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Edaravone for Amyotrophic Lateral Sclerosis

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Background: Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neurodegenerative disorder.[1] The incidence of ALS is comparable to multiple sclerosis with an occurrence rate of 2 in 100,000, however its prevalence is much lower since its mortality rate is much higher; median survival time is 3 to 5 years from the time of diagnosis with only 10% living ≥ 10 years.[2,3] Although the exact cause of ALS is unknown, proposed mechanisms include: abnormalities in glutamate signaling, oxidative stress, and dysfunction of mitochondria.[4] Patients with ALS may present with muscle spasms, cognitive dysfunction, and dysphagia; respiratory failure is most often the cause of death.[5] Although several medications have been used off-label for the treatment of ALS, riluzole (Rilutek®; Sanofi Aventis) was the only medication that was approved by the Food and Drug Administration (FDA) for this indication; this approval occurred in December 1995. Therefore, the approval of edaravone (Radicava®; Mitsubishi Tanabe Pharma) in May 2017, for the treatment of ALS, was considered a breakthrough.[6]

Mechanism of Action: Abnormalities in mitochondria and evidence of oxidative stress have been found in ALS patients, including elevated protein carbonyl levels and increased 3-nitrotyrosine levels.[4] Edaravone is a free radical scavenger, which may inhibit the progression of ALS by preventing oxidative damage to cell membranes.[7]

Key Clinical Trial: Edaravone's FDA approval was based on the results of a phase 3 trial in a specific subgroup of ALS patients that included those with a definite or probable ALS diagnosis, disease duration ≤2 years, Japan Severity Classification grade 1 or 2, scores of at least 2 points on all Revised ALS Functional Rating Scale (ALSFRS-R) items, and a decrease of 1-4 points in the ALSFRS-R score during the 12 week observation period.[7] The ALSFRS-R evaluates motor, respiratory, and bulbar function in patients with ALS; it consists of 12 questions, each rated from 0-4, with higher scores signifying greater functional ability.[5] This randomized, parallel group study analyzed 134 patients, 68 patients in the edaravone group and 66 in the placebo group.[7] Patients were randomized 1:1 to receive either 60 mg intravenous (IV) edaravone or IV saline placebo for six cycles, with a total treatment duration of 24 weeks. The initial treatment cycle included treatment for 14 consecutive days, followed by a 14-day drug-free period; subsequent cycles included treatment for 10 days in a 14-day period, followed by a 14-day drug-free period. The primary endpoint was change in ALSFRS-R score from baseline to 24 weeks. For the primary outcome, the change in ALSFRS-R score was –5.01 (SE 0.64) in the edaravone group and –7.50 (SE 0.66) in the placebo group. The least-squares mean difference between groups was 2.49 (SE 0.76, 95% CI 0.99–3.98; p=0.0013). The authors concluded that use of

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edaravone in the specified subpopulation of early stage ALS patients resulted in a significantly smaller decline in the ALSFRS-R score compared to placebo.

Safety: The most common adverse reactions that have occurred in ≥ 10% of patients with edaravone administration are contusion, gait disturbance, and headache.[6] Other adverse events include dermatitis, eczema, respiratory insufficiencies (e.g., failure, disorders, and hypoxia), glycosuria, and tinea infection. Allergic, anaphylactic, and asthma-type severe reactions may occur due to the presence of sodium bisulfite; specific caution should be considered in patients with a sulfite allergy, or asthma. Effects on pregnancy and lactation and use in pediatrics have not been established.

Dosing and Administration: The recommended dose of edaravone for ALS is 60 mg, given via an IV infusion over 60 minutes, once daily for 14 days, followed by a drug-free period of 14 days for the initial treatment cycle.[6] Dosing for subsequent cycles is 60 mg IV once daily for 10 days within a 14-day period, followed by a drug-free period of 14 days. There are no dosage adjustments for those with renal or hepatic impairment. Edaravone is available as a 30 mg/100 mL polypropylene infusion bag; other medications should not be mixed with this infusion. Edaravone is administered as two 30 mg infusions (60 mg total), consecutively, with an infusion rate of approximately 1 mg/minute or 3.33 mL/minute. During administration, patients should be closely monitored for hypersensitivity, which would prompt immediate discontinuation. Infusion bags should be protected from light and stored at room temperature up to 25°C (77°F); with permitted excursions to 15°C to 30°C (59°F to 86°F). Once the overwrap covering the infusion bag is removed, the bag should be used within 24 hours. Oxygen exposure indicators are provided on the infusion bags; if the oxygen indicator has turned blue or purple prior to opening the bag, it should not be used.

