Olaratumab (Lartruvo)

Manufacturer: Eli Lilly and Company, Indianapolis, Indiana
Date of Approval: October 19, 2016

Indication: Olaratumab, a platelet-derived growth factor receptor-alpha (PDGFR-α)-blocking antibody, is indicated in combination with doxorubicin for the treatment of adult patients with soft tissue sarcoma (STS) that is not amenable to curative treatment with radiotherapy or surgery and that has a histological subtype for which an anthracycline-containing regimen is appropriate.

Drug Class: PDGFR-α antagonist

Uniqueness of Drug: Olaratumab was approved by the Food and Drug Administration (FDA) under its accelerated program in combination with doxorubicin as a first-line therapy for patients with STS. Continued approval for this indication will be contingent upon verification and description of clinical benefit in the confirmatory phase 3 study, ANNOUNCE.

Warnings and Precautions:

Infusion-related reactions. Infusion-related reactions (IRRs) occurred in 70 of 485 patients (14%) who received at least one dose of olaratumab across clinical trials. For 68 of those 70 patients (97%), the first occurrence of an IRR was in the first or second cycle. Grade 3 or higher IRRs occurred in 11 of 485 patients (2.3%), with one fatality (0.2%). IRRs caused permanent discontinuation of olaratumab in 2.3% of patients, and interruption of infusion occurred in 10% of patients. All 59 patients with grade 1 or 2 IRRs resumed olaratumab; 12 of these patients (20%) had a grade 1 or 2 IRR with rechallenge. The incidence of IRRs in the overall safety database (N = 485) was similar (18% versus 12%) between those who did (56%) and those who did not (44%) receive premedication. The symptoms of IRR included flushing, shortness of breath, bronchospasm, or fever/chills. In severe IRR cases, symptoms manifested as hypotension, anaphylactic shock, or cardiac arrest. Monitor patients during and following the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. Discontinue olaratumab for grade 3 or 4 IRRs.

Embryo-fetal toxicity. Based on animal data and its mechanism of action, olaratumab can cause fetal harm when administered to a pregnant woman. Advise women of the potential risk to the fetus and to use effective contraception during treatment with olaratumab and for three months after the last dose.

In patients who experience grade 1 or 2 IRRs, interrupt the olaratumab infusion. After resolution, resume the infusion at 50% of the initial rate. In patients with neutropenic fever/infection or grade 4 neutropenia lasting longer than one week, discontinue administration of olaratumab until the absolute neutrophil count recovers to 1,000/mcL or greater and then permanently reduce the dose to 12 mg/kg.

Commentary: The FDA approval of olaratumab is based on the results of a phase 2 study that showed a significant improvement in patient survival with a combination of doxorubicin plus olaratumab compared with doxorubicin alone (a median gain of 11.8 months). The most common adverse reactions of olaratumab plus doxorubicin in 20% or more of patients were nausea, fatigue, musculoskeletal pain, mucositis, alopecia, vomiting, diarrhea, decreased appetite, abdominal pain, neuropathy, and headache. The most common laboratory abnormalities occurring in 20% or more of patients were lymphopenia, neutropenia, thrombocytopenia, hyperglycemia, elevated activated partial thromboplastin time, hypokalemia, and hypophosphatemia.

Sources: Eli Lilly and Company, Lartruvo prescribing information

Bezlotoxumab (Ziplima)

Manufacturer: Merck and Co., Inc., Whitehouse Station, New Jersey
Date of Approval: October 18, 2016

Indication: Bezlotoxumab, a human monoclonal antibody that binds to Clostridium difficile toxin B, is indicated to reduce recurrence of C. difficile infection (CDI) in patients 18 years of age or older who are receiving antibacterial drug treatment for CDI and are at a high risk for CDI recurrence. It is not indicated for the treatment of CDI and should only be used in conjunction with antibacterial drug treatment of CDI.

Drug Class: Monoclonal antibody

Uniqueness of Drug: The Centers for Disease Control and Prevention estimated that CDI caused almost 500,000 illnesses and 29,000 deaths within one month of initial diagnosis in 2011. CDI recurs in roughly 20% of people who have had the infection. Bezlotoxumab is specifically indicated for adults who are taking an antibiotic for CDI and are at risk of becoming infected again. Not an antibiotic itself, bezlotoxumab binds to and neutralizes toxin B, one of several toxins produced by C. difficile and the one considered central to the life-threatening virulence of the bacteria.

Warnings and Precautions:

Heart failure. Heart failure was reported more commonly in the two phase 3 clinical trials in bezlotoxumab-treated patients compared with placebo-treated patients. These adverse reactions occurred primarily in patients with underlying congestive heart failure (CHF). In patients with a history of CHF, 15 of 118 bezlotoxumab-treated patients (12.7%) and five of 104 placebo-treated patients (4.8%) had the serious adverse reaction of heart failure during the 12-week study period.

