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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease resulting in the loss of motor neurons in the brain and spinal cord. People with ALS experience gradual muscle weakness and respiratory failure typically leading to death within 3 to 5 years of symptom onset. The functional impairment associated with the disease leads to increased need for care, often provided by a patient’s network of informal caregivers, and has a negative impact on the quality of life of both patient and caregiver. Approximately 25,000 Americans live with ALS.

There is no cure for the illness, and treatment is largely focused on symptom management, nutritional support, noninvasive ventilation support, and physical and speech therapy. Multidisciplinary care from specialized ALS clinics is the gold standard of care and is associated with improved health outcomes and quality of life. However, geographic availability, travel requirements, and insurance reimbursement remain barriers to access. Prior to 2022, riluzole and intravenous edaravone were the only 2 therapies approved by the US Food and Drug Administration (FDA) as disease-modifying treatments of ALS. There is some evidence of a small survival benefit (approximately 2 months) with riluzole. Although there is general consensus for the use of riluzole, interpretations of the evidence on intravenous edaravone are more mixed. Intravenous edaravone is not endorsed by the American Academy of Neurology or approved for use in Europe and requires burdensome infusion regimens with risks of catheter-related complications. Thus, there remains a strong unmet need for the treatment of ALS.

There are 2 new FDA-approved treatments for ALS. The FDA approved an oral formulation of edaravone (Radicava ORS, Mitsubishi Tanabe Pharma) in May 2022 based on bioequivalence with the intravenous formulation. The oral formulation presents a lower burden for patients and eliminates the risks of intravenous administration, thus most patients are expected to switch to the oral formulation, and more patients overall are expected to begin use of edaravone now that an oral formulation is available. The FDA has also now approved the drug AMX0035 (Relyvrio, Amylyx Pharmaceuticals), an oral combination therapy of sodium phenylbutyrate and taurursodiol, after 2 reviews by the FDA Peripheral and Central Nervous System Drugs Advisory Committee.

The Institute for Clinical and Economic Review (ICER) performed a systematic literature review and cost-effectiveness analysis to evaluate the health and economic outcomes of AMX0035 and oral edaravone for the treatment of ALS. Here, we present...
The effectiveness and value of AMX0035 and oral edaravone for amyotrophic lateral sclerosis: A summary from the Institute for Clinical and Economic Review’s Midwest Comparative Effectiveness Public Advisory Council

Vol. 29, No. 2 | February 2023 | JMCP.org

Summary of Findings

CLINICAL EFFECTIVENESS

We evaluated the clinical effectiveness of adding AMX0035 to standard of care (SOC) (multidisciplinary care ± riluzole ± intravenous edaravone). Separately, we evaluated the clinical effectiveness of adding edaravone to SOC (multidisciplinary care ± riluzole).

AMX0035. Our evaluation of AMX0035 was based on data from one phase 2 trial, CENTAUR (N = 137), and its open-label extension, CENTAUR-OLE (N = 90), including reviews of analyses of these trials performed by the FDA. In the modified intention-to-treat population of CENTAUR, AMX0035 slowed ALS progression on a functional scale by 25% over 24 weeks compared with placebo. AMX0035 did not affect survival during the randomized portion of the trial, but in the CENTAUR-OLE patients originally randomly assigned to AMX0035 survived a median of 4.8 months longer than those originally randomly assigned to placebo (Hazard ratio = 0.64, 95% CI = 0.42–0.995; p = 0.048).

AMX0035 had minimal serious harms. The most common side effect was transient gastrointestinal-related adverse events during the first 2 weeks, which in part led to more discontinuations because of adverse effects (19% vs 8% in the placebo arm).

Oral Edaravone. Our assessment of oral edaravone was based on evidence from the MCI-186 clinical trial program of intravenous edaravone; pharmacological studies conducted by the manufacturer led the FDA to conclude bioequivalence. There was no significant treatment benefit in the first trial of patients with ALS in the early stage (MCI-18; N = 205). A small exploratory trial of patients with later-stage ALS found a similar lack of benefit (MCI-18; N = 25). However, a post-hoc analysis of MCI-16 found a modest statistically significant slowing of disease progression in a narrower, well-defined subgroup of patients with shorter disease duration and slower rate of progression prior to random assignment. This benefit was assessed prospectively in the MCI-19 (“Study 19”) trial (N = 137), in which patients randomly assigned to edaravone in the primary modified intention-to-treat analysis had 33% slowing of disease progression. There was insufficient evidence to evaluate edaravone’s effect on survival because of zero deaths in the randomly assigned portion of Study 19. The most common adverse events associated with edaravone use were confusion, gait disturbance, and headache. Preliminary results from an open-label safety study of oral edaravone were consistent with prior intravenous studies.

