FDA Approves First Treatment for Niemann-Pick Disease, Type C

Today, the U.S. Food and Drug Administration approved Miplyffa (arimoclomol), an oral medication for the treatment of Niemann-Pick disease, type C (NPC). Miplyffa, in combination with the enzyme inhibitor miglustat, is approved to treat neurological symptoms associated with NPC in adults and children 2 years of age and older. Miplyffa is the first drug approved by the FDA to treat NPC.

NPC is a rare genetic disease that results in progressive neurological symptoms and organ dysfunction. It is caused by changes in either the NPC1 or NPC2 gene, affecting the necessary transport of cholesterol and other lipids within a cell. As a result, these cells do not function as they should, ultimately causing organ damage. On average, individuals affected by this devastating disease only live for about 13 years.

"NPC is a serious disease that leads to enormous adverse impacts on patients and families. Despite extensive research efforts, there have not been approved treatments to meet the significant needs of patients," said Janet Maynard, M.D., M.H.S., director of the Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM), in the FDA's Center for Drug Evaluation and Research. "The first-ever approval of a safe and effective drug option for NPC will undoubtedly support the essential medical needs of those suffering."

Miplyffa was the first product application to be discussed at the inaugural meeting of the Genetic Metabolic Diseases Advisory Committee (GeMDAC) in August. GeMDAC was established in December 2023 to advise the agency on products used for the diagnosis, prevention or treatment of genetic metabolic diseases.

The safety and effectiveness of Miplyffa were evaluated in a randomized, double-blind, placebo-controlled 12-month trial in patients two to 19 years of age who had a molecularly confirmed diagnosis of NPC. Fifty patients were randomized 2:1 to treatment with weight-adjusted Miplyffa (31 to 124 mg) or placebo orally three times per day. Among these 50 patients, 39 (78%) received miglustat as background treatment in the trial.

Miplyffa's efficacy was demonstrated by the rescored 4-domain NPC Clinical Severity Scale (R4DNPCCSS) score in the patients who used miglustat as their background treatment. The R4DNPCCSS is a measure of NPC disease progression that looks at four items that patients with NPC, their caregivers and physicians have identified as most relevant including ambulation, speech, swallow and fine motor skills. Higher scores signify a greater severity of the disease. Compared to placebo, Miplyffa resulted in a slower disease progression as measured by the R4DNPCCSS score.

The prescribing information for Miplyffa contains a warning for hypersensitivity reactions including hives and angioedema (swelling under the skin). Individuals experiencing these adverse reactions should stop using the drug. Females who are pregnant or plan to become pregnant should not use Miplyffa.

The most common side effects of Miplyffa include upper respiratory tract infection, diarrhea and decreased weight.

Miplyffa, along with miglustat, should be taken orally with or without food according to the recommended dose for the patient's body weight.

The FDA granted Miplyffa priority review, orphan drug, rare pediatric disease, fast track and breakthrough therapy designations for this application.

The FDA granted approval of Miplyffa to Zevra Therapeutics.

FDA News released Sep 20, 2024. www.fda.gov.

FDA Approves Drug with New Mechanism of Action for Treatment of Schizophrenia

Today, the U.S. Food and Drug Administration approved Cobenfy (xanomeline and trospium chloride) capsules for oral use for the treatment of schizophrenia in adults. It is the first antipsychotic drug approved to treat schizophrenia that targets cholinergic receptors as opposed to dopamine receptors, which has long been the standard of care.

"Schizophrenia is a leading cause of disability worldwide. It is a severe, chronic mental illness that is often damaging to a person's quality of life," said Tiffany Farchione, M.D., director of the Division of Psychiatry, Office of Neuroscience in the FDA's Center for Drug Evaluation and Research. "This drug takes the first new approach to schizophrenia treatment in decades. This approval offers a new alternative to the antipsychotic medications people with schizophrenia have previously been prescribed."

Schizophrenia can cause psychotic symptoms including hallucinations (such as hearing voices), difficulty controlling one's thoughts and being suspicious of others. It can also be associated with cognitive problems and difficulty with social interactions and motivation. About 1% of Americans have this illness and globally it is one of the 15 leading causes of disability. Individuals with schizophrenia are at greater risk of dying at a younger age, and nearly 5% die by suicide.

Cobenfy's effectiveness for the treatment of schizophrenia in adults was evaluated in two studies with identical designs. Study 1 and Study 2 were 5-week, randomized, double-blind, placebo-controlled, multi-center studies in adults with a diagnosis of schizophrenia according to DSM-5 criteria.

The primary efficacy measure was the change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score at week 5. The PANSS is a 30-item scale that measures symptoms of schizophrenia. Each item is rated by a clinician on a seven-point scale. In both studies, the participants who received Cobenfy experienced a meaningful reduction in symptoms from baseline to Week 5 as measured by the PANSS Total Score compared to the placebo group.

