Formulary Drug Review: Edaravone

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Generic Name: Edaravone

Proprietary Name: *Radicava* (Mitsubishi Tanabe Pharma America)

Approval Rating: 1S, Orphan

Therapeutic Class: Central Nervous System Agents

Similar Drugs: Riluzole (*Rilutek*)

Sound- or Look-Alike Names: *Edarbi*, *Edarbyclor*, *Radiogardase*

Indications

Edaravone is Food and Drug Administration (FDA) approved for the treatment of amyotrophic lateral sclerosis (ALS).^{1,2}

Edaravone has also been shown to be neuroprotective following acute cerebral infarction and acute diabetic stroke, and to improve locomotor function following acute stroke.³⁻¹¹ Edaravone has also reduced reperfusion injury following acute myocardial infarction.¹²⁻¹⁴

Clinical Pharmacology

The exact mechanism of action in treating ALS is unknown, but may be through reduction in oxidative stress.^{1,15} Edaravone can scavenge hydroxyl radicals and peroxynitrite radicals, which may reduce inflammatory or neurodegenerative processes.^{9,10,15}

Pharmacokinetics

Edaravone solution for intravenous (IV) infusion exhibits nonlinear pharmacokinetics.¹ After a single 60 mg dose, the steady-state area under the curve (AUC) was 11.25 mg·h/L, and the maximum plasma concentration (C_{max}) was 4.54 µg/mL, which occurred by the end of infusion.¹⁵

Edaravone is 92% bound to plasma proteins, with a volume of distribution of 20.7 L/kg.^{1,15}

Edaravone is metabolized by sulfotransferases to a sulfate conjugate and a glucuronide conjugate, both of which are pharmacologically inactive; the glucuronide conjugation involves multiple uridine diphosphate glucuronosyltransferases (UGT1A6, 1A9, 2B7, and 2B17). The mean terminal half-life of edaravone is 4.5 to 6 hours, and the half-lives of the metabolites range from 2 to 2.8 hours. Edaravone is primarily excreted in the urine (70%-90%) as the glucuronide conjugate; only 1% of the dose was recovered unchanged.¹

The pharmacokinetic parameters of edaravone are not altered by age, race (Japanese vs white), or gender. Effects of renal impairment or hepatic impairment on the pharmacokinetics of edaravone have not been studied.¹

Comparative Efficacy

Indication: *Amyotrophic Lateral Sclerosis*

Guidelines

Guideline: Practice parameter updates: The care of the patient with amyotrophic lateral sclerosis

Reference: American Academy of Neurology, 2009^{16,17}

Comments: American Academy of Neurology guidelines recommend symptom management and palliative therapies for patients with ALS.¹⁷ Riluzole, a disease-modifying medication approved for the treatment of

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ALS, offers modest benefit, but is recommended to slow disease progression in patients with ALS.¹⁶ Supportive care is recommended for management of symptoms such as sialorrhea, spasticity, cramps, pseudobulbar affect, fatigue, depression, anxiety, and insomnia. Pharmacologic options for sialorrhea include amitriptyline, botulinum toxin A, and botulinum toxin B, the latter being the preferred agent after the patient has tried anticholinergics. Pseudobulbar affect may be managed with dextromethorphan/quinidine combination therapy, but benefits must be weighed against the adverse effects of these medications. There are insufficient data to support or refute the use of medications to manage fatigue, spasticity, cramps, depression, anxiety, and insomnia.¹⁷ Respiratory therapies (noninvasive ventilation or tracheostomy invasive ventilation) and nutritional care are recommended as palliative measures.^{16,17} Edaravone is not discussed in the guidelines.

