

Pharmaceutical Approval Update

Michele B. Kaufman, PharmD, BCGP, RPh

L-Glutamine Oral Powder (Endari)

Manufacturer: Emmaus Medical, Inc., Torrance, California

Date of Approval: July 7, 2017

Indication: L-glutamine oral powder is indicated for patients 5 years of age and older to reduce the acute complications of sickle cell disease.

Drug Class: Amino acid; antioxidant

Uniqueness of Drug: Sickle cell disease is an inherited blood disorder that affects approximately 100,000 people in the U.S., most often in African-Americans, Latinos, and other minority groups, according to data from the National Institutes of Health. This is the first treatment approved for patients with sickle cell disease in almost 20 years.

Warnings and Precautions:

Contraindications. There are no known contraindications to the use of L-glutamine oral powder; however, certain populations have yet to be studied.

Special populations. The safety and effectiveness of this treatment have not been established in pregnant or lactating women, or in patients younger than 5 years of age or older than 65 years of age. Although limited trial data and clinical experience have not identified differences in responses between elderly and younger patients, dose selection for elderly patients should be cautious. Patients older than 65 years of age should be initiated at the lower end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapies.

Adverse events. The most common adverse events that occur with the use of L-glutamine oral powder include abdominal pain, constipation, cough, extremity pain, back pain, chest pain, headache, and nausea.

Dosage and Administration: The recommended dose of L-glutamine oral powder is 5–15 g orally, twice daily, based on body weight as outlined in the prescribing information. Each dose should be mixed in 240 mL of cold or room-temperature beverage or in 4–6 oz. of food immediately before consuming.

Commentary: The efficacy and safety of L-glutamine oral powder were studied in a randomized trial of patients 5–58 years of age with sickle cell disease who had two or more painful crises within the 12 months prior to enrollment in the trial. Patients were randomly assigned to treatment with L-glutamine oral powder or placebo for 48 weeks. Patients treated with L-glutamine oral powder experienced fewer hospital visits for pain treated with a parenterally administered narcotic or ketorolac; fewer hospitalizations for sickle cell pain; and fewer days in the hospital (median, 6.5 days versus 11 days) compared with placebo-treated patients. These patients also had a lower incidence of acute

chest syndrome, a life-threatening complication of sickle cell disease, compared with placebo-treated patients (8.6% versus 23.1%).

Sources: Emmaus Medical, Inc., Endari prescribing information



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Edaravone (Radicava)

Manufacturer: MT Pharma America, Inc., Jersey City, New Jersey

Date of Approval: May 5, 2017

Indication: Edaravone is indicated for the treatment of amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease.

Drug Class: Substituted 2-pyrazolin-5-one

Uniqueness of Drug: ALS is a rare disease that attacks and kills voluntary muscle nerve cells responsible for initiating essential movements such as chewing, walking, breathing, and talking. The nerves lose their capacity to activate specific muscles, which causes the muscles to become weak, eventually leading to paralysis. ALS is a progressive disorder that affects approximately 12,000–15,000 Americans. Most patients with ALS succumb to respiratory failure, which occurs within three to five years of the appearance of the first ALS symptoms. Edaravone is only the second drug approved in the U.S. to treat patients with ALS, and the first in more than 20 years. The Food and Drug Administration previously granted this application an orphan drug designation.

Warnings and Precautions:

Hypersensitivity reactions. Redness, wheals, and erythema multiforme, and cases of anaphylaxis (e.g., urticaria, decreased blood pressure, and dyspnea) have been reported in spontaneous post-marketing reports of edaravone. Patients should be monitored carefully for these reactions. If they occur, the drug should be discontinued until the reaction resolves.

Sulfite allergic reactions. Edaravone contains sodium bisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible people.

Renal or hepatic impairment. The effect of edaravone in patients with renal or hepatic impairment has not been studied. However, renal impairment is not expected to significantly affect exposure to the drug, and the manufacturer recommends no specific dose adjustments for these patients. While there is no recommended dosage for patients with severe hepatic impairment, those with mild or moderate hepatic impairment do not require dose adjustment.

Geriatric patients. In edaravone clinical trials, 53 patients were 65 years of age and older, two of whom were at least 75 years old. No overall differences in effectiveness or safety were observed in these patients compared with younger patients; however, some older individuals may exhibit greater sensitivity.

Dosage and Administration: The recommended dosage of edaravone is 60 mg administered as an intravenous infusion over 60 minutes in an initial treatment cycle of daily dosing for

Michele B. Kaufman, PharmD, BCGP, RPh, is a freelance medical writer living in New York City and a Pharmacist in the NewYork-Presbyterian Lower Manhattan Hospital Pharmacy Department.

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14 days followed by a 14-day drug-free period. In subsequent treatment cycles, patients receive daily dosing for 10 days of a 14-day period, followed by a 14-day drug-free period.