The prescribing information includes warnings that Cobenfy can cause urinary retention, increased heart rate, decreased gastric movement or angioedema (swelling beneath the skin) of the face and lips. Cobenfy is not recommended for patients with mild hepatic (liver) impairment. It should not be used in patients with known hepatic impairment. There is also a risk of liver damage. Patients should stop using Cobenfy if experiencing signs or symptoms of substantial liver disease (including yellowing of the skin or the white part of the eyes, dark urine and unexplained itching). Cobenfy is substantially excreted by the kidney and is not recommended in patients with moderate to severe renal impairment.

Cobenfy should not be prescribed to patients with urinary retention, moderate or severe kidney or liver disease, gastric retention, untreated narrow-angle glaucoma or a history of hypersensitivity to either Cobenfy or its components.

The most common side effects of Cobenfy are nausea, indigestion, constipation, vomiting, hypertension, abdominal pain, diarrhea, tachycardia (increased heartbeat), dizziness and gastroesophageal reflux disease.

The approval of Cobenfy was granted to Bristol-Myers Squibb Company.

FDA News released Sep 26, 2024. www.fda.gov.

FDA Approves First Gene Therapy for Treatment of Aromatic L-amino Acid Decarboxylase Deficiency

The U.S. Food and Drug Administration approved Kebilidi (eladocagene exuparvovec-tneq), an adeno-associated virus vector-based gene therapy indicated for the treatment of adult and pediatric patients with aromatic L-amino acid decarboxylase (AADC) deficiency. Kebilidi is the first FDA-approved gene therapy for treatment of AADC deficiency.

"Clinical advancements in the field of gene therapy continue to lead to the discovery and availability of innovative treatment options for rare diseases that are otherwise difficult to manage," said Peter Marks, M.D., Ph.D., director of the FDA's Center for Biologics Evaluation and Research (CBER). "Today's approval underscores our commitment to help make safe and effective treatments available for patients in need."

Aromatic L-amino acid decarboxylase deficiency is a rare genetic disorder that affects the production of some neurotransmitters, which are chemical messengers that allow cells in the body's nervous system to communicate with each other. Affected individuals may experience symptoms such as delays in gross motor function (head control, sitting, standing, and walking), hypotonia (weak muscle tone), and developmental and cognitive delays.

"AADC deficiency can cause a range of debilitating symptoms, including life-threatening complications," said Nicole Verdun, M.D., director of the Office of Therapeutic Products in CBER. "Today's approval represents important progress in the advancement and availability of safe and effective treatments for debilitating genetic disorders."

Kebilidi is administered via four infusions in one surgical session into a large structure in the brain involved in motor control. Kebilidi should be administered in a medical center that specializes in pediatric stereotactic neurosurgery — a technique that uses imaging and special equipment to deliver therapies to specific areas in the brain. After infusion of Kebilidi, treatment results in the expression of AADC and subsequent increase in the production of dopamine, a critical neurotransmitter in the brain associated with movement, attention, learning and memory.

The safety and effectiveness of Kebilidi were demonstrated in an open-label, single-arm clinical

study in 13 pediatric patients with confirmed diagnosis of AADC deficiency. At the start of the study, all patients had no gross motor function (the most severe presentation of AADC deficiency) and decreased AADC activity in the plasma. Patients treated with Kebilidi were compared to untreated patients (natural history). Motor milestone assessments were completed for 12 of the 13 patients at week 48 after receiving the treatment. The efficacy of Kebilidi was demonstrated based on gross motor function improvement in 8 of 12 treated patients, which has not been reported in untreated patients with the severe presentation of AADC deficiency.

The most common adverse reactions of Kebilidi are dyskinesia (involuntary muscle movements), fever, low blood pressure, anemia (low red blood cell count), increased saliva production, insomnia, low levels of potassium, phosphate, and/or magnesium, and procedural complications such as respiratory and cardiac arrest. It is also contraindicated in patients who have not achieved skull maturity assessed by neuroimaging.

Kebilidi was approved using the Accelerated Approval pathway. Accelerated approval allows the FDA to approve certain products for serious or life-threatening conditions based on evidence of a product's effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit. In the FDA's evaluation of Kebilidi for accelerated approval, evidence of effectiveness is based on early improvements in gross motor function measured at 48 weeks after treatment. Continued approval for this indication may be contingent upon verification and description of clinical benefit of the product, such as the durability of the improvements, in a confirmatory clinical trial. A confirmatory trial is ongoing to verify Kebilidi's clinical benefit.

The application received Priority Review and Orphan Drug designation, and was granted a rare pediatric disease priority review voucher by the FDA.

The FDA also authorized the SmartFlow Neuro Cannula, an infusion tube inserted into a target in the brain (parenchymal tissue), to deliver Kebilidi.

The SmartFlow Neuro Cannula is currently the only FDA authorized device indicated for use to administer Kebilidi. The FDA granted authorization of the SmartFlow Neuro Cannula to ClearPoint Neuro, Inc.

The FDA granted approval of Kebilidi to PTC Therapeutics, Inc.

FDA News released Nov 14, 2024. www.fda.gov.