Studies

Drug: Edaravone vs Placebo

Reference: Abe K, et al, 2017^{1,18-20}

Study Design: Randomized, double-blind, placebo-controlled, parallel-group, multicenter phase 3 study trial

Study Funding: Mitsubishi Tanabe Pharma Corporation

Patients: 137 patients (20 to 75 years of age) with definite or probable ALS (per revised El Escorial criteria). Patients had Japanese ALS Severity Classification grade 1 or 2 (scale of 1 to 5, with lower scores indicating early disease), Revised ALS Functional Rating Scale (ALSFRS-R) score of at least 2 on all 12 items, forced vital capacity (FVC) of 80% or more, and disease duration of 2 years or less. Exclusion criteria included Parkinson disease, schizophrenia, dementia, renal failure, or other severe complication; hypersensitivity to edaravone; pregnancy (or plan to become pregnant) or breastfeeding; or current or recent (within 12 weeks before consent) participation in other clinical trials.

Intervention: Patients were randomized 1:1 to receive IV edaravone 60 mg or matching placebo for 24 weeks (28-day cycles). For the first cycle, patients received study medication once daily for 14 days, followed by a 14-day observation period; for subsequent cycles, study medication was administered for 10 of the 14 days, followed by a 2-week drug-free period. Riluzole was used by more than 90% of patients in both treatment groups.

Results:

Primary End Point(s):

- Least squares mean change in ALSFRS-R score from baseline to week 24: -5.01 with edaravone compared with -7.5 with placebo (intergroup difference in adjusted mean change, 2.49; 95% confidence interval [CI], 0.99 to 3.98; $P = .001$).

Comments: Patients treated with edaravone had slower progression, as measured by change in ALSFRS-R score from baseline to 24 weeks. Treatment-emergent adverse reactions were reported in 84% of both groups, and serious adverse reactions (eg, dysphagia, respiratory disorder, speech disorder) occurred in 16% of patients receiving edaravone compared with 24% in the placebo group.

Limitations: The study had a relatively small sample size and was conducted only in Japanese patients with early-stage ALS (Japanese ALS Severity Classification grade 1 or 2) who were living independently and met enrollment criteria. The 24-week study duration may not appropriately capture patient response for this disease state.¹

Reference: Abe K, et al, 2014³

Study Design: Randomized, double-blind, placebo-controlled, multicenter phase 3 study

Study Funding: Mitsubishi Tanabe Pharma Corporation

Patients: 206 patients (20 to 75 years of age) with diagnosis of definite, probable, or probable laboratory-supported ALS (per the revised Airlie House diagnostic criteria). Patients were required to have FVC of 70% or more; disease duration of 3 years or less; change in ALSFRS-R score during the 12-week preobservation period of -1 to -4 points; and Japanese ALS Severity Classification of grade 1 or 2. Patients were excluded if they had reduced respiratory function and complaints of dyspnea; comorbidities that would impact evaluation of drug efficacy, such as Parkinson disease, schizophrenia, or dementia; complications that require hospitalization, including liver, cardiac, and renal disease; creatinine clearance of 50 mL/min or less 28 days prior to treatment initiation; or were undergoing treatment for cancer. Patient demographic characteristics at baseline were well balanced between the treatment groups. The majority of the study population was male (64%) with probable (52%) or definite (24%) ALS, Japanese ALS Severity Classification grade 2 disease (63%), and ALSFRS-R change of -2 or -1 in the preobservation phase (70%). The majority of patients (89%) were taking riluzole.

Intervention: Patients were randomized 1:1 to receive either edaravone 600 mg or matching placebo (28-day cycles). For the first cycle, edaravone was administered once daily for 14 days, followed by a 14-day observation period; for subsequent cycles, patients received study medication for 10 of the 14 days. Patients received study medications for 24 weeks of the 36-week study period and were assessed during the 12-week preobservation period, before the start of the first treatment cycle, and at the end of each treatment cycle (after the 14-day observation period and before the first dosage of the next cycle).

