FDA Approves First Targeted Therapy for Lung Cancer Mutation Previously Considered Resistant to Drug Therapy

Today, the U.S. Food and Drug Administration approved Lumakras (sotorasib) as the first treatment for adult patients with non-small cell lung cancer whose tumors have a specific type of genetic mutation called KRAS G12C and who have received at least one prior systemic therapy. This is the first approved targeted therapy for tumors with any KRAS mutation, which accounts for approximately 25% of mutations in non-small cell lung cancers. KRAS G12C mutations represent about 13% of mutations in non-small cell lung cancers.

"KRAS mutations have long been considered resistant to drug therapy, representing a true unmet need for patients with certain types of cancer," 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. "Today's approval represents a significant step towards a future where more patients will have a personalized treatment approach."

Lung cancer, the most common cancer type with the highest mortality, can largely be categorized by the genetic mutations that cause it. KRAS is a type of mutation in a group of genes that help regulate cell growth and division.

Researchers evaluated the efficacy of Lumakras in a study of 124 patients with locally advanced or metastatic KRAS G12C-mutated non-small cell lung cancer with disease progression after receiving an immune checkpoint inhibitor and/or platinum-based chemotherapy. The major outcomes measured were objective response rate (proportion of patients whose tumor is destroyed or reduced) and duration of response. The objective response rate was 36% and 58% of those patients had a duration of response of six months or longer.

The approved 960 milligram dose is based on available clinical data, as well as pharmacokinetic and pharmacodynamic modeling that support the approved dose. As part of the evaluation for this accelerated approval, the agency is requiring a postmarketing trial to investigate whether a lower dose will have a similar clinical effect.

The most common side effects of Lumakras include diarrhea, musculoskeletal pain, nausea, fatigue, liver damage and cough. Lumakras should be withheld if patients develop symptoms of interstitial lung disease and permanently discontinued if interstitial lung disease is confirmed. Health care professionals should monitor a patient's liver function tests prior to starting and when taking Lumakras. If a patient develops liver damage, Lumakras should be withheld, dose reduced or permanently discontinued. Patients should avoid taking acid-reducing agents, drugs that induce or are substrates for certain enzymes in the liver and drugs that are substrates of the P-glycoprotein while taking Lumakras.

Lumakras 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 Lumakras.

The FDA granted this application Fast Track, Priority Review and Breakthrough Therapy designations.

Lumakras also received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases.

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 (TGA), the Brazilian Health Regulatory Agency (ANVISA), Health Canada and Medicines and Healthcare products Regulatory Agency (MHRA; United Kingdom). The application reviews are ongoing at the other regulatory agencies.

The FDA granted approval of Lumakras to Amgen Inc.

Along with Lumakras, the FDA also approved the QIAGEN therascreen KRAS RGQ PCR kit (approval granted to QIAGEN GmbH) and the Guardant360 CDx (approval granted to Guardant Health, Inc.) as companion diagnostics for Lumakras today. The QIAGEN GmbH test analyzes tumor tissue and the Guardant Health, Inc. test analyzes plasma specimens to determine if Lumakras is an appropriate treatment for patients. If no mutation is

detected in a plasma specimen, the patient's tumor should be tested.

FDA News released May 28, 2021. www.fda.gov.

FDA Grants Accelerated Approval for Alzheimer's Drug

Today, the U.S. Food and Drug Administration approved Aduhelm (aducanumab) for the treatment of Alzheimer's, a debilitating disease affecting 6.2 million Americans. Aduhelm was approved using the accelerated approval pathway, which can be used for a drug for a serious or life-threatening illness that provides a meaningful therapeutic advantage over existing treatments. Accelerated approval can be based on the drug's effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients, with a required post-approval trial to verify that the drug provides the expected clinical benefit.

"Alzheimer's disease is a devastating illness that can have a profound impact on the lives of people diagnosed with the disease as well as their loved ones," said Patrizia Cavazzoni, M.D., director of the FDA's Center for Drug Evaluation and Research. "Currently available therapies only treat symptoms of the disease; this treatment option is the first therapy to target and affect the underlying disease process of Alzheimer's. As we have learned from the fight against cancer, the accelerated approval pathway can bring therapies to patients faster while spurring more research and innovation."

Alzheimer's is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills, and eventually, the ability to carry out simple tasks. While the specific causes of Alzheimer's disease are not fully known, it is characterized by changes in the brain—including amyloid plaques and neurofibrillary, or tau, tangles—that result in loss of neurons and their connections. These changes affect a person's ability to remember and think.

Aduhelm represents a first-of-its-kind treatment approved for Alzheimer's disease. It is the first new treatment approved for Alzheimer's since 2003 and is the first therapy that targets the fundamental pathophysiology of the disease.

Researchers evaluated Aduhelm's efficacy in three separate studies representing a total of 3,482 patients. The studies consisted of double-blind, randomized, placebo-controlled dose-ranging studies in patients with Alzheimer's disease. Patients receiving the treatment had significant dose-and time-dependent reduction of amyloid beta plaque, while patients in the control arm of the studies had no reduction of amyloid beta plaque.

These results support the accelerated approval of Aduhelm, which is based on the surrogate endpoint of reduction of amyloid beta plaque in the brain—a hallmark of Alzheimer's disease. Amyloid beta plaque was quantified using positron emission tomography (PET) imaging to estimate the brain levels of amyloid beta plaque in a composite of brain regions expected to be widely affected by Alzheimer's disease pathology compared to a brain region expected to be spared of such pathology.