Commentary: The efficacy of edaravone was shown in a six-month, randomized, placebo-controlled, double-blind clinical trial of ALS in Japan. Participants (N = 137) were randomized to receive edaravone or placebo. The primary efficacy endpoint was measured with the ALS Functional Rating Scale–Revised (ALSFRS–R) total score from baseline to week 24. The ALSFRS–R scale consists of 12 questions that evaluate the fine-motor, gross-motor, bulbar, and respiratory function of patients with ALS, including actions such as speech, swallowing, and walking. At week 24, the edaravone-treated patients experienced less decline on a clinical assessment of daily functioning compared with the placebo-treated patients. The most common adverse reactions were bruising and gait disturbances.

Sources: MT Pharma America, Inc., Radicava prescribing information

Midostaurin (Rydapt)

Manufacturer: Novartis Pharmaceuticals Corp., East Hanover, New Jersey

Date of Approval: April 28, 2017

Indication: Midostaurin is indicated for the treatment of adults with newly diagnosed acute myeloid leukemia (AML) that is *FLT3* mutation-positive (as detected by the Invivoscribe LeukoStrat CDx *FLT3* mutation assay), in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation. It was also approved to treat aggressive systemic mastocytosis, systemic mastocytosis with associated hematological neoplasm, and mast cell leukemia.

Drug Class: Kinase inhibitor

Uniqueness of Drug: AML, a rapidly progressing cancer, was projected by the National Cancer Institute to be diagnosed in approximately 19,930 people in 2016, and 10,430 were projected to die of the disease. Midostaurin is the first targeted therapy approved by the Food and Drug Administration to treat patients with AML in combination with chemotherapy. The LeukoStrat companion diagnostic test was simultaneously approved by the agency to detect the *FLT3* mutation.

Warnings and Precautions:

Embryo-fetal toxicity. Midostaurin may cause fetal harm when administered to a pregnant woman. Animal studies with midostaurin caused embryo-fetal toxicities, including late embryo-fetal death and reduced fetal birth weight, with delays in fetal growth at doses lower than the recommended human dose. Women should be advised of the potential risk to the fetus. The pregnancy status of women of reproductive potential should be verified within seven days prior to initiating midostaurin therapy. Advise women of reproductive potential to use effective contraception during treatment and for at least four months after the last dose. Advise men with female partners to use effective contraception during midostaurin treatment and for four months after the last dose.

Lactation. Women should be advised not to breastfeed.

Pulmonary toxicity. Cases of interstitial lung disease and pneumonitis, with some fatalities, occurred in midostaurin-treated patients, either as monotherapy or in combination with

chemotherapy. Patients should be monitored for pulmonary symptoms. Midostaurin should be discontinued in patients who experience signs or symptoms of interstitial lung disease or pneumonitis without an infectious etiology.

Geriatric patients. Of 142 patients with advanced systemic mastocytosis in midostaurin clinical studies, 64 (45%) were 65 years of age and older, and 16 (11%) were older than 75 years of age. No overall differences in safety or response rates were seen in patients older than 65 years of age compared with younger patients. However, greater sensitivity in older individuals cannot be ruled out because the AML trial of midostaurin did not include sufficient numbers of patients older than 65 years of age.

Drug interactions. Strong cytochrome P450 (CYP) 3A4 inhibitors (e.g., boceprevir [Victrelis, Schering Corp.], clarithromycin, cobicistat [Tybost, Gilead]) may increase exposure to midostaurin and its active metabolites. Strong CYP3A4 inducers (e.g., carbamazepine, rifampin, St. John's wort) decrease circulating levels of midostaurin and its active metabolites, which leads to decreased midostaurin efficacy, and should be avoided. Alternative therapies that do not strongly inhibit or induce CYP3A4 should be considered for patients receiving midostaurin therapy. Patients should be monitored for increased risk of adverse reactions. Consult the full prescribing information for a list of CYP3A4 inhibitors and inducers.

Dosage and Administration: The recommended dosage of midostaurin for AML is 50 mg orally, twice daily with food. The recommended dosage for aggressive systemic mastocytosis, systemic mastocytosis with associated hematological neoplasm, or mast cell leukemia is 100 mg orally, twice daily with food.

Commentary: The efficacy and safety of midostaurin were studied in a randomized trial in patients with AML who had not been treated previously for the disease (N = 717). Patients in the study treated with midostaurin plus chemotherapy lived longer than patients treated with chemotherapy alone, although a specific median survival rate could not be reliably estimated. In addition, patients treated with midostaurin plus chemotherapy were able to undergo treatment longer without certain complications compared with patients receiving only chemotherapy (median, 8.2 months). These complications included: failure to achieve complete remission within 60 days of starting treatment, progression of leukemia, and/or death. Common side effects in the midostaurin patients treated for AML included: device-related infection, epistaxis, febrile neutropenia, headache, hyperglycemia, mucositis, nausea, pain, petechiae, upper respiratory tract infection, and vomiting. Adverse reactions reported in 10% or more of patients with advanced systemic mastocytosis included nausea, vomiting, diarrhea, constipation, abdominal pain, edema, musculoskeletal pain, headache, arthralgia, cough, and cytopenia.

Sources: Novartis Pharmaceuticals, Inc., Rydapt prescribing information, FDA ■