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FDA Approves the first targeted therapy to treat a rare mutation in patients with gastrointestinal stromal tumors

Today, the U.S. Food and Drug Administration approved Ayvakit (avapritinib) for the treatment of adults with unresectable (unable to be removed with surgery) or metastatic (when cancer cells spread to other parts of the body) gastrointestinal stromal tumor (GIST) – a type of tumor that occurs in the gastrointestinal tract, most commonly in the stomach or small intestine – harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation. This approval includes GIST that harbors a PDGFRA D842V mutation, which is the most common exon 18 mutation. Ayvakit is a kinase inhibitor, meaning it blocks a type of enzyme called a kinase and helps keeps the cancer cells from growing.

"GIST harboring a PDGFRA exon 18 mutation do not respond to standard therapies for GIST. However, today's approval provides patients with the first drug specifically approved for GIST harboring this 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. "Clinical trials showed a high response rate with almost 85% of patients experiencing tumor shrinkage with this targeted drug."

GISTs arise from specialized nerve cells found in the walls of the gastrointestinal tract. One or more mutations in the DNA of one of these cells may lead to the development of GIST. These cells aid in the movement of food through the intestines and control various digestive processes. More than half of GISTs start in the stomach. Most of the others start in the small intestine, but GISTs can start anywhere along the gastrointestinal tract. The activating mutations in PDGFRA have been linked to the development of GISTs, and up to approximately 10% of GIST cases involve mutations of this gene.

The FDA approved Ayvakit based on the results of a clinical trial involving 43 patients with GIST harboring a PDGFRA exon 18 mutation, including 38 patients with PDGFRA D842V mutation. Patients received Ayvakit 300 mg or 400 mg orally once daily until disease progression or they experienced unacceptable toxicity. The recommended dose was determined to be 300 mg once daily. The trial measured how many patients experienced complete or partial shrinkage (by a certain amount) of their tumors during treatment (overall response rate). For patients harboring a PDGFRA exon 18 mutation, the overall response rate was 84%, with 7% having a complete response and 77% having a partial response. For the subgroup of patients with PDGFRA D842V mutations, the overall response rate was 89%, with 8% having a complete response and 82% having a partial response. While the median duration of response was not reached, 61% of the responding patients with exon 18 mutations had a response lasting six months or longer (31% of patients with an ongoing response were followed for less than six months).

Common side effects for patients taking Ayvakit were edema (swelling), nausea, fatigue/asthenia (abnormal physical weakness or lack of energy), cognitive impairment, vomiting, decreased appetite, diarrhea, hair color changes, increased lacrimation (secretion of tears), abdominal pain, constipation, rash and dizziness. Ayvakit can cause intracranial hemorrhage (bleeding that occurs inside the skull) in which case the dose should be reduced, or the drug should be discontinued. Ayvakit can also cause central nervous system effects including cognitive impairment, dizziness, sleep disorders, mood disorders, speech disorders and hallucinations. If this happens, depending on the severity, Ayvakit should be withheld and then resumed at the same or reduced dose upon improvement or permanently discontinued.

Health care professionals should advise pregnant women that Ayvakit may cause harm to a developing fetus or newborn baby. Additionally, the FDA advises health care professionals to tell females of reproductive potential, and males with female partners of reproductive potential, to use effective contraception during treatment with Ayvakit and for six weeks after the final dose.

The FDA granted this application Breakthrough Therapy designation, which expedites the development and review of drugs that are intended to treat a serious condition, when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies. Ayvakit was also granted Fast Track designation, which expedites the review of drugs to treat serious conditions and fill an unmet medical need. Ayvakit received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases.

The FDA granted approval of Ayvakit to Blueprint Medicines Corporation.

FDA News released Jan 9, 2020. www.fda.gov.

FDA Approves Three Drugs for Nonprescription Use Through Rx-to-OTC Switch Process

The U.S. Food and Drug Administration today approved three drugs for nonprescription, or over-the-counter (OTC), use through a process called a prescription (Rx)-to-OTC switch. The FDA approved Voltaren Arthritis Pain (diclofenac sodium topical gel, 1%) for the temporary relief of arthritis pain; Pataday Twice Daily Relief (olopatadine HCl ophthalmic solution/drops, 0.1%) for the temporary relief of itchy and red eyes due to pollen, ragweed, grass, animal hair or dander; and Pataday Once Daily Relief (olopatadine HCl ophthalmic solution/drops, 0.2%) for the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair or dander, for nonprescription use.