UNCERTAINTIES BECAUSE OF LIMITATIONS IN THE CLINICAL EVIDENCE

AMX0035. The evidence for AMX0035 is derived from a single small phase 2 randomized controlled trial and its extension study. There was an implementation error in the randomization of the treatment, as well as a concern of functional unblinding because of the bitter taste and

| TABLE 1 Results for the Conventional Base Case for AMX0035 or Oral Edaravone Plus SOC Compared With SOC Alone, Health Care Sector Perspective |
|---|---|---|---|---|---|---|
| Treatment | Total cost, $ | QALYs | evLYs | LYs | Incremental cost-effectiveness ratios of treatment + SOC vs SOC alone, $ |
| | | | | | Cost per QALY | Cost per evLY | Cost per LY |
| AMX0035 | | | | | | |
| AMX0035 + SOCa | 569,000b | 1.03 | 1.21 | 3.01 | 2,136,000b | 952,000b | 810,000b |
| SOCa alone | 271,000 | 0.89 | 0.89 | 2.64 | — | — | — |
| Oral edaravone | | | | | | |
| Oral edaravone + SOCc | 598,000 | 0.93 | 0.94 | 2.70 | 11,981,000 | 8,186,000 | 6,975,000 |
| SOCc alone | 166,000 | 0.89 | 0.89 | 2.64 | — | — | — |

aMultidisciplinary care ± riluzole ± intravenous edaravone.
bBased on placeholder price ($169,000).
cMultidisciplinary care ± riluzole.
evLY = equal value of life-year; QALY = quality-adjusted life-year; SOC = standard of care.
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The annual net price of AMX0035 was unavailable at the time of analysis and was assumed for modeling to be equal to that of intravenous edaravone. At a placeholder price of $169,000, treatment with AMX0035 resulted in an incremental gain of 0.14 QALYs and 0.31 evLYs with an added incremental cost of $298,000 over a lifetime time horizon. At an annual cost of $171,000, oral edaravone treatment resulted in an incremental gain of 0.04 QALYs and 0.05 evLYs with an added incremental cost of $432,000 over a lifetime time horizon. The incremental cost–effectiveness ratio for AMX0035 and oral edaravone treatment surpassed all commonly used thresholds (Table 1).

ALS is a disease area with high background health costs and may result in situations in which a treatment that can slow disease progression or extend survival may not be cost-effective at any price using traditional methods. To address this, and in accordance with ICER’s Reference Case, we conducted a scenario analysis that excluded health state and SOC drug costs from the model. The incremental cost–effectiveness ratios of both interventions in this scenario analysis did not differ markedly from base-case results (Table 2). Results from the modified societal perspective scenario analysis were similarly in alignment with base-case results.

**KEY UNCERTAINTIES IN THE MODELING OF LONG-TERM COST-EFFECTIVENESS**

The treatment effect of AMX0035 and oral edaravone on disease progression and mortality risk were the key drivers of cost-effectiveness results. Thus, the limitations of the clinical evidence for AMX0035 and oral edaravone remain relevant in our discussion of cost-effectiveness. In alignment with the clinical evidence, the model assumed no benefit on survival (hazard ratio = 1) for oral edaravone.

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**TABLE 2**

Results for the Institute for Clinical and Economic Review Reference Case Scenario Analysis: Assuming $0 Health State and SOC Drug Costs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comparator</th>
<th>Cost per QALY gained, $</th>
<th>Cost per evLY gained, $</th>
<th>Cost per LY gained, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMX0035 plus SOC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>SOC&lt;sup&gt;a&lt;/sup&gt; alone</td>
<td>1,858,000&lt;sup&gt;b&lt;/sup&gt;</td>
<td>828,000&lt;sup&gt;b&lt;/sup&gt;</td>
<td>705,000&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Oral edaravone plus SOC&lt;sup&gt;c&lt;/sup&gt;</td>
<td>SOC&lt;sup&gt;c&lt;/sup&gt; alone</td>
<td>11,828,000</td>
<td>8,081,000</td>
<td>6,886,000</td>
</tr>
</tbody>
</table>

<sup>a</sup>Multidisciplinary care ± riluzole ± intravenous edaravone.

