April 3, 2023

David Cordani  
Chairman and Chief Executive Officer  
Cigna Corporation  
Bloomfield, CT

Dear Mr. Cordani:

Thank you again for meeting with us to discuss Cigna’s coverage criteria for Relyvrio. We strongly encourage Cigna to urgently adopt more rational utilization criteria that align with the FDA’s decision and label for Relyvrio, insurance industry standards, clinical standards, and the fundamental biology of ALS.

As we discussed, five of the eight criteria create unnecessary and discriminatory barriers to accessing Relyvrio that neither align with the FDA-approved labeling for the drug nor with other public and private U.S. insurers. These unconscionable barriers are not evidence-based and have the potential to do irreparable harm to patients’ overall quality and length of life by denying them early or complete access to an approved disease-modifying treatment.

Per Cigna’s request, we address each of the criteria for coverage created in the April 1 policy as follows:

1. **18 years of age or older.**

   We agree with this criterion. Covering treatment for people with ALS age 18 and over is consistent with the FDA label, which states: “RELYVROIO is indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults.”

2. **Documented diagnosis of definite amyotrophic lateral sclerosis (ALS) is confirmed by ALL of the following:**
   A. **ONE of the following:**
      a. *The presence of upper motor neuron (UMN) and lower motor neuron (LMN) signs in three spinal regions.*
      b. *The presence of upper motor neuron (UMN) as well as lower motor neuron (LMN) signs in the bulbar region and at least two spinal regions.*
   B. **Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination.**
   C. **Absence of electrophysiological or pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration.**
   D. **Absence of neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.**

   We disagree with these criteria for three reasons:
   - Elements A–D listed above are an attempt to mirror the inclusion criteria used to enroll patients in the CENTAUR phase 2/3 trial of Relyvrio (AMX0035). Trial inclusion criteria are deliberately focused and targeted, especially for a disease as complex and heterogeneous as ALS. These constraints seek to reduce heterogeneity in the trial population and allow trial investigators to see a robust disease trajectory during a six-month trial period and distinguish the effect of the drug compared to placebo.
In its draft guidance Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format, the FDA states (emphasis added): “The indicated population may mirror the studied population, … but can sometimes differ. In some cases, FDA’s expert reviewers may fairly and responsibly conclude, based on their scientific training and experience, that the available evidence supports approval of an indication that is broader … in scope than the precise population studied.”

In the case of Relyvrio, the FDA took this trial population into consideration, and based on their scientific training and experience, approved the broadest indication for the drug: “RELYVRIIO is indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults.”

- By requiring a “definite diagnosis,” Cigna is prohibiting access to Relyvrio to people with ALS who may be early in their disease journey and could be characterized as having probable, possible or suspected ALS. It takes, on an average, about 12–14 months for someone to get a definite diagnosis of ALS. During this time, the disease continues to ravage their motor neurons, leading to pathological progression and functional decline. Data from the CENTAUR phase 2/3 trial and its Open Label Extension showed that earlier initiation of treatment (by just six months) with Relyvrio resulted in a 47% reduction in tracheostomy, permanent assisted ventilation, or hospitalization and an average of 6.5 more months of life. These benefits are significantly meaningful in a disease where functional decline cannot be reversed, and the mean survival time is 2–5 years. This is time, function, and independence people with ALS will never get back.

- Inclusion of “absence of neuroimaging evidence of other disease processes” is irrelevant and unfounded. There are no reliable or validated imaging tests (such as CT, MRI or PET) that differentiate ALS from Parkinson’s disease, Alzheimer’s disease, or any other chronic neurological or progressive neurodegenerative disease.

3. **Onset of ALS symptoms began within the preceding 18 months.**

We disagree with this criterion for these four reasons:

- There are no safety data from the CENTAUR trial that would preclude people with ALS who have been experiencing symptoms for more than 18 months from taking the drug, nor is there any evidence that they would not gain any benefit. Therefore, the FDA label states: “RELYVRIIO is indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults.” There is no mention of any “limitations of usefulness” (21 CFR 201.57 (c)(2)(i)(B)).

- Onset of ALS symptoms within less than 18 months is generally used as an inclusion criterion by clinical trial investigators specifically to increase the likelihood they will be able to follow a person with ALS during a six-month trial and be able to observe a disease trajectory without the patient dropping out of the trial (usually because of disease burden or progression). As stated previously, the mean survival time for people with ALS is 2–5 years, so investigators must take time since symptom onset into consideration when designing clinical trials.