"As a result of the Rx-to-OTC switch process, many products sold over-the-counter today use ingredients or dosage strengths that were available only by prescription 30 years ago," said Karen Mahoney, M.D., acting deputy director of the Office of Nonprescription Drugs in the FDA's Center for Drug Evaluation and Research. "Approval of a wider range of nonprescription drugs has the potential to improve public health by increasing the types of drugs consumers can access and use that would otherwise only be available by prescription. This includes providing the millions of people that suffer with joint pain from arthritis daily over-the-counter access to another non-opioid treatment option."

The process of changing the status of a drug from prescription to nonprescription is called an Rx-to-OTC switch. It is usually initiated by the manufacturer of the prescription drug. For a drug to switch to nonprescription status, the data provided must demonstrate that the drug is safe and effective for use in self-medication as directed in proposed labeling. The manufacturer must show that consumers can understand how to use the drug safely and effectively without the supervision of a healthcare professional.

Voltaren Arthritis Pain is a nonsteroidal anti-inflammatory drug (NSAID) and works by reducing substances in the body that cause pain and inflammation. This product, previously referred to as Voltaren Gel 1%, was first approved by the FDA in 2007 as a prescription drug and was indicated for the relief of the pain of osteoarthritis of joints responsive to topical treatment, in particular, the joints of the hands, knees and feet. It has not been shown to work for strains, sprains, bruises or sports injuries.

Voltaren Arthritis Pain is intended for the temporary relief of joint pain due to the most common type of arthritis, osteoarthritis, which increases with age, affects millions of people in the U.S., and can generally be self-diagnosed. Arthritis is the swelling and tenderness of one or more of your joints. Symptoms of arthritis include pain, swelling, stiffness, and difficulty moving a joint.

Voltaren Arthritis Pain is not for immediate relief and may take up to 7 days to work. Consumers should stop use and seek medical attention if their arthritis pain is not improved in 7 days or they need to use the product for more than 21 days. The active ingredient in Voltaren Arthritis Pain, diclofenac, may cause a severe allergic reaction, especially in people allergic to aspirin. If an allergic reaction occurs, consumers are advised to stop use and seek medical care immediately. Liver damage may occur if this product is used more or longer than directed or when using other products containing diclofenac. This product contains an NSAID, which may cause severe stomach bleeding. NSAIDS, except aspirin, increase the risk of heart attack, heart failure and stroke. These can be fatal. The risk is higher if consumers use more than directed or for longer than directed. If pregnant or breastfeeding, consumers should talk to a health care professional about use. This product should not be used during the last 3 months of pregnancy unless the consumer is definitely directed to do so by a doctor because diclofenac may cause problems in the unborn child or complications during the delivery.

Pataday Twice Daily Relief was first approved by the FDA in 1996 under the name Patanol as a prescription drug and was indicated for the treatment of the signs and symptoms of allergic conjunctivitis (referring to ocular redness and itching due to allergies). Pataday – now Pataday Once Daily Relief – was first approved by the FDA in 2004 as a prescription drug and was indicated for the treatment of ocular itching associated with allergic conjunctivitis. These drugs are mast cell stabilizers, which work by preventing the release of histamine and therefore prevent or control allergic disorders. Ocular itching caused by allergens is a common ailment in the U.S., affecting millions of people. Consumers are advised to stop use and talk to their health care professional if they experience eye pain,

changes in vision, increased redness of the eye, worsening of itching or itching lasting for more than 72 hours.

All three products will be marketed in the U.S. as nonprescription drugs and will no longer be available as prescription drugs. Consumers should read and follow the Drug Facts labels for the nonprescription products. Patients who currently take prescription versions of these products and have questions about the Rx-to-OTC switch should talk to their health care professional.

The FDA granted the approval of nonprescription Voltaren Arthritis Pain to GlaxoSmithKline plc. The FDA granted the approvals of nonprescription Pataday Twice Daily Relief and Pataday Once Daily Relief to Alcon.

FDA News released Feb 14, 2020. www.fda.gov.

FDA Approves New Therapy for Triple Negative Breast Cancer That Has Spread, Not Responded to Other Treatments

Today, the U.S. Food and Drug Administration granted accelerated approval to Trodelvy (sacituzumab govitecan-hziy) for the treatment of adult patients with triple-negative breast cancer that has spread to other parts of the body. Patients must have received at least two prior therapies before taking Trodelvy.

