Albiglutide (Tanzeum)

**Manufacturer:** GlaxoSmithKline, Wilmington, Delaware

**Date of Approval:** April 15, 2014

**Indication:** Albiglutide is indicated for subcutaneous once-weekly injection to improve glycemic control, along with diet and exercise, in adults with type-2 diabetes mellitus.

**Biological Class:** Albiglutide is a dipeptidyl peptidase-4 (DPP4)-resistant glucagon-like peptide-1 (GLP-1) dimer fused to human albumin. It is a GLP-1 agonist that helps to enhance the body’s natural insulin production in patients with type-2 diabetes.

**Uniqueness of Biological:** Albiglutide (an important incretin hormone) is a macromolecule made of two copies of a 30 amino acid sequence of DPP4-resistant human GLP-1, fused to recombinant human albumin. The tandem structure increases potency compared with having only one GLP-1 molecule bound to albumin, and the average plasma half-life is five to eight days.

**GLP-1** helps reduce blood glucose levels in people with type-2 diabetes, but, in people with the disease, its production is often reduced or absent. Once-weekly administration of albiglutide could improve patients’ hemoglobin A1c concentrations both when used as a monotherapy and in tandem with other anti-diabetes drugs. GLP-1 drugs (Byetta, Victoza) are currently only available for subcutaneous administration on a daily basis, so a GLP-1 drug with a longer half-life is highly desirable.

**Boxed Warning:** Thyroid C-cell tumors have been observed in rodent studies with GLP-1 receptor agonists at clinically relevant exposures. It is unknown whether albiglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans. Albiglutide is contraindicated in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2).

**Warnings and Precautions:**

**Pancreatitis.** Discontinue promptly if pancreatitis is suspected and do not restart if confirmed. Consider other anti-diabetic therapies in patients with a history of pancreatitis.

**Hypoglycemia.** When albiglutide is used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin, hypoglycemia may occur. Consider lowering sulfonylurea or insulin dosage when starting albiglutide.

**Hypersensitivity reactions.** Discontinue albiglutide if such reactions are suspected. Monitor and treat promptly per standard of care until signs and symptoms resolve.

**Renal impairment.** Monitor renal function in patients with renal impairment who report severe adverse gastrointestinal reactions.

**Macrovascular outcomes.** There have been no clinical trials establishing conclusive evidence of macrovascular risk reduction with albiglutide or any other anti-diabetic drug.

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Dosage and Administration: Albiglutide is administered once weekly using an injector pen supplied with a 5-mm, 29-gauge thin-walled needle.

**Commentary:** Diabetes is a global epidemic affecting 382 million individuals, including more than 22 million in the U.S. Up to 90% of these patients have type-2 diabetes. Type-2 diabetes is a lifelong, progressive, and, in some cases, preventable condition characterized by hyperglycemia. A lack of physical activity, obesity, increasing age, high blood pressure, and genetics are known risk factors that can contribute to the development of type-2 diabetes. Treatment options include lifestyle changes, such as increased physical activity and diet improvements, but, as the condition progresses, patients may require the addition of oral or injectable medications to control blood sugar levels and, ultimately, the use of insulin, either daily or with meals.

Albiglutide belongs to the same class of injectable GLP-1 drugs as liraglutide (Victoza, Novo Nordisk), exenatide (Byetta, AstraZeneca/Bristol-Myers Squibb), and exenatide extended release (Bydureon, AstraZeneca). Albiglutide is not recommended as first-line therapy for patients inadequately controlled on diet and exercise.


Ramucirumab (Cyramza)

**Manufacturer:** Eli Lilly, Indianapolis, Indiana

**Date of Approval:** April 21, 2014

**Indication:** Ramucirumab is indicated for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression on or after fluoropyrimidine- or platinum-containing chemotherapy.

**Drug Class:** Ramucirumab is a fully human monoclonal antibody (IgG1) developed for the treatment of solid tumors.

**Uniqueness of Drug:** Ramucirumab is directed against the vascular endothelial growth factor receptor 2 (VEGFR2). Binding to VEGFR2 receptors, ramucirumab works as a receptor antagonist, blocking the binding of vascular endothelial growth factor (VEGF) to VEGFR2. VEGFR2 is known to mediate the majority of the downstream effects of VEGF in angiogenesis. Thus, ramucirumab is an angiogenesis inhibitor that blocks the blood supply to tumors. Ramucirumab was developed by ImClone Systems Inc. and was isolated from the native phage display technology library derived from the Dyax Corporation.

