period 2). The efficacy was demonstrated based on the incidence of thrombotic thrombocytopenic purpura (TTP) events, and TTP manifestations, as well as the incidence of the need for supplemental doses.

The efficacy of on demand ERT was evaluated based on the proportion of acute TTP events responding to Adzynma in both the prophylactic and the on-demand cohorts throughout the duration of the study. All acute and subacute TTP events resolved after treatment with either Adzynma or plasma based therapies.

The most common side effects associated with Adzynma include headache, diarrhea, migraine, abdominal pain, nausea, upper respiratory tract infection, dizziness and vomiting. During the clinical studies, no adverse events, including allergic reactions, were observed during the administration of Adzynma.

The application was awarded a Rare Pediatric Disease Priority Review Voucher, and granted Priority Review, Fast Track and Orphan designations.

The FDA granted approval of Adzynma to Takeda Pharmaceuticals U.S.A. Inc.

FDA News released Nov 9, 2023. www.fda.gov.

FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease

Today, the U.S. Food and Drug Administration approved approved two milestone treatments, Casgevy and Lyfgenia, representing the first cell-based gene therapies for the treatment of sickle cell disease (SCD) in patients 12 years and older.

Additionally, one of these therapies, Casgevy, is the first FDA-approved treatment to utilize a type of novel genome editing technology, signaling an innovative advancement in the field of gene therapy.

Sickle cell disease is a group of inherited blood disorders affecting approximately 100,000 people in the U.S. It is most common in African Americans and, while less prevalent, also affects Hispanic Americans. The primary problem in sickle cell disease is a mutation in hemoglobin, a protein found in red blood cells that delivers oxygen to the body's tissues. This mutation causes red blood cells to develop a crescent or "sickle" shape. These sickled red blood cells restrict the flow in blood vessels and limit oxygen delivery to the body's tissues, leading to severe pain and organ damage called vaso-occlusive events (VOEs) or vaso-occlusive crises (VOCs). The recurrence of these events or crises can lead to life-threatening disabilities and/or early death.

"Sickle cell disease is a rare, debilitating and life-threatening blood disorder with significant unmet need, and we are excited to advance the field especially for individuals whose lives have been severely disrupted by the disease by approving two cell-based gene therapies today," said Nicole Verdun, M.D., director of the Office of Therapeutic Products within the FDA's Center for Biologics Evaluation and Research. "Gene therapy holds the promise of delivering more targeted and effective treatments, especially for individuals with rare diseases where the current treatment options are limited."

Casgevy, a cell-based gene therapy, is approved for the treatment of sickle cell disease in patients 12 years of age and older with recurrent vaso-occlusive crises. Casgevy is the first FDA-approved therapy utilizing CRISPR/Cas9, a type of genome editing technology. Patients' hematopoietic (blood) stem cells are modified by genome editing using CRISPR/Cas9 technology.

CRISPR/Cas9 can be directed to cut DNA in targeted areas, enabling the ability to accurately edit (remove, add, or replace) DNA where it was cut. The modified blood stem cells are transplanted back into the patient where they engraft (attach and multiply) within the bone marrow and increase the production of fetal hemoglobin (HbF), a type of hemoglobin that facilitates oxygen delivery. In patients with sickle cell disease, increased levels of HbF prevent the sickling of red blood cells.

Lyfgenia is a cell-based gene therapy. Lyfgenia uses a lentiviral vector (gene delivery vehicle) for genetic modification and is approved for the treatment of patients 12 years of age and older with sickle cell disease and a history of vaso-occlusive events. With Lyfgenia, the patient's blood stem cells are genetically modified to produce HbAT87Q, a gene-therapy derived hemoglobin that functions similarly to hemoglobin A, which is the normal adult hemoglobin produced in persons not affected by sickle cell disease. Red blood cells containing HbAT87Q have a lower risk of sickling and occluding blood flow. These modified stem cells are then delivered to the patient.

Both products are made from the patients' own blood stem cells, which are modified, and are given back as a one-time, single-dose infusion as part of a hematopoietic (blood) stem cell transplant. Prior to treatment, a patients' own stem cells are collected, and then the patient must undergo myeloablative conditioning (high-dose chemotherapy), a process that removes cells from the bone marrow so they can be replaced with the modified cells in Casgevy and Lyfgenia. Patients who received Casgevy or Lyfgenia will be followed in a long-term study to evaluate each product's safety and effectiveness.

"These approvals represent an important medical advance with the use of innovative cell-based gene therapies to target potentially devastating diseases and improve public health," said Peter Marks, M.D., Ph.D., director of the FDA's Center for Biologics Evaluation and Research. "Today's actions follow rigorous evaluations of the scientific and clinical data needed to support approval, reflecting the FDA's commitment to facilitating development of safe and effective treatments for conditions with severe impacts on human health."

Data Supporting Casgevy

The safety and effectiveness of Casgevy were evaluated in an ongoing single-arm, multi-center trial in adult and adolescent patients with SCD. Patients had a history of at least two protocol-defined severe VOCs during each of the two years prior to screening. The primary efficacy outcome was freedom from severe VOC episodes for at least 12 consecutive months during the 24-month follow-up period. A total of 44 patients were treated with Casgevy. Of the 31 patients with sufficient follow-up time to be evaluable, 29 (93.5%) achieved this outcome. All treated patients achieved successful engraftment with no patients experiencing graft failure or graft rejection.

The most common side effects were low levels of platelets and white blood cells, mouth sores, nausea, musculoskeletal pain, abdominal pain, vomiting, febrile neutropenia (fever and low white blood cell count), headache and itching.

Data Supporting Lyfgenia

The safety and effectiveness of Lyfgenia is based on the analysis of data from a single-arm, 24-month multicenter study in patients with sickle cell disease and history of VOEs between the ages of 12- and 50-years old. Effectiveness was evaluated based on complete resolution of VOEs (VOE-CR) between 6 and 18 months after infusion with Lyfgenia. Twenty-eight (88%) of 32 patients achieved VOE-CR during this time period.

The most common side effects included stomatitis (mouth sores of the lips, mouth, and throat), low levels of platelets, white blood cells, and red blood cells, and febrile neutropenia (fever and low white blood cell count), consistent with chemotherapy and underlying disease.

Hematologic malignancy (blood cancer) has occurred in patients treated with Lyfgenia. A black box warning is included in the label for Lyfgenia with information regarding this risk. Patients receiving this product should have lifelong monitoring for these malignancies.

Both the Casgevy and Lyfgenia applications received Priority Review, Orphan Drug, Fast Track and Regenerative Medicine Advanced Therapy designations.

The FDA granted approval of Casgevy to Vertex Pharmaceuticals Inc. and approval of Lyfgenia to Bluebird Bio Inc.

FDA News released Dec 8, 2023. www.fda.gov.

Source: FDA