"Metastatic triple-negative breast cancer is an aggressive form of breast cancer with limited treatment options. Chemotherapy has been the mainstay of treatment for triple-negative breast cancer. The approval of Trodelvy today represents a new targeted therapy for patients living with this aggressive malignancy," 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. "There is intense interest in finding new medications to help treat metastatic triple-negative breast cancer. Today's approval provides patients who've already tried two prior therapies with a new option."

Trodelvy is a Trop-2-directed antibody and topoisomerase inhibitor drug conjugate, meaning that the drug targets the Trop-2 receptor that helps the cancer grow, divide and spread, and is linked to topoisomerase inhibitor, which is a chemical compound that is toxic to cancer cells. Approximately two of every 10 breast cancer diagnoses worldwide are triple-negative. Triple-negative breast cancer is a type of breast cancer that tests negative for estrogen receptors, progesterone receptors and human epidermal growth factor receptor 2 (HER2) protein. Therefore, triple-negative breast cancer does not respond to hormonal therapy medicines or medicines that target HER2.

"As part of FDA's ongoing and aggressive commitment to address the novel coronavirus pandemic, we continue to keep a strong focus on patients with cancer who constitute a vulnerable population at risk of contracting the disease," said Pazdur. "At this critical time, we continue to expedite oncology product development. This application was approved more than a month ahead of the FDA goal date – an example of that commitment. Our staff is continuing to meet with drug developers, academic investigators, and patient advocates to push forward the coordinated review of treatments for cancer."

The FDA approved Trodelvy based on the results of a clinical trial of 108 patients with metastatic triple-negative breast cancer who had received at least two prior treatments for metastatic disease. The efficacy of Trodelvy was based on the overall response rate (ORR) – which reflects the percentage of patients that had a certain amount of tumor shrinkage. The ORR was 33.3%, with a median duration of response of 7.7 months. Of the patients with a response to Trodelvy, 55.6% maintained their response for 6 or more months and 16.7% maintained their response for 12 or more months.

The prescribing information for Trodelvy includes a Boxed Warning to advise health care professionals and patients about the risk of severe neutropenia (abnormally low levels of white blood cells) and severe diarrhea. Health care professionals should monitor patient's blood cell counts periodically during treatment with Trodelvy and consider treatment with a type of therapy called granulocyte-colony stimulating factor (G-CSF), which stimulates the bone marrow to produce white blood cells called granulocytes and stem cells and releases them into the bloodstream, to help prevent infection, and should initiate anti-infective treatment in patients with febrile neutropenia (development of fever when white blood cell are abnormally low).

Additionally, health care professionals should monitor patients with diarrhea and give fluid, electrolytes, and supportive care medications, as needed. Trodelvy may need to be withheld, dose reduced or permanently discontinued for neutropenia

or diarrhea. Trodelvy can cause hypersensitivy reactions including severe anaphylactic (allergic) reactions. Patients should be monitored for infusion-related reactions and health care professionals should discontinue Trodelvy if severe or life-threatening reactions occur. If patients experience nausea or vomiting while taking Trodelvy, health care professionals should use antiemetic preventive treatment, to prevent nausea and vomitting. Patients with reduced uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) activity are at increased risk for neutropenia following initiation of Trodelvy treatment.

The most common side effects for patients taking Trodelvy were nausea, neutropenia, diarrhea, fatigue, anemia, vomiting, alopecia (hair loss), constipation, decreased appetite, rash and abdominal pain.

Women who are pregnant should not take Trodelvy because it may cause harm to a developing fetus or newborn baby. The FDA advises health care professionals to inform females of reproductive age to use effective contraception during treatment with Trodelvy and for 6 months after the last dose. Male patients with female partners of reproductive potential should also use effective contraception during treatment with Trodelvy and for three months after the last dose.

Trodelvy was granted accelerated approval, which enables the FDA to approve drugs for serious conditions to fill an unmet medical need based on a result that is reasonably likely to predict a clinical benefit to patients. Further clinical trials are required to verify and describe Trodelvy's clinical benefit.

The FDA granted this application Priority Review and Breakthrough Therapy designation, which expedites the development and review of drugs that are intended to treat a serious condition when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies. Trodelvy was also granted Fast Track designation, which expedites the review of drugs to treat serious conditions and fill an unmet medical need.

The FDA granted approval of Trodelvy to Immunomedics, Inc.

FDA News released April 22, 2020. www.fda.gov.

Source: FDA