FDA Approves Novel, Dual-Targeted Treatment for Type 2 Diabetes

In Clinical Trials, Treatment Proved More Effective Than Other Therapies Evaluated

Today, the U.S. Food and Drug Administration approved Mounjaro (tirzepatide) injection to improve blood sugar control in adults with type 2 diabetes, as an addition to diet and exercise. Mounjaro was effective at improving blood sugar and was more effective than the other diabetes therapies with which it was compared in clinical studies.

"Given the challenges many patients experience in achieving their target blood sugar goals, today's approval of Mounjaro is an important advance in the treatment of type 2 diabetes," said Patrick Archdeacon, M.D., associate director of the Division of Diabetes, Lipid Disorders, and Obesity in the FDA's Center for Drug Evaluation and Research.

Type 2 diabetes, the most common form of diabetes, is a chronic and progressive condition in which the body does not make or use insulin normally, leading to high levels of glucose (sugar) in the blood. More than 30 million Americans have type 2 diabetes. Despite the availability of many medications to treat diabetes, many patients do not achieve the recommended blood sugar goals.

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are hormones involved in blood sugar control. Mounjaro is a first-in-class medicine that activates both the GLP-1 and GIP receptors, which leads to improved blood sugar control. Mounjaro is administered by injection under the skin once weekly, with the dose adjusted as tolerated to meet blood sugar goals.

Three different doses of Mounjaro (5 milligrams, 10 milligrams and 15 milligrams) were evaluated in five clinical trials as either a stand-alone therapy or as an add-on to other diabetes medicines. The efficacy of Mounjaro was compared to placebo, a GLP-1 receptor agonist (semaglutide) and two long-acting insulin analogs.

On average, patients randomized to receive the maximum recommended dose of Mounjaro (15 milligrams) had lowering of their hemoglobin A1c (HbA1c) level (a measure of blood sugar control) by 1.6% more than placebo when used as stand-alone therapy, and 1.5% more than placebo when used in combination with a long-acting insulin. In trials comparing Mounjaro to other diabetes medications, patients who received the maximum recommended dose of Mounjaro had lowering of their HbA1c by 0.5% more than semaglutide, 0.9% more than insulin degludec and 1.0% more than insulin glargine.

Obesity was common among study participants, with an average body mass index of 32 to 34 kilograms/height in meters squared reported at the time of enrollment. Among patients randomized to the maximum recommended dose, the average weight loss with Mounjaro was 15 pounds more than placebo when neither were used with insulin and 23 pounds more than placebo when both were used with insulin. The average weight loss with the maximum recommended dose of Mounjaro was 12 pounds more than semaglutide, 29 pounds more than insulin degludec and 27 pounds more than insulin glargine. Those patients receiving insulin without Mounjaro tended to gain weight during the study.

Mounjaro can cause nausea, vomiting, diarrhea, decreased appetite, constipation, upper abdominal discomfort and abdominal pain.

Mounjaro causes thyroid C-cell tumors in rats. It is unknown whether Mounjaro causes such tumors, including medullary thyroid cancer, in humans. Mounjaro should not be used in patients with a personal or family history of medullary thyroid cancer or in patients with Multiple Endocrine Neoplasia syndrome type 2.

Mounjaro has not been studied in patients with a history of pancreas inflammation (pancreatitis), and it is not indicated for use in patients with type 1 diabetes.

Mounjaro received priority review designation for this indication. A priority review designation 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.

The FDA granted the approval of Mounjaro to Eli Lilly and Co.

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FDA Approves First Systemic Treatment for Alopecia Areata

Today, the U.S. Food and Drug Administration approved Olumiant (baricitinib) oral tablets to treat adult patients with severe alopecia areata, a disorder that often appears as patchy baldness and

affects more than 300,000 people in the U.S. each year. Today's action marks the first FDA approval of a systemic treatment (i.e. treats the entire body rather than a specific location) for alopecia areata.

"Access to safe and effective treatment options is crucial for the significant number of Americans affected by severe alopecia," said Kendall Marcus, M.D., director of the Division of Dermatology and Dentistry in the FDA's Center for Drug Evaluation and Research. "Today's approval will help fulfill a significant unmet need for patients with severe alopecia areata."

Alopecia areata, commonly referred to as just alopecia, is an autoimmune disorder in which the body attacks its own hair follicles, causing hair to fall out, often in clumps. Olumiant is a Janus kinase (JAK) inhibitor which blocks the activity of one or more of a specific family of enzymes, interfering with the pathway that leads to inflammation.

The efficacy and safety of Olumiant in alopecia areata was studied in two randomized, double-blind, placebo-controlled trials (Trial AA-1 and Trial AA-2) with patients who had at least 50% scalp hair loss as measured by the Severity of Alopecia Tool for more than six months. Patients in these trials received either a placebo, 2 milligrams of Olumiant, or 4 milligrams of Olumiant every day. The primary measurement of efficacy for both trials was the proportion of patients who achieved at least 80% scalp hair coverage at week 36.

In Trial AA-1, 22% of the 184 patients who received 2 milligrams of Olumiant and 35% of the 281 patients who received 4 milligrams of Olumiant achieved adequate scalp hair coverage, compared to 5% of the 189 patients who received a placebo. In Trial AA-2, 17% of the 156 patients who received 2 milligrams of Olumiant and 32% of the 234 patients who received 4 milligrams of Olumiant achieved adequate scalp hair coverage, compared to 3% of the 156 patients who received a placebo.