Results:

Primary End Point(s):

- Mean change in ALSFRS-R score: -5.7 with edaravone, compared with -6.35 with placebo (intergroup difference in adjusted mean change, 0.65 ; 95% CI, -0.9 to 2.19 ; $P = .411$). Changes in the ALSFRS-R scores according to diagnostic category were as follows:
- Definite ALS ($n = 49$): -6.7 with edaravone and -8.7 with placebo (intergroup difference in adjusted mean change, 2 ; $P = .33$)
- Probable ALS ($n = 102$): -5.2 with edaravone and -6.1 with placebo (intergroup difference in adjusted mean change, 0.9 ; $P = .374$)
- Probable laboratory-supported ALS ($n = 47$): -3.6 with edaravone and -4 with placebo (intergroup difference in adjusted mean change, 0.4 ; $P = .702$)

Secondary End Point(s):

- Mean change in FVC: -14.57 with edaravone and -17.49 with placebo (intergroup difference in adjusted mean change, 2.92 ; 95% CI, -1.49 to 7.33 ; $P = .193$).
- Mean change in grip strength (left and right side): -4.81 with edaravone compared with -5.71 with placebo (intergroup difference in adjusted mean change, 0.89 ; 95% CI, -0.37 to 2.16 ; $P = .165$).
- Mean change in pinch strength (left and right side): -0.83 with edaravone and -1.03 with placebo (intergroup difference in adjusted mean change, 0.2 ; 95% CI, -0.08 to 0.48 ; $P = .165$). For the repeated measures analysis, the intergroup difference for pinch strength was 0.21 ($P = .038$).
- Mean change in Modified Norris Scale score: -14.12 with edaravone compared with -16.15 with placebo (intergroup difference in adjusted mean change, 2.03 ; 95% CI, -1.69 to 5.75 ; $P = .284$).
- Mean change in ALS Assessment Questionnaire (ALSAQ-40): 19.6 with edaravone and 19.13 with placebo (intergroup difference in adjusted mean change, 0.48 ; 95% CI, -6.44 to 7.39 ; $P = .892$).
- Proportion of patients with disease progression or death: A greater proportion of patients in the edaravone group had disease progression or death (31% in the edaravone group compared with 26% receiving placebo).

Comments: This was a multicenter study conducted in Japan, with patients enrolled in a 2-phase trial (12 weeks preobservation followed by 24 weeks of treatment). Patients were stratified by change in ALSFRS-R score during the preobservation phase (-4 , -3 or -2 , -1), initial symptom presentation (predominantly bulbar or limb involvement), and use of riluzole (yes or no). The estimated sample size was 200 (100 patients per arm) randomized 1:1 to edaravone or placebo, to achieve 85% power for a difference of 2.2 in the change in ALSFRS-R score. Changes in ALSFRS-R score were assessed at

baseline (before treatment), and then at the beginning of each treatment cycle, until 2 weeks after the last dose of medication. Efficacy analyses were performed in the full analysis set, which excluded 1 patient (diagnosed with a different disease [unspecified]). Two methods were used to handle missing data: for patients with 1 or more events, survival time was based on the onset date for the first event, and the end date of observation was used as the cutoff date for censored cases; for patients with missing data at 24 weeks after starting treatment, last observation carried forward was used to impute missing values. There was no significant difference in the change in ALSFRS-R score for patients receiving edaravone compared with placebo, but subgroup analyses showed that change in ALSFRS-R score was greater in patients with a definite diagnosis for ALS. In addition, with the exception of a slight difference in pinch strength, patients did not see benefit in terms of FVC, motor symptoms, or grip strength compared with placebo. Common adverse effects of edaravone included nasopharyngitis, gait disturbance, dysphagia, muscle weakness, contusion, insomnia, and headache.

Limitations: The study enrolled Japanese patients with probable or definite ALS and disease duration of up to 3 years. The clinical application of the data may be limited to Asian patients with early disease. In addition, the relatively short study duration may not appropriately capture patient response for this disease state.

