Molecular and Cellular Pharmacology
www.mcpharmacol.com

FDA Approval Brings First Gene Therapy to the United States

CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia

This release was updated on Aug. 30, 2017 to correctly identify the FDA designations granted to Kymriah.

The U.S. Food and Drug Administration issued a historic action today making the first gene therapy available in the United States, ushering in a new approach to the treatment of cancer and other serious and life-threatening diseases.

The FDA approved Kymriah (tisagenlecleucel) for certain pediatric and young adult patients with a form of acute lymphoblastic leukemia (ALL).

"We're entering a new frontier in medical innovation with the ability to reprogram a patient's own cells to attack a deadly cancer," said FDA Commissioner Scott Gottlieb, M.D. "New technologies such as gene and cell therapies hold out the potential to transform medicine and create an inflection point in our ability to treat and even cure many intractable illnesses. At the FDA, we're committed to helping expedite the development and review of groundbreaking treatments that have the potential to be life-saving."

Kymriah, a cell-based gene therapy, is approved in the United States for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.

Kymriah is a genetically-modified autologous T-cell immunotherapy. Each dose of Kymriah is a customized treatment created using an individual patient's own T-cells, a type of white blood cell known as a lymphocyte. The patient's T-cells are collected and sent to a manufacturing center where they are genetically modified to include a new gene that contains a specific protein (a chimeric antigen receptor or CAR) that directs the T-cells to target and kill leukemia cells that have a specific antigen (CD19) on the surface. Once the cells are modified, they are infused back into the patient to kill the cancer cells.

ALL is a cancer of the bone marrow and blood, in which the body makes abnormal lymphocytes. The disease progresses quickly and is the most common childhood cancer in the U.S. The National Cancer Institute estimates that approximately 3,100 patients aged 20 and younger are diagnosed with ALL each year. ALL can be of either T- or B-cell origin, with B-cell the most common. Kymriah is approved for use in pediatric and young adult patients with B-cell ALL and is intended for patients whose cancer has not responded to or has returned after initial treatment, which occurs in an estimated 15-20 percent of patients.

"Kymriah is a first-of-its-kind treatment approach that fills an important unmet need for children and young adults with this serious disease," said Peter Marks, M.D., Ph.D., director of the FDA's Center for Biologics Evaluation and Research (CBER). "Not only does Kymriah provide these patients with a new treatment option where very limited options existed, but a treatment option that has shown promising remission and survival rates in clinical trials."

The safety and efficacy of Kymriah were demonstrated in one multicenter clinical trial of 63 pediatric and young adult patients with relapsed or refractory B-cell precursor ALL. The overall remission rate within three months of treatment was 83 percent.

Treatment with Kymriah has the potential to cause severe side effects. It carries a boxed warning for cytokine release syndrome (CRS), which is a systemic response to the activation and proliferation of CAR T-cells causing high fever and flu-like symptoms, and for neurological events. Both CRS and neurological events can be life-threatening. Other severe side effects of Kymriah include serious infections, low blood pressure (hypotension), acute kidney injury, fever, and decreased oxygen (hypoxia). Most symptoms appear within one to 22 days following infusion of Kymriah. Since the CD19 antigen is also present on normal B-cells, and Kymriah will also destroy those normal B cells that produce antibodies, there may be an increased risk of infections for a prolonged period of time.

The FDA today also expanded the approval of Actemra (tocilizumab) to treat CAR T-cell-induced severe or life-threatening CRS in patients 2 years of age or older. In clinical trials in patients treated with CAR-T cells, 69 percent of patients had complete resolution of CRS within two weeks following one or two doses of Actemra.

Because of the risk of CRS and neurological events, Kymriah is being approved with a risk evaluation and mitigation strategy (REMS), which includes elements to assure safe use (ETASU). The

FDA is requiring that hospitals and their associated clinics that dispense Kymriah be specially certified.

As part of that certification, staff involved in the prescribing, dispensing, or administering of Kymriah are required to be trained to recognize and manage CRS and neurological events. Additionally, the certified health care settings are required to have protocols in place to ensure that Kymriah is only given to patients after verifying that tocilizumab is available for immediate administration. The REMS program specifies that patients be informed of the signs and symptoms of CRS and neurological toxicities following infusion – and of the importance of promptly returning to the treatment site if they develop fever or other adverse reactions after receiving treatment with Kymriah.