**Boxed Warning:** Ramucirumab increases the risk of hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue ramucirumab in patients who experience severe bleeding.

**Warnings and Precautions:**

**Hemorrhage.** Ramucirumab increases the risk of hemorrhage, including severe and sometimes fatal hemorrhagic events. The risk of gastric hemorrhage in ramucirumab-treated patients with gastric tumors receiving nonsteroidal anti-inflammatory drugs is unknown. Permanently discontinue ramucirumab in patients who experience severe bleeding.
**Arterial thromboembolic events.** Serious, sometimes fatal arterial thromboembolic events (ATEs), including myocardial infarctions, cardiac arrests, cerebrovascular accidents, and cerebral ischemia, occurred in clinical trials, affecting 1.7% of 236 patients who received ramucirumab as a single agent for gastric cancer. Permanently discontinue ramucirumab in patients who experience a severe ATE.

**Hypertension.** An increased incidence of severe hypertension occurred in patients receiving ramucirumab as a single agent (8%) compared with placebo (3%). Control hypertension prior to initiating treatment with ramucirumab. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Temporarily suspend ramucirumab for severe hypertension until it is medically controlled. Permanently discontinue ramucirumab if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crises or hypertensive encephalopathy.

**Infusion-related reactions (IRRs).** Prior to the institution of premedication recommendations across clinical trials of ramucirumab, IRRs occurred in six out of 37 patients (16%), including two severe events. The majority of IRRs across trials occurred during or following a first or second ramucirumab infusion. Symptoms of IRRs included rigors, tremors, back pain and/or spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Monitor patients during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Immediately and permanently discontinue ramucirumab for grade 3 or 4 IRRs.

**Gastrointestinal perforations.** Ramucirumab is an antiangiogenic therapy that can increase the risk of gastrointestinal perforation, a potentially fatal event. Four of 570 patients (0.7%) who received ramucirumab as a single agent in clinical trials experienced gastrointestinal perforation. Permanently discontinue ramucirumab in patients who experience a gastrointestinal perforation.

**Impaired wound healing.** Ramucirumab has not been studied in patients with serious or nonhealing wounds. Ramucirumab is an antiangiogenic therapy with the potential to adversely affect wound healing. Withhold ramucirumab prior to surgery. Resume ramucirumab following the surgical intervention based on clinical judgment of adequate wound healing. If a patient develops wound-healing complications during therapy, discontinue ramucirumab until the wound is fully healed.

**Clinical deterioration in Child-Pugh B or C cirrhosis.** Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepaticorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single-agent ramucirumab. Use ramucirumab in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.

**Reversible posterior leukoencephalopathy syndrome (RPLS).** RPLS has been reported at a rate of more than 0.1% in clinical studies with ramucirumab. Confirm the diagnosis of RPLS with magnetic resonance imaging and discontinue ramucirumab in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurological sequelae or death.

**Dosage and Administration:** The recommended ramucirumab dose and schedule is 8 mg/kg administered as a 60-minute intravenous infusion every two weeks.

**Commentary:** Results in a clinical trial of 355 stomach cancer patients showed those treated with ramucirumab experienced a median overall survival of 5.2 months, compared with 3.8 months in participants receiving placebo. Additionally, participants who took ramucirumab experienced a delay in tumor growth (progression-free survival) compared with participants who were given placebo. Results from a second clinical trial that evaluated the efficacy of ramucirumab plus paclitaxel (a mitotic inhibitor) versus paclitaxel alone also showed an improvement in overall survival.

Stomach cancer forms in the tissues lining the stomach and mostly affects older adults. According to the National Cancer Institute, an estimated 22,220 Americans will be diagnosed with stomach cancer and 10,990 will die from the disease this year. Although the U.S. rates of stomach cancer have decreased over the past 40 years, patients require new treatment options, particularly when they no longer respond to other therapies. Ramucirumab is a new option that in clinical trials has demonstrated an ability to extend patients’ lives and slow tumor growth.