The most common side effects associated with Olumiant include: upper respiratory tract infections, headache, acne, high cholesterol (hyperlipidemia), increase of an enzyme called creatinine phosphokinase, urinary tract infection, liver enzyme elevations, inflammation of hair follicles (folliculitis), fatigue, lower respiratory tract infections, nausea, genital yeast infections (Candida infections), anemia, low number of certain types of white blood cells (neutropenia), abdominal pain, shingles (herpes zoster) and weight increase.

Olumiant is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, cyclosporine or other potent immunosuppressants. Olumiant comes with warnings and precautions including recommending close monitoring for the development of signs and symptoms of infection during and after treatment; evaluating patients for active tuberculosis infection and testing for latent tuberculosis prior to treatment with Olumiant; and the potential for viral reactivation. In addition, other warnings and precautions include hypersensitivity (allergic reactions), gastrointestinal perforations (tears in stomach or intestine), and laboratory abnormalities including low white and red blood cell counts, liver enzyme elevations and lipid elevations.

Olumiant comes with a boxed warning for serious infections, mortality, malignancy, major adverse cardiovascular events and thrombosis.

Olumiant received priority review and breakthrough therapy designations for this indication.

Olumiant was originally approved in 2018. It is approved as a treatment for certain adult patients with moderately to severely active rheumatoid arthritis. Olumiant is also approved for the treatment of COVID-19 in certain hospitalized adults.

The FDA granted the approval of Olumiant to Eli Lilly and Company.

FDA News released June 13, 2022. www.fda.gov.

FDA Approves First Targeted Therapy for HER2-Low Breast Cancer

Today, the U.S. Food and Drug Administration approved Enhertu (fam-trastuzumab-deruxtecan-nxki), an IV infusion for the treatment of patients with unresectable (unable to be removed) or metastatic (spread to other parts of the body) HER2-low breast cancer. This is the first approved therapy targeted to patients with the HER2-low breast cancer subtype, which is a newly defined subset of HER2-negative breast cancer.

It is estimated that 287,850 new cases of female breast cancer will be diagnosed in 2022 in the U.S. Approximately 80-85% of those new cases were previously considered to be HER2-negative subtype (including hormone receptor positive and triple negative breast cancer), which means the tumors do not overexpress, or make too many copies of the HER2 protein. Of that proportion of breast cancer diagnoses, about 60% of patients previously classified as having HER2-negative subtype can now be

considered as HER2-low. Prior to today's approval, HER2-low patients received endocrine therapy or chemotherapy.

"Today's approval highlights the FDA's commitment to be at the forefront of scientific advances, making targeted cancer treatment options available for more patients," 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. "Having therapies that are specially tailored to each patient's cancer subtype is a priority to ensure access to safe and innovative treatments."

As part of the Administration's Cancer Moonshot program, President Biden tapped federal agencies to develop ways to reduce the rate of cancer deaths and improve the lives of cancer patients and their families through advancements in cancer research and technology, and development of new programs. Enhertu's approval further illustrates how the FDA's efforts align with the Cancer Moonshot goals of targeting the right treatments to the right patients, speeding progress against the most deadly and rare cancers, and learning from the experience of all patients.

HER2 receptors, which are proteins made by the HER2 gene, are important in determining a patient's treatment. HER2-negative includes hormone receptor positive and triple negative breast cancers. HER2-low is a new classification of the HER2 subtype. It describes a new subtype of breast cancer that has some HER2 proteins on the cell surface, but not enough to be classified as HER2-positive.

Patients with HER2-low breast cancer are eligible for Enhertu if they have received a prior chemotherapy in the metastatic setting, or their cancer returned during, or within 6 months of completing, adjuvant chemotherapy.

This approval is based on DESTINY-Breast04, a randomized, multicenter, open label clinical trial that enrolled 557 adult patients with unresectable or metastatic HER2-low breast cancer. The trial included two cohorts: 494 hormone receptor positive (HR+) patients and 63 hormone receptor negative (HR-) patients. Of these patients, 373 randomly received Enhertu by intravenous infusion every three weeks and 184 randomly received physician's choice of chemotherapy (eribulin, capecitabine, gemcitabine, nab paclitaxel or paclitaxel). The results showed improvement in both progression-free survival and overall survival in people with unresectable or metastatic HER2-low breast cancer.

The median age of trial participants was 57 years old, ranging from 28 to 81 years of age. Among the 557 patients, 24% were age 65 or older. Females comprised 99.6% of the trial population. Trial participants' race was reported as 48% White, 40% Asian, 2% Black or African American, and 3.8% Hispanic/Latino.

The most common adverse reactions in patients receiving Enhertu in DESTINY-Breast04 are nausea, fatigue, alopecia, vomiting, constipation, decreased appetite, musculoskeletal pain and diarrhea. The prescribing information includes a boxed warning to advise health care professionals of the risk of interstitial lung disease and embryo-fetal toxicity. Enhertu is not recommended for women who are pregnant.

Enhertu received priority review and breakthrough therapy designations for this indication.

The FDA granted the approval of Enhertu to Daiichi Sankyo four months ahead of the Prescription Drug User Fee Act (PDUFA) deadline.

This review was conducted under Project Orbis, an initiative of the FDA Oncology Center of Excellence. Project Orbis provides a framework for concurrent submission and review of oncology drugs among international partners. For this review, FDA collaborated with the Australian Therapeutic Goods Administration, Health Canada, and Switzerland's Swissmedic. The application reviews may be ongoing at the other regulatory agencies.

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Source: FDA