To further evaluate the long-term safety, Novartis is also required to conduct a post-marketing observational study involving patients treated with Kymriah.

The FDA granted Kymriah Priority Review and Breakthrough Therapy designations. The Kymriah application was reviewed using a coordinated, cross-agency approach. The clinical review was coordinated by the FDA's Oncology Center of Excellence, while CBER conducted all other aspects of review and made the final product approval determination.

The FDA granted approval of Kymriah to Novartis Pharmaceuticals Corp. The FDA granted the expanded approval of Actemra to Genentech Inc.

FDA News released Aug 30, 2017. www.fda.gov.

FDA Approves First Continuous Glucose Monitoring System for Adults Not Requiring Blood Sample Calibration

The U.S. Food and Drug Administration today approved the FreeStyle Libre Flash Glucose Monitoring System, the first continuous glucose monitoring system that can be used by adult patients to make diabetes treatment decisions without calibration using a blood sample from the fingertip (often referred to as a "fingerstick").

The system reduces the need for fingerstick testing by using a small sensor wire inserted below the skin's surface that continuously measures and monitors glucose levels. Users can determine glucose levels by waving a dedicated, mobile reader above the sensor wire to determine if glucose levels are too high (hyperglycemia) or too low (hypoglycemia), and how glucose levels are changing. It is intended for use in people 18 years of age and older with diabetes; after a 12-hour start-up period, it can be worn for up to 10 days.

"The FDA is always interested in new technologies that can help make the care of people living with chronic conditions, such as diabetes, easier and more manageable," said Donald St. Pierre, acting director of the Office of In Vitro Diagnostics and Radiological Health and deputy director of new product evaluation in the FDA's Center for Devices and Radiological Health. "This system allows people with diabetes to avoid the additional step of fingerstick calibration, which can sometimes be painful, but still provides necessary information for treating their diabetes—with a wave of the mobile reader."

People with diabetes must regularly test and monitor their blood sugar to make sure it is at an appropriate level, which is often done multiple times per day by taking a fingerstick sample and testing it with a blood glucose meter. Typically patients use results of a traditional fingerstick test to make diabetes treatment decisions; however, fingerstick testing is not needed to inform appropriate care choices or to calibrate glucose levels with this system.

According to the Centers for Disease Control and Prevention, more than 29 million people in the U.S. have diabetes. People with diabetes either do not make enough insulin (type 1 diabetes) or cannot use insulin properly (type 2 diabetes). When the body doesn't have enough insulin or cannot use it effectively, sugar builds up in the blood. High blood sugar levels can lead to heart disease; stroke; blindness; kidney failure; and amputation of toes, feet or legs.

The FDA evaluated data from a clinical study of individuals aged 18 and older with diabetes, and reviewed the device's performance by comparing readings obtained by the FreeStyle Libre Glucose Monitoring System to those obtained by an established laboratory method used for analysis of blood glucose.

Risks associated with use of the system may include hypoglycemia or hyperglycemia in cases where information provided by the device is inaccurate and used to make treatment decisions, as well as mild skin irritations around the insertion site. It does not provide real-time alerts or alarms in the absence of a user-initiated action; for example, it

cannot alert users to low blood glucose levels while they are asleep.

The FreeStyle Libre Flash Glucose Monitoring System is manufactured by Abbott Diabetes Care Inc.

FDA News released Sep 27, 2017. www.fda.gov.

FDA Approves CAR-T Cell Therapy to Treat Adults With Certain Types of Large B-cell Lymphoma

Yescarta is the second gene therapy product approved in the U.S.

The U.S. Food and Drug Administration today approved Yescarta (axicabtagene ciloleucel), a cell-based gene therapy, to treat adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment. Yescarta, a chimeric antigen receptor (CAR) T cell therapy, is the second gene therapy approved by the FDA and the first for certain types of non-Hodgkin lymphoma (NHL).

"Today marks another milestone in the development of a whole new scientific paradigm for the treatment of serious diseases. In just several decades, gene therapy has gone from being a promising concept to a practical solution to deadly and largely untreatable forms of cancer," said FDA Commissioner Scott Gottlieb, M.D. "This approval demonstrates the continued momentum of this promising new area of medicine and we're committed to supporting and helping expedite the development of these products. We will soon release a comprehensive policy to address how we plan to support the development of cell-based regenerative medicine. That policy will also clarify how we will apply our expedited programs to breakthrough products that use CAR-T cells and other gene therapies. We remain committed to supporting the efficient development of safe and effective treatments that leverage these new scientific platforms."

Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL in adults. NHLs are cancers that begin in certain cells of the immune system and can be either fast-growing (aggressive) or slow-growing. Approximately 72,000 new cases of NHL are diagnosed in the U.S. each year, and DLBCL represents approximately one in three newly diagnosed cases. Yescarta is approved for use in adult patients with large B-cell lymphoma after at least two other kinds of treatment failed, including DLBCL, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma. Yescarta is not indicated for the treatment of patients with primary central nervous system lymphoma.

Each dose of Yescarta is a customized treatment created using a patient's own immune system to help fight the lymphoma. The patient's T-cells, a type of white blood cell, are collected and genetically modified to include a new gene that targets and kills the lymphoma cells. Once the cells are modified, they are infused back into the patient.

"The approval of Yescarta brings this innovative class of CAR-T cell therapies to an additional group of cancer patients with few other options – those adults with certain types of lymphoma that have not responded to previous treatments," said Peter Marks, M.D., Ph.D., director of the FDA's Center for Biologics Evaluation and Research (CBER).

The safety and efficacy of Yescarta were established in a multicenter clinical trial of more than 100 adults with refractory or relapsed large B-cell lymphoma. The complete remission rate after treatment with Yescarta was 51 percent.

Treatment with Yescarta has the potential to cause severe side effects. It carries a boxed warning for cytokine release syndrome (CRS), which is a systemic response to the activation and proliferation of CAR-T cells causing high fever and flu-like symptoms, and for neurologic toxicities. Both CRS and neurologic toxicities can be fatal or life-threatening. Other side effects include serious infections, low blood cell counts and a weakened immune system. Side effects from treatment with Yescarta usually appear within the first one to two weeks, but some side effects may occur later.

Because of the risk of CRS and neurologic toxicities, Yescarta is being approved with a risk evaluation and mitigation strategy (REMS), which includes elements to assure safe use (ETASU). The FDA is requiring that hospitals and their associated clinics that dispense Yescarta be specially certified. As part of that certification, staff involved in the prescribing, dispensing or administering of Yescarta are required to be trained to recognize and manage CRS and nervous system toxicities. Also, patients must be informed of the potential serious side effects and of the importance of promptly returning to the treatment site if side effects develop.

To further evaluate the long-term safety, the FDA is also requiring the manufacturer to conduct a post-marketing observational study involving patients treated with Yescarta.

The FDA granted Yescarta Priority Review and Breakthrough Therapy designations. Yescarta also received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases. The Yescarta application was reviewed using a coordinated, cross-agency approach. The clinical review was conducted by the FDA's Oncology Center of Excellence, while CBER conducted all other aspects of review and made the final product approval determination.

The FDA granted approval of Yescarta to Kite Pharma, Inc.

FDA News released Oct 18, 2017. www.fda.gov.

FDA Approves First Once-Monthly Buprenorphine Injection, a Medication-assisted Treatment Option for Opioid Use Disorder

Agency encourages safe adoption and more widespread use of FDA-approved treatments to help combat opioid addiction

The U.S. Food and Drug Administration today approved Sublocade, the first once-monthly injectable buprenorphine product for the treatment of moderate-to-severe opioid use disorder (OUD) in adult patients who have initiated treatment with a transmucosal (absorbed through mucus membrane) buprenorphine-containing product. It is indicated for patients that have been on a stable dose of buprenorphine treatment for a minimum of seven days.

Buprenorphine for the treatment of OUD is currently approved to administer as a tablet or film that dissolves in the mouth, or as an implant. Sublocade provides a new treatment option for patients in recovery who may value the benefits of a once-monthly injection compared to other forms of buprenorphine, such as reducing the burden of taking medication daily as prescribed (medical adherence). An independent FDA advisory committee supported the approval of Sublocade at a meeting held last month.