The prescribing information for Aduhelm includes a warning for amyloid-related imaging abnormalities (ARIA), which most commonly presents as temporary swelling in areas of the brain that usually resolves over time and does not cause symptoms, though some people may have symptoms such as headache, confusion, dizziness, vision changes, or nausea. Another warning for Aduhelm is for a risk of hypersensitivity reactions, including angioedema and urticaria. The most common side effects of Aduhelm were ARIA, headache, fall, diarrhea, and confusion/delirium/altered mental status/disorientation.

Under the accelerated approval provisions, which provide patients suffering from the disease earlier access to the treatment, the FDA is requiring the company, Biogen, to conduct a new randomized, controlled clinical trial to verify the drug's clinical benefit. If the trial fails to verify clinical benefit, the FDA may initiate proceedings to withdraw approval of the drug.

Aduhelm was granted Fast Track designation, which seeks to expedite the development and review of drugs that are intended to treat serious conditions where initial evidence showed the potential to address an unmet medical need.

Aduhelm is made by Biogen of Cambridge, Massachusetts.

FDA News released June 07, 2021. www.fda.gov.

FDA Approves New Drug Treatment for Chronic Weight Management, First Since 2014

Today, the U.S. Food and Drug Administration approved Wegovy (semaglutide) injection (2.4 mg once weekly) for chronic weight management in

adults with obesity or overweight with at least one weight-related condition (such as high blood pressure, type 2 diabetes, or high cholesterol), for use in addition to a reduced calorie diet and increased physical activity. This under-the-skin injection is the first approved drug for chronic weight management in adults with general obesity or overweight since 2014. The drug is indicated for chronic weight management in patients with a body mass index (BMI) of 27 kg/m2 or greater who have at least one weight-related ailment or in patients with a BMI of 30 kg/m2 or greater.

"Today's approval offers adults with obesity or overweight a beneficial new treatment option to incorporate into a weight management program," said John Sharretts, M.D., deputy director of the Division of Diabetes, Lipid Disorders, and Obesity in the FDA's Center for Drug Evaluation and Research. "FDA remains committed to facilitating the development and approval of additional safe and effective therapies for adults with obesity or overweight."

Approximately 70% of American adults have obesity or overweight. Having obesity or overweight is a serious health issue associated with some leading causes of death, including heart disease, stroke and diabetes, and is linked to an increased risk of certain types of cancer. Losing 5% to 10% of body weight through diet and exercise has been associated with a reduced risk of cardiovascular disease in adult patients with obesity or overweight.

Wegovy works by mimicking a hormone called glucagon-like peptide-1 (GLP-1) that targets areas of the brain that regulate appetite and food intake. The medication dose must be increased gradually over 16 to 20 weeks to 2.4 mg once weekly to reduce gastrointestinal side effects.

Wegovy should not be used in combination with other semaglutide-containing products, other GLP-1 receptor agonists, or other products intended for weight loss, including prescription drugs, over-the-counter drugs, or herbal products. Wegovy has not been studied in patients with a history of pancreatitis.

Wegovy's safety and efficacy were studied in four 68-week trials. Three were randomized, double-blind, placebo-controlled trials (including 16 weeks of dose increases) and one was a double-blind, placebo-controlled, randomized withdrawal trial in which patients receiving Wegovy either continued with the treatment or switched to a placebo. More than 2,600 patients received Wegovy for up to 68 weeks in these four studies and more than 1,500 patients received placebo.

The largest placebo-controlled trial enrolled adults without diabetes. The average age at the start of the trial was 46 years and 74% of patients were female. The average body weight was 231 pounds (105 kg) and average BMI was 38 kg/m2. Individuals who received Wegovy lost an average of 12.4% of their initial body weight compared to individuals who received placebo. Another trial enrolled adults with type 2 diabetes. The average age was 55 years and 51% were female. The average body weight was 220 pounds (100 kg) and average BMI was 36 kg/m2. In this trial, individuals who received Wegovy lost 6.2% of their initial body weight compared to those who received placebo.

The most common side effects of Wegovy include nausea, diarrhea, vomiting, constipation, abdominal (stomach) pain, headache, fatigue, dyspepsia (indigestion), dizziness, abdominal distension, eructation (belching), hypoglycemia (low blood sugar) in patients with type 2 diabetes, flatulence (gas buildup), gastroenteritis (an intestinal infection) and gastroesophageal reflux disease (a type of digestive disorder).

The prescribing information for Wegovy contains a boxed warning to inform healthcare professionals and patients about the potential risk of thyroid C-cell tumors. Wegovy should not be used in patients with a personal or family history of medullary thyroid carcinoma or in patients with a rare condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Wegovy should not be used in patients with a history of severe allergic reactions to semaglutide or any of the other components of Wegovy. Patients should stop Wegovy immediately and seek medical help if a severe allergic reaction is suspected. Wegovy also contains warnings for inflammation of the pancreas (pancreatitis), gallbladder problems (including gallstones), low blood sugar, acute kidney injury, diabetic retinopathy (damage to the eye's retina), increased heart rate and suicidal behavior or thinking. Patients should discuss with their healthcare professional if they have symptoms of pancreatitis or gallstones. If Wegovy is used with insulin or a substance that causes insulin secretion, patients should speak to their health care provider about potentially lowering the dose of insulin or the insulin-inducing drug to reduce the risk of low blood sugar. Healthcare providers should monitor patients with kidney disease, diabetic retinopathy and depression or suicidal behaviors or thoughts.

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Source: FDA