Cost and Availability: Each infusion bag comes in a concentration of 30 mg/100 mL with a suggested wholesale price of about $651 per 100 mL bag.[8] The cost for the initial 14-day treatment is approximately $18,000 and about $13,000 for subsequent 10-day treatments. With one treatment cycle occurring per 28 days, the annual cost would be approximately $175,000. Edaravone has limited distribution and requires various authorization and enrollment forms to be completed prior to product procurement.[9]

Formulary Status: Edaravone was added to the CCHS Formulary restricted to the Department of Neurology for the treatment of patients with ALS for outpatient use only.

References:

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Axicabtagene ciloleucel (Yescarta®)	Antineoplastic Agent	Large B-cell lymphoma	Restricted to the Department of Hematology and Medical Oncology/BMT
Dupilumab (Dupixent®)	Monoclonal Antibody	Atopic dermatitis	Restricted to Dermatology for outpatient use only in patients whose atopic dermatitis is not adequately controlled with topical prescription therapies (e.g., corticosteroids)
Durvalumab (Imfinzi®)	Antineoplastic Agent	NSCLC	Restricted to the Department of Hematology and Medical Oncology for patients with NSCLC for outpatient use only
Edaravone (Radicava®)	Free Radical Scavenger	ALS	Restricted to the Department of Neurology for the treatment of patients with ALS for outpatient use only
Gemtuzumab ozogamicin (Mylotarg®)	Antineoplastic Agent	AML	Restricted to the Department of Hematology and Medical Oncology
Meropenem-vaborbactam (Vabomere™)	Antibiotic	Treatment of documented or suspected carbapenem-resistant Enterobacteriaceae	Restricted to Infectious Diseases Physicians for the treatment of documented or suspected carbapenem-resistant Enterobacteriaceae

BMT=Bone marrow transplant NSCLC=Non-small cell lung cancer ALS=Amyotrophic lateral sclerosis AML=Acute myeloid leukemia

Product Standardizations of the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Cefoxitin	Cephalosporin (Second Generation)	Treatment of various infections	CCHS Formulary will carry cefoxitin as the second generation cephalosporin. Cefotetan will be non-formulary.
Nitrofurantoin (Macrobid™)	Antibiotic	UTI	CCHS Formulary will carry Macrobid™ as the oral nitrofurantoin product. Macrodantin™ will be non-formulary.

UTI=Urinary tract infection

Changes to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Cefazolin (Ancef®)	Antibiotic	Surgical prophylaxis	**Automatic interchange:** For cefazolin orders on pre-operative surgical prophylaxis order-sets: **For patients weighing ≥120 kg** **1 gram** and **2 grams** orders will be **converted** to **3 grams** **For patients weighing <120 kg** **1 gram** or **2 grams** orders will be **converted** to **2 grams**
Ketorolac Ophthalmic Drops (Acular®)	NSAID	Ocular pain	**Automatic interchange:** **Flurbiprofen** ophthalmic drops and **diclofenac** ophthalmic drops will be automatically **converted** to **ketorolac** ophthalmic drops as a cost-savings measure
Tocilizumab (Actemra®)	Interleukin-6 Receptor Antagonist	Severe CRS	Modify restrictions to include management of severe CRS from haploidentical transplant

NSAID=Nonsteriodal anti-inflammatory drug CRS=Cytokine release syndrome

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Abobotulinumtoxin A (Dysport™)	Neuromuscular Blocker Agent	Lower limb spasticity	Restricted to the Departments of Pediatric Neurology and Physiatry for outpatient use only in patients at least 2 years of age with lower limb spasticity
Meropenem-vaborbactam (Vabomere™)	Antibiotic	Treatment of documented or suspected carbapenem-resistant Enterobacteriaceae	Restricted to Infectious Diseases Physicians for the treatment of documented or suspected carbapenem-resistant Enterobacteriaceae
Nivolumab (Opdivo™)	Antineoplastic Agent	Recurrent or metastatic colorectal cancer with dMMR or MSI-H disease	Restricted to the Department of Pediatric Hematology/ Oncology for outpatient use only in patient at least 12 years of age with recurrent or metastic colorectal cancer with dMMR or MSI-H disease

dMMR=Mismatch repair deficient MSI-H=Microsatellite instability high

Product Standardizations of the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Cefoxitin	Cephalosporin (Second Generation)	Treatment of various infections	CCHS Formulary will carry cefoxitin as the second generation cephalosporin. Cefotetan will be non-formulary.
Nitrofurantoin (Macrodantin™)	Antibiotic	UTI	The CCHS Pediatric Formulary will NOT align with the CCHS Adult Formulary to utilize Macrobid® as the standardized product because it is not available as an oral liquid. Pediatrics will continue to use the nitrofurantoin 25 mg/5 mL oral suspension.

UTI=Urinary tract infection

Changes to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Palivizumab (Synagis®)	Monoclonal Antibody	RSV prophylaxis	Restricted for outpatient use only All requests for inpatient use require Pediatric Infectious Disease Staff Physician Approval.

RSV=Respiratory syncytial virus