<sup>b</sup>Based on placeholder price ($169,000).

<sup>c</sup>Multidisciplinary care ± riluzole.

evLY = equal value of life-year; QALY = quality-adjusted life-year; SOC = standard of care.

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gastrointestinal side effects of AMX0035, such that 73% of the placebo arm correctly guessed treatment assignment in an exit interview. The clinical benefit of AMX0035 on slowing disease progression was not consistently substantiated by the trial’s secondary endpoint of biomarker of neuronal death. Sensitivity analyses conducted by the FDA demonstrated lower efficacy and less statistical persuasiveness on the outcomes of slowing disease progression and survival. Lastly, the survival benefit emerged only during the CENTAUR-OLE and was out of proportion to the modest decline in progression. More robust evidence from a multicenter phase 3 trial of AMX0035 (PHOENIX) is expected in 2024.

Edaravone. Despite its broad FDA label for treatment of all patients with ALS, there are generalizability and replicability concerns regarding the evidence given that the clinical benefit of edaravone was demonstrated in a single small trial of a narrow, well-defined population in Japan with ALS in the early stage that only represents 10% or less of the entire population of people living with ALS. Also, the use of intravenous edaravone was not beneficial in 2 of the 3 clinical trials among patients with more advanced ALS than those enrolled in Study 19 and was not associated with improvement in survival in a high-quality observational study.

**LONG-TERM COST-EFFECTIVENESS**

We evaluated the lifetime cost-effectiveness of adding AMX0035 or oral edaravone to their respective SOC compared with SOCs alone. A Markov model based on the King’s clinical staging system was used to represent progression of disease across 6 health states; relative risk of progression along the King’s stages and likelihood of survival were modeled using inputs derived from clinical trial data. A health care system perspective was used as the base case, and outcomes included quality-adjusted life years (QALYs) gained, LYs gained, equal value of LYs (evLYs) gained, and total lifetime costs. A scenario analysis from a modified societal perspective was also conducted to capture societal costs (eg, patient absenteeism, informal care, transportation, and home and vehicle modification costs). Informal caregiver health-related quality-of-life impacts were included in a separate scenario analysis.
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Vol. 29, No. 2 | February 2023 | JMCP.org

of medical evidence experts, including practicing clinicians, methodologists, and leaders in patient engagement and advocacy. Their deliberation includes input from clinical experts and patient representatives specific to the condition under review, as well as formal comment from manufacturers and the public. A policy roundtable concludes each meeting during which representatives from insurers and manufacturers join clinical experts and patient representatives to discuss how best to apply the findings of the evidence to clinical practice, insurance coverage, and pricing negotiations.

The ICER report on AMX0035 and oral edaravone for ALS was the subject of a Midwest CEPAC meeting on August 19, 2022. Following the discussion, the CEPAC members deliberated on key questions raised by ICER’s report. The majority of the panel (11–4) voted that the current available evidence is adequate to demonstrate that AMX0035 added to SOC provides a superior net health benefit compared with SOC alone. Similarly, a majority (13–2) voted that the evidence was adequate to demonstrate that oral edaravone added to SOC is superior to SOC alone.

### Policy Discussion

The Midwest CEPAC is one of the independent appraisal committees convened by ICER to engage in the public deliberation of the evidence on clinical and cost-effectiveness of health care interventions. The Midwest CEPAC is composed of medical evidence experts, including practicing clinicians, methodologists, and leaders in patient engagement and advocacy. Their deliberation includes input from clinical experts and patient representatives specific to the condition under review, as well as formal comment from manufacturers and the public. A policy roundtable concludes each meeting during which representatives from insurers and manufacturers join clinical experts and patient representatives to discuss how best to apply the findings of the evidence to clinical practice, insurance coverage, and pricing negotiations.