- A significant number of people with ALS might not be within the required 18-month window following symptom onset at the time of diagnosis, which is grossly unfair and not reflective of the realities of accessing ALS care. As previously stated, people with ALS often experience significant diagnostic delays. Studies have found that, in general, people wait almost 6 months after ALS symptom onset before seeing a physician, most often their primary care provider. Then, it can take another 12 months or more to get an ALS diagnosis, depending on which type of specialist they are referred to.
Given the recall bias in asking a person with ALS on the timing and onset of their symptoms, this criterion is ambiguous and discriminatory. Studies from the last two decades have described a pre-symptomatic and prodromal period preceding clinically manifest ALS, which could present years prior to diagnosis (see review www.ncbi.nlm.nih.gov/pmc/articles/PMC8967095/pdf/awab404.pdf). These symptoms have been described as mild motor, mild behavioral, or mild cognitive impairments, and have been shown to exist along a continuum. This means it can be extremely difficult for a person to pinpoint exactly when their symptoms first began – if they are even able to discern which are ALS symptoms and which are not.

4. **Does not have a tracheostomy.**

There is no reason why people with a tracheostomy should not be able to take Relyvrio. There is no contraindication in FDA’s label, and there were no safety concerns raised based on the data from the CENTAUR trial. Tracheostomy is essential for many people with ALS as this surgical procedure allows them to connect to a ventilator that breathes for them when they cannot on their own and can lead to better clinical outcomes and survival. Patients with a tracheostomy are generally excluded from clinical trials as the procedure is considered “equivalent to death” in studies evaluating survival outcomes associated with disease modification.

5. **Documentation of pre-treatment percent-predicted slow vital capacity (SVC) or forced vital capacity (FVC) greater than or equal to 60% based on gender, height, and age.**

This criterion seems to have been selected based on the inclusion criteria for the CENTAUR trial. The FDA label does not list any contraindications that would necessitate setting a specific level of SVC or FVC to initiate treatment with Relyvrio. Given the heterogeneity in the clinical aspects of the disease and the heterogeneity in the pathology and regions of the spinal cord affected, people with ALS progress differently when it comes to respiratory function. A patient could be at 75% FVC and still be progressing at a faster rate when it comes to motor changes in their legs. There is no reason to tie or link respiratory function to access to a disease-modifying treatment that can work on other elements of the pathophysiology of the disease.

6. **Concurrent use of riluzole product or documentation of contraindication or intolerance to a riluzole product.**

The FDA label is broad and does not require, nor prohibit, the concurrent use of riluzole and Relyvrio. In the CENTAUR trial, 77% of participants were either taking riluzole or Radicava at or before entry into the trial based on the current standard of care. While the investigators found that neither drug affected the primary results of the study nor caused significant safety issues, clinical trials specifically testing the efficacy of Relyvrio as a combination therapy have not been conducted. Thus, there is no scientific evidence supporting this criterion.

7. **Will not use Relyvrio concomitantly with any other medications containing phenylbutyrate or taurursodiol.**

We agree with this criterion.

8. **Medication is prescribed by, or in consultation with, a neurologist, a neuromuscular disease specialist, or a physician specializing in the treatment of ALS.**

We agree with this criterion.
Based on our evaluation of Cigna’s coverage criteria for Relyvrio, five of the eight appear to be based on the inclusion/exclusion criteria for the CENTAUR trial and not the FDA-approved indication or label, which is what guides clinical decision-making and prescription. Clinical trial inclusion criteria, especially for rare, heterogenous, and progressive diseases like ALS, are developed to support the generation of statistically meaningful results within a time-limited treatment window and are not necessarily indicative of who can or will benefit from a drug in real world clinical practice. In fact, people with ALS who had a forced vital capacity of 60% of the expected value or less and/or had undergone tracheostomy were not eligible to participate in the clinical trials for riluzole.

Approximately 60% of people with ALS are already excluded from clinical trial participation the day they are diagnosed. To use these same criteria to deny people access to a disease-modifying treatment that has been deemed safe and effective by the FDA is not only discriminatory but also cruel.

For all these reasons, we strongly encourage you to urgently adopt more rational utilization criteria that align with the FDA’s approval and label for Relyvrio, insurance industry standards, clinical standards, and the fundamental biology of ALS.

We respectfully request a response to this letter in writing by April 11, 2023. Thank you in advance for your prompt response.

Sincerely,

Kuldip Dave, Ph.D.
Senior Vice President, Research
The ALS Association

CC: Harold Carter, PharmD, Chief Pharma Trade Relations Officer, Express Scripts
Mary Parke Dunn, Principal, Business Communications, Express Scripts