CENTENE PHARMACY AND THERAPEUTICS
NEW DRUG REVIEW
3Q17 July – August

BRAND NAME
Radicava™

GENERIC NAME
edaravone

MANUFACTURER
MT Pharma America, Inc.

DATE OF APPROVAL
May 5, 2017

PRODUCT LAUNCH DATE
May 5, 2017

REVIEW TYPE

☒ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☐ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Reviews for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)
For the treatment of amyotrophic lateral sclerosis (ALS)

OFF-LABEL USES
Not applicable

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CLINICAL EFFICACY[1,2]

The efficacy of Radicava for the treatment of ALS was established in a 6-month, randomized, placebo-controlled, double-blind, parallel-group study conducted in Japanese patients with ALS who were living independently and met the following criteria at screening:

1. Functionality retained most activities of daily living (defined as scores of 2 points or better on each individual item of the ALS Functional Rating Scale – Revised or ALSFRS-R)
2. Normal respiratory function (defined as percent-predicted forced vital capacity values of [%FVC] ≥ 80%)
3. Definite or Probable ALS based on El Escorial revised criteria
4. Disease duration of 2 years or less
5. Age 20 to 75 years
6. ALS grade 1 or 2 in Japan ALS Severity Classification, indicating independent living status
7. A decrease in 1 to 4 points in the ALSFRS-R score during a 12-week observation period before randomization

The study enrolled 69 patients in the Radicava arm and 68 in the placebo arm. Baseline characteristics were similar between these groups, with over 90% of patients in each group being treated with riluzole. Radicava was administered as an intravenous infusion of 60 mg given over a 60 minute period according to the following schedule:

- An initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug-free period (Cycle 1)
- Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods (Cycles 2-6)

The primary efficacy endpoint was a comparison of the change between treatment arms in the ALSFRS-R total scores 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 (speech, salivation, swallowing, handwriting, cutting food, dressing/hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency). Each item is scored from 0-4, with higher scores representing greater functional ability. The decline in ALSFRS-R scores from baseline was significantly less in the Radicava -treated patients as compared to placebo are as follows:

Treatment	**Change from Baseline Least Squares Mean ± SE (95% CI)**	**Treatment Difference (Radicava – placebo [95% CI])**	***p*-value**
Radicava 60mg	−5.01±0.64	2.49 (0.99, 3.98)	0.0013
Placebo	−7.50±0.66		

The secondary outcomes included:

- The change in FVC
- Modified Norris Scale scores (limb, bulbar, and total)
- ALS Assessment Questionnaire (ALSAQ-40) score
- Grip and pinch strength
- Time to death or time to a specified state of disease progression (defined as disability of independent ambulation, loss of upper-limb function, tracheotomy, use of a respirator, use of tube feeding, or loss of useful speech) occurring during the 6 cycles

The results of the secondary outcomes are as follows:

	Least-squares mean change		**Least-squares mean difference (95% CI)**	**p value**
	Radicava (n)	**Placebo (n)**		
FVC (%)	–15·61, 2·41 (67)	–20·40, 2·48 (66)	4·78, 2·84 (–0·83 to 10·40)	0·0942
Modified Norris Scale scores (total)	–15·91, 1·97 (68)	–20·80, 2·06 (63)	4·89, 2·35 (0·24 to 9·54)	0·0393
Modified Norris Scale scores (Limb scale)	–11·47, 1·61	–14·91, 1·68	3·44, 1·92 (–0·36 to 7·24)	0·0757
Modified Norris Scale scores (bulbar scale)	–4·44, 0·76	–5·89, 0·79	1·46, 0·90 (–0·33 to 3·24)	0·1092
ALSAQ-40 score	17·25, 3·39 (68)	26·04, 3·53 (64)	–8·79, 4·03 (–16·76 to –0·82)	0·0309
Grip strength (kg)	–4·08, 0·54 (68)	–4·19, 0·56 (66)	0·11, 0·64 (–1·15 to 1·38)	0·8583
Pinch strength (kg	–0·78, 0·14 (68)	–0·88, 0·14 (66)	0·10, 0·16 (–0·23 to 0·42)	0·5478

Death or a specified state of disease progression occurred in two patients in the Radicava group (one tracheotomy and one loss of useful speech) and in six patients in the placebo group (three loss of useful speech, two disabilities of independent ambulation, and one use of tube feeding). The difference between groups for this secondary endpoint was not significant (log-rank test p=0·13, generalized Wilcoxon test p=0·14).

There were no reports of patients who discontinued treatment due to lack of efficacy.

CONTRAINDICATIONS

Patients with a history of hypersensitivity to edaravone or any of the inactive ingredients in Radicava

BLACK BOX WARNINGS

Not applicable

DRUG INTERACTIONS
Not applicable

ADVERSE REACTIONS
The most common adverse reactions that occurred in ≥10% of Radicava-treated patients were contusion, gait disturbance, and headache.

Adverse reactions that occurred in ≥ 2% of patients in the Radicava-treated group and that occurred at least 2% more frequently than in the placebo-treated group in randomized placebo-controlled ALS trials included:

- Dermatitis
- Eczema
- Respiratory failure/disorder, hypoxia
- Glycosuria
- Tinea infection

DOSAGE AND ADMINISTRATION
The recommended dosage is 60 mg of Radicava injection, as two consecutive 30 mg intravenous infusion bags, administered as an intravenous infusion over 60 minutes (infusion rate of approximately 1 mg per minute; 3.33 mL per minute) as follows:

- Initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period
- Subsequent treatment cycles: daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods.

PRODUCT AVAILABILITY
Single-dose polypropylene bag for injection: 30 mg/100 mL

THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
riluzole (Rilutek)	50 mg PO BID	

Boldface indicates generic availability

Utilization Management Recommendation[3,4,5]
• There is significant potential for inappropriate use and utilization management should be considered for the following reason(s): i) Opportunity exists to obtain clinically significant medical or laboratory information necessary to determine appropriate use of the medication

(1) Confirmatory phase III trial was based on strict eligibility criteria from a post-hoc analysis of the prior trial, indicating that only a subset of patients with ALS will benefit from treatment with Radicava. ii) Recommended utilization management tool(s): (check all that apply) (1) ☒ Prior authorization (2) ☐ Quantity limits (3) ☐ Provider newsletter (4) ☐ Hard block (plan exclusion) (5) ☐ Messaging (6) ☐ Electronic step therapy (7) ☐ Clinical Program
Product Comparison
• Not scored

REFERENCES

[1] Radicava [package insert]. Jersey City, NJ: MT Phrama America, Inc.; May 2016.
[2] The Writing Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomized, double-blind, placebo-controlled trial. Lancet Neurol. 2017; S1474-4422(17)30115-1
[3] Abe K, Itoyama Y, Sobue G, et al. Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2014;15(7-8), 610-617.
[4] Yoshino H and Kimura A. Investigation of the therapeutic effects of edaravone, a free radical scavenger, on amyotrophic lateral sclerosis (Phase II study). Amyotrophic Lateral Sclerosis. 2006;7(4), 247-251.
[5] Anderson PM, Borasio GD, Dengler R, et al. Good practice in the management of amyotrophic lateral sclerosis: Clinical guidelines. An evidence-based review with good practice points. EALSC Working Group. Amyotrophic Lateral Sclerosis. 2007; 8:195-231.