"Given the scale of the opioid crisis, with millions of Americans already affected, the FDA is committed to expanding access to treatments that can help people pursue lives of sobriety. Everyone who seeks treatment for opioid use disorder deserves the opportunity to be offered the treatment best suited to the needs of each individual patient, in combination with counseling and psychosocial support, as part of a comprehensive recovery plan," said FDA Commissioner Scott Gottlieb, M.D. "As part of our ongoing work in supporting the treatment of those suffering from addiction to opioids, the FDA plans to issue guidance to expedite the development of new addiction treatment options. We'll continue to pursue efforts to promote more widespread use of existing, safe and effective FDA-approved therapies to treat addiction."

Improving access to prevention, treatment and recovery services, including the full range of medication-assisted treatments (MAT), is a focus of the FDA's ongoing work to reduce the scope of the opioid crisis and one part of the U.S. Department of Health and Human Services' Five-Point Strategy to Combat the Opioid Crisis.

OUD is the diagnostic term used for a chronic neurobiological disease characterized by a problematic pattern of opioid use leading to significant impairment or distress and includes signs and symptoms that reflect compulsive, prolonged self-administration of opioid substances for no legitimate medical purpose or, if another medical condition is present that requires opioid treatment, the opioid is used in doses far greater than the amount needed for treatment of that medical condition.

MAT is a comprehensive approach that combines approved medications (currently, methadone, buprenorphine or naltrexone) with counseling and other behavioral therapies to treat patients with OUD. Regular adherence to MAT with buprenorphine reduces opioid withdrawal symptoms and the desire to use opioids, without causing the cycle of highs and lows associated with opioid misuse or abuse. At proper doses, buprenorphine also decreases the pleasurable effects of other opioids, making continued opioid abuse less attractive. According to the Substance Abuse and Mental Health Services Administration, patients receiving MAT for their OUD cut their risk of death from all causes in half.

Sublocade should be used as part of a complete treatment program that includes counseling and psychosocial support. Sublocade is a drug-device combination product that utilizes buprenorphine and the Atrigel Delivery System in a pre-filled syringe. It is injected by a health care professional (HCP) under the skin (subcutaneously) as a solution, and the delivery system forms a solid deposit, or depot, containing buprenorphine. After initial formation of the depot, buprenorphine is released by the breakdown (biodegradation) of the depot. In clinical trials, Sublocade provided sustained therapeutic plasma levels of buprenorphine over the one-month dosing interval.

The safety and efficacy of Sublocade were evaluated in two clinical studies (one randomized controlled clinical trial and one open-label clinical trial) of 848 adults with a diagnosis of moderate-to-severe OUD who began treatment with buprenorphine/naloxone sublingual film (absorbed under the tongue). Once the dose was determined stable, patients were given Sublocade by injection. A response to MAT was measured by urine drug screening and self-reporting of illicit opioid use during the six-month treatment period. Results indicated that Sublocade-treated patients had more weeks without positive urine tests or self-reports of opioid use, and a higher proportion of patients had no evidence of illicit opioid use throughout the treatment period, compared to the placebo group.

The most common side effects from treatment with Sublocade include constipation, nausea, vomiting, headache, drowsiness, injection site pain, itching (pruritus) at the injection site and abnormal liver function tests. The safety and efficacy of Sublocade have not been established in children or adolescents less than 17 years of age. Clinical studies of Sublocade did not include participants over the age of 65.

The FDA is requiring postmarketing studies to assess which patients would benefit from a higher dosing regimen, to determine whether Sublocade can be safely initiated without a dose stabilization period of sublingual buprenorphine, to assess the feasibility of administering Sublocade at a longer inter-dose interval than once-monthly and to determine a process for transitioning patients with long-term stability on a transmucosal buprenorphine dose to a monthly dose of Sublocade without the use of a higher dose for the first two months of treatment (loading dose).

Sublocade has a boxed warning that provides important safety information, including the risks of intravenous self-administration. If the product were to be administered intravenously rather than subcutaneously, the solid mass could cause occlusion (blockage), tissue damage or embolus (solid material that is carried in the blood and can become lodged in a blood vessel, which can lead to death). Sublocade must be prescribed and dispensed as part of a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the product is not distributed directly to patients. Sublocade will be provided to HCPs through a restricted program, administered only by HCPs in a health care setting, and will require health care settings and pharmacies that dispense Sublocade to complete an enrollment form attesting that they have procedures in place to ensure that Sublocade is dispensed only to HCPs and not directly to patients.

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

The FDA granted the approval of Sublocade to Indivior Inc.

FDA News released Nov 30, 2017. www.fda.gov.

Source: FDA