Contraindications, Warnings, and Precautions

Contraindications

Edaravone is contraindicated in patients with hypersensitivity to the medication or to any of its excipients (L-cysteine hydrochloride hydrate, sodium bisulfate, sodium chloride, phosphoric acid, and sodium hydroxide).¹

Warnings and Precautions

Hypersensitivity reactions (redness, wheals, erythema multiforme) and anaphylaxis (urticaria, decreased blood pressure, dyspnea) are potential severe adverse events in patients taking edaravone. Patients should be monitored for signs and symptoms of hypersensitivity reactions and edaravone should be discontinued if a hypersensitivity reaction occurs.¹

Edaravone contains sodium bisulfite, a sulfite that may potentiate allergic-type (anaphylactic) reactions, especially in patients with sulfite sensitivity. Patients with asthma may be especially predisposed to sulfite sensitivity.¹

The carcinogenic potential of edaravone has not been fully assessed, and assays were negative for mutagenicity.¹

There are currently no clinical data regarding developmental risk associated with edaravone use in pregnancy.

Animal study data showed adverse developmental effects, including increased mortality, decreased growth, delayed sexual development, and altered behavior, as well as maternal toxicity, at clinically relevant doses of edaravone.¹

There are currently no data regarding the presence of edaravone or its metabolites in human breast milk or its effects on breastfeeding infants or milk production; however, the drug and its metabolites were detected in the milk of lactating rats. The developmental and health benefits of breastfeeding should be weighed against the mother's clinical need for the drug and potential for adverse effects in breastfeeding infants due to edaravone or the underlying maternal condition.¹

The safety and efficacy of edaravone in pediatric patients have not been established.¹

Adverse Reactions

In pooled clinical trials of Japanese patients with ALS (184 patients received edaravone, 184 received placebo; median age, 60 years [range, 29-75 years]), the most commonly reported adverse effects associated with edaravone and occurring at least 2% more frequently than with placebo were contusion (15% vs 9%), gait disturbance (13% vs 9%), and headache (10% vs 6%). Other adverse effects include dermatitis, eczema, respiratory failure (hypoxia), glycosuria, and tinea infections.¹

Drug Interactions

In vitro studies suggest that edaravone does not significantly inhibit cytochrome P450 enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4), UGT1A1 or 2B7, or transporters (P-glycoprotein; BCRP; OATP1B1, OATP1B3, OAT1, and OAT3; and OCT2), nor is it expected to induce CYP1A2, 2B6, or 3A4 metabolic enzymes. Edaravone is a substrate of UGT1A6, 1A9, 2B7, and 2B17.¹

Recommended Monitoring

Patients should be monitored for hypersensitivity reactions.¹

Dosing

The recommended dose of edaravone is 60 mg given by IV infusion over 60 minutes once daily using a 28-day cycle. For the initial treatment cycle, 60 mg is administered once daily for 14 days, followed by a 14-day drug-free period. For subsequent cycles, patients should receive once-daily edaravone for 10 days of the 14-day period, followed by a 14-day drug-free period.¹

The 60 mg dose should be administered as 2 consecutive 30 mg IV infusion bags over a total of 60 minutes (infusion rate approximately 1 mg/minute [3.33 mL/minute]). Discontinue the infusion if the patient exhibits signs

or symptoms of a hypersensitivity reaction. Other medications should not be injected into the infusion bag or mixed with edaravone.¹

Product Availability

Edaravone was approved on May 5, 2017.² It is available as a 30 mg per 100 mL aqueous solution for injection in a single-dose polypropylene bag.¹

The solution for injection should be stored at 25°C (77°F), with excursions permitted to between 15°C and 30°C (59°F and 86°F). The medication should be protected from light and from oxygen degradation until time of use [the oxygen indicator will turn blue or purple if the oxygen levels exceed acceptable levels; if this occurs, the product should not be used]. The medication should be used within 24 hours of opening the protective packaging.¹

Drug Safety/Risk Evaluation and Mitigation Strategy (REMS)

No REMS is required for edaravone.^{1,2}

Conclusion

Edaravone is FDA approved for the treatment of ALS based on evidence from clinical trials conducted in Japan. Patients with well-defined, advanced disease may be more likely to benefit from treatment. Common adverse effects include gait disturbance, contusion, and headache, and severe adverse effects include hypersensitivity reactions, especially in patients with sulfite allergy. Edaravone offers marginal benefit in slowing disease progression, and does not reverse disease modality.

Declaration of Conflicting Interests

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