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### TABLE 3

<table>
<thead>
<tr>
<th>Contextual consideration</th>
<th>Very low priority</th>
<th>Low priority</th>
<th>Average priority</th>
<th>High priority</th>
<th>Very high priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acuity of need for treatment of individual patients based on short-term risk of death</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>or progression to permanent disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnitude of the lifetime impact on individual patients of the condition being treated</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

What are the relative effects of AMX0035 plus standard of care vs standard of care alone on the following outcomes that inform judgment of the overall long-term value for money of AMX0035?

<table>
<thead>
<tr>
<th>Potential other benefit or disadvantage</th>
<th>Major negative effect</th>
<th>Minor negative effect</th>
<th>No difference</th>
<th>Minor positive effect</th>
<th>Major positive effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients’ ability to achieve major life goals related to education, work, or family</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>life</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregivers’ quality of life and/or ability to achieve major life goals related to</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>education, work, or family life</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What are the relative effects of oral edaravone plus standard of care vs standard of care alone on the following outcomes that inform judgment of the overall long-term value for money of oral edaravone?

<table>
<thead>
<tr>
<th>Potential other benefit or disadvantage</th>
<th>Major negative effect</th>
<th>Minor negative effect</th>
<th>No difference</th>
<th>Minor positive effect</th>
<th>Major positive effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients’ ability to achieve major life goals related to education, work, or family</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>life</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregivers’ quality of life and/or ability to achieve major life goals related to</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>education, work, or family life</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients’ ability to manage and sustain treatment given the complexity of regimen</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>compared with intravenous edaravone</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

ALS = amyotrophic lateral sclerosis.
in patients with ALS that meet the narrow Study 19 criteria. However, a majority of the panel (13-2) voted that evidence was not adequate to demonstrate that treatment with oral edaravone is superior to SOC alone in the broader ALS population (patients who do not meet the Study 19 criteria).

The panel also voted on “other potential benefits” and “contextual considerations” as part of the process intended to signal to policymakers whether there are important considerations when making judgments about long-term value for money not adequately captured in analyses of clinical and/or cost-effectiveness. The results of the vote are shown in Table 3. They highlighted several factors beyond the results of cost-effectiveness modeling that the CEPAC panel felt were particularly important for judgments of overall long-term value for money.

Lastly, the panel voted on the long-term value for money of AMX0035 at its proposed placeholder price at the time of the meeting ($169,000) and oral edaravone at its current price ($171,000). A majority voted that both AMX0035 (13 of 15) and oral edaravone (14 of 15) provide low long-term value for money at those prices.

The policy roundtable discussion explored how best to translate the evidence and additional considerations into clinical practice and into pricing and insurance coverage policies. The full set of policy recommendations can be found in the Final Evidence Report on the ICER website.9

Several key policy perspectives include the following:

Recommendation 1. To expand access and reduce health inequities, all stakeholders have a responsibility to facilitate the use of telehealth to deliver high-quality multidisciplinary care from specialized ALS clinics.

Recommendation 2. Given that ALS is a relentlessly progressive and fatal disease, payers should initiate the procedures needed to create formal coverage policies for new ALS treatments well in advance of likely FDA approval dates to minimize the use of “new-to-market blocks.” Payers should consider scheduling their internal coverage criteria development in advance of FDA approval to formulate coverage policies that are operationally ready as soon as possible after market entry.

Recommendation 3. Payers should consider a benefit structure for ALS that covers necessary ancillary home health services, including assistive devices, home and vehicle modification, transportation, and caregiving.

Recommendation 4. Manufacturers should moderate launch pricing in the context of significant uncertainty that will be addressed by clinical trials that are ongoing. One specific approach to consider is to set the launch price at a far lower price close to the cost of production until the benefits of treatment can be adequately evaluated.

Recommendation 5. For conditions that are rapidly progressive and fatal, considering FDA approval of drugs on the basis of a single trial that shows benefit in clinically meaningful patient-centered outcomes is not unreasonable. However, there are known risks to approving drugs on the basis of such limited evidence, and if the FDA wishes to follow this course with AMX0035 and other drugs in similar circumstances, it should be more formal in creating a specific, well-defined pathway for conditional approval.

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REFERENCES