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tion, there were more deaths in bezlotoxumab-treated patients (23 of 118; 19.5%) than in placebo-treated patients (13 of 104; 12.5%) during the 12-week study period. The causes of death varied and included cardiac ischemia, infections, and respiratory failure. In patients with a history of CHF, bezlotoxumab should be reserved for use when the benefit outweighs the risk.

**Dosage and Administration:** Administer bezlotoxumab during antibacterial drug treatment for CDI. A single dose of 10 mg/kg administered as an intravenous infusion over 60 minutes is recommended. Bezlotoxumab must be diluted prior to infusion.

**Commentary:** The Food and Drug Administration approval of bezlotoxumab was based on two phase 3 trials, MODIFY I and II. MODIFY I enrolled 1,452 patients (median age, 65 years) in 19 countries, and the MODIFY II study enrolled 1,203 patients (median age, 67 years) in 17 countries. The studies were conducted in both hospital and outpatient settings, and the primary outcome measure in each trial was the number of participants who had CDI recurrence in the 12 weeks following bezlotoxumab administration. CDI recurrence was defined as the development of a new episode of diarrhea (three or more loose stools in 24 or fewer hours) and a positive lab stool test for toxigenic *C. difficile* after clinical cure of the initial episode. Nausea, fatigue, fever, and headache were among the most common adverse events experienced on the day of infusion or within four weeks of infusion. Heart failure emerged as a serious adverse reaction 12 weeks after infusion.

**Sources:** Merck and Co., Inc., Zinplava prescribing information

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**Doxylamine Succinate/Pyridoxine Hydrochloride (Bonjesta)**

**Manufacturer:** Duchesnay USA, Inc., Bryn Mawr, Pennsylvania

**Date of Approval:** November 14, 2016

**Indication:** Bonjesta is a fixed-dose combination of doxylamine succinate and pyridoxine hydrochloride indicated for the treatment of nausea and vomiting during pregnancy in women who do not respond to conservative management. Each extended-release tablet contains 20 mg of doxylamine succinate, an antihistamine, and 20 mg of pyridoxine hydrochloride, a vitamin B6 analogue.

**Drug Class:** Antiemetic agent

**Uniqueness of Drug:** The combination of doxylamine succinate and pyridoxine hydrochloride has been the subject of many epidemiologic studies designed to detect possible teratogenicity. No increased risk for congenital malformations has been reported based on these studies.

**Warnings and Precautions:**

**Sommolence.** This medication may cause somnolence due to the anticholinergic properties of doxylamine succinate, an antihistamine. Women should avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using this medication until cleared to do so by their health care provider. Doxylamine succinate and pyridoxine hydrochloride use is not recommended if a woman is concurrently using central nervous system depressants, including alcohol. The combination may result in severe drowsiness leading to falls or accidents.

**Concomitant medical conditions.** This medication has anticholinergic properties and therefore should be used with caution in women with asthma, increased intracranial pressure, narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, or urinary bladder-neck obstruction.

**Dosage and Administration:** The initial recommended dose is one extended-release tablet orally at bedtime (day 1). If this dose adequately controls symptoms, the patient should continue taking one tablet daily at bedtime on the next day. However, if symptoms persist on day 2, the daily dose may be increased to one tablet in the morning and one tablet at bedtime. The maximum recommended dose is two tablets per day, one in the morning and one at bedtime. The medication should be taken on an empty stomach with a glass of water, and should be swallowed whole. The tablets should not be crushed, chewed, or split.

**Commentary:** There have been no efficacy and safety trials conducted with Bonjesta. A double-blind, randomized, multicenter, placebo-controlled study was conducted to support the safety and efficacy of 10-mg doxylamine succinate and 10-mg pyridoxine hydrochloride tablets (a different formulation and dosage strength) in the treatment of nausea and vomiting during pregnancy. Women 18 years of age or older at seven to 14 weeks gestation (median, nine weeks) with nausea and vomiting were randomized to 14 days of 10-mg doxylamine succinate and 10-mg pyridoxine hydrochloride tablets or placebo. The primary efficacy endpoint was the change from baseline at day 15 in the Pregnancy Unique-Quantification of Emesis (PUQE) score. The PUQE score incorporates the number of daily vomiting episodes, number of daily heaves, and length of daily nausea in hours for an overall score of symptoms rated from 3 (no symptoms) to 15 (most severe). At baseline, the mean PUQE score was 9.0 in the 10-mg doxylamine succinate and 10-mg pyridoxine hydrochloride tablets arm and 8.8 in the placebo arm. There was a 0.7-point mean decrease in nausea and vomiting symptoms from baseline in PUQE score at day 15 with 10-mg doxylamine succinate and 10-mg pyridoxine hydrochloride tablets compared with placebo.

**Sources:** Duchesnay USA, Inc., Bonjesta prescribing information