Currently, most chemotherapy treatments are based on the combination of at least two drugs, fluorouracil and cisplatin (Platinol, Bristol-Myers Squibb). Newer drugs similar to fluorouracil, such as capecitabine (Xeloda, Genentech), and similar to cisplatin, such as oxaliplatin (Eloxatin, Sanofi-Aventis), appear to work equally well. Other drugs commonly used include docetaxel (Docetrex, Sun Pharma Global), paclitaxel (Taxol, HQ Specialty Pharma), irinotecan (Camptosar, Pfizer), and epirubicin (Ellence, Pfizer).

Sources: Cyramza prescribing information, www.drugs.com

**Ceritinib (Zykadia)**

**Manufacturer:** Novartis Pharmaceuticals, East Hanover, New Jersey

**Date of Approval:** April 29, 2014

**Indication:** For the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non–small-cell lung cancer (NSCLC) with disease progression on or intolerance to crizotinib.

**Drug Class:** Ceritinib is an ALK tyrosine kinase inhibitor that blocks proteins that promote the development of cancerous cells. It is intended for patients with metastatic ALK-positive NSCLC who were previously treated with crizotinib, the only other approved ALK tyrosine kinase inhibitor.

**Uniqueness of Drug:** Ceritinib is a targeted drug that works by blocking proteins that help cancer cells grow. It specifically targets cells with mutations in the ALK gene. Only a small percentage of NSCLC patients test positive for the ALK gene mutation.

**Warnings and Precautions:**

**Severe or persistent gastrointestinal toxicity.** Dose reduction due to diarrhea, nausea, vomiting, or abdominal pain occurred in 38% of patients. Withhold the drug if patients are not responsive to antiemetics or anti diarrheals, then reduce the dose of ceritinib.

continued on page 520
Pharmaceutical Approval Update

continued from page 482

Hepatotoxicity. Since ceritinib can cause hepatotoxicity, monitor liver laboratory testing at least monthly. Withhold the drug, then reduce the dose or permanently discontinue ceritinib.

Interstitial lung disease (ILD)/pneumonitis. This occurred in 4% of patients. Permanently discontinue ceritinib in patients diagnosed with treatment-related ILD/pneumonitis.

QT interval prolongation. Ceritinib can cause QTc interval prolongation. Monitor electrocardiograms and electrolytes in patients with congestive heart failure, bradyarrhythmias, or electrolyte abnormalities or patients taking medications that are known to prolong the QTc interval. Withhold the drug, reduce the dose, or permanently discontinue ceritinib as necessary.

Hyperglycemia. Ceritinib can produce hyperglycemia. Monitor glucose and initiate or optimize antihyperglycemic medications as indicated. Withhold the drug, then reduce the dose or permanently discontinue ceritinib.

Bradycardia. Ceritinib can elicit bradycardia. Monitor heart rate and blood pressure regularly. If bradycardia occurs, withhold the drug, then reduce the dose or permanently discontinue ceritinib.

Embryofetal toxicity. Ceritinib may evoke fetal harm. Advise females who could become pregnant of the potential risk to a fetus.

Dosage and Administration: The recommended dose of ceritinib is 750 mg orally (five 150-mg capsules) once daily on an empty stomach until disease progression or unacceptable toxicity occurs. Approximately 60% of patients initiating treatment at the recommended dose required at least one dose reduction.

Commentary: Lung cancer is the leading cause of cancer deaths worldwide. The most common type of lung cancer is NSCLC, accounting for 85% to 90% of all cases. Of those, 2% to 7% are driven by a rearrangement of the ALK gene, which increases the growth of cancer cells and can be identified by a molecular test of the cancer tumor. Despite significant treatment advances for patients with ALK-positive NSCLC, disease progression is often inevitable, and more options are needed.

Ceritinib was approved under the FDA’s accelerated approval program for drugs that show promise against a serious disease. Ceritinib works by blocking proteins that help cancer cells grow, specifically targeting cells with mutations in the ALK gene. Ceritinib is intended for people with ALK-positive NSCLC that metastasized after they were treated with crizotinib, the only other FDA-approved drug that targets cells with a mutated ALK gene.

The FDA based its decision on a clinical trial of 163 people with metastatic ALK-positive NSCLC, all of whom were treated with ceritinib. Tumors shrank in about half the patients, and the improvement lasted on average for about seven months. Additional clinical information must be submitted to the FDA to confirm ceritinib’s benefit.

The wholesale acquisition cost for a one-month supply of ceritinib (750 mg/day) is around $13,500. Novartis has a number of programs to help defray some of the cost.

Sources: Reuters, www.novartis.com