

DATE: December 3, 2020

#### OHA P&T Committee Meeting New Drug Evaluation for TEPEZZA (teprotumumab-trbw) Handout

On December 3<sup>rd</sup> Oregon Health Authority's Pharmacy & Therapeutics Committee will be reviewing TEPEZZA (teprotumumab-trbw) during the New Drug Evaluation Section. In addition to the oral testimony, we submit this written summary of TEPEZZA (teprotumumab-trbw) clinical data and comments on the proposed prior authorization criteria for the attendees.

TEPEZZA, an insulin-like growth factor-1 receptor (IGF-1R) inhibitor, is the first and only FDA-approved treatment for Thyroid Eye Disease (TED), a rare, serious, and vision-threatening autoimmune eye disease<sup>1</sup>. TEPEZZA is the only FDA-approved medicine that targets the IGF-1R which has been implicated in the pathogenesis of TED. The symptoms of TED include severe inflammation of the eyes, dry eye, double vision, eye lid retraction, ulcers of the cornea, and site-threatening compressive optic neuropathy<sup>2</sup>. TED dramatically impacts patients' quality of life (QOL) due to disfigurement and disability, and, when severe, vision can be threatened due to optic nerve compression<sup>2</sup>.

On January 21, 2020, TEPEZZA was approved after a rigorous review and with unanimous support from the FDA's 12-member Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC)<sup>3,4</sup>. Given the unmet medical need for an approved TED treatment, TEPEZZA was previously granted FDA orphan, fast track, and breakthrough therapy designations<sup>5</sup>. TEPEZZA has been studied in two of the most extensive randomized controlled trials in TED<sup>6,7</sup>. Notably, both studies underwent thorough FDA review and results were published in *The New England Journal of Medicine*. Moreover, Dr. Roger Dailey, a leading oculoplastic surgeon at the Casey Eye Institute in Portland, participated in the clinical trials and was a co-author of the peer-reviewed articles. Published studies of off-label medications used in TED (e.g., high dose steroids and biologics) have not shown improvements in either proptosis or diplopia and are associated with significant side effects<sup>8</sup>. The FDA summarized the Benefit-Risk Dimensions for TEPEZZA in their review, highlighting the importance of the proptosis reduction, which had not been observed in published studies of other medicines such as corticosteroids, and TEPEZZA's favorable safety profile<sup>9</sup>. Since the launch of TEPEZZA, more than 1,000 patients with TED have received treatment, and importantly, the safety profile is similar to that of the clinical trials<sup>10</sup>.

TEPEZZA was evaluated in two randomized, double-masked, placebo-controlled studies<sup>6,7</sup> that included 171 patients with TED. A total of 84 patients were randomized to TEPEZZA and 87 patients were randomized to placebo. The primary endpoint or proptosis responder rate at week 24 (percentage of patients with  $\geq 2$  mm reduction in proptosis from baseline) was significantly higher in the TEPEZZA group compared to placebo (PH2: 71% vs. 20%,  $P < 0.001$ ; PH3: 83% vs. 10%,  $P < 0.001$ )<sup>6,7</sup>. All secondary endpoints (proptosis mean change from baseline, diplopia, clinical activity score, and quality of life) were highly significant, favoring TEPEZZA. All the patients in the TEPEZZA cohort had proptosis reduction at week 24 regardless of initial proptosis measurement. The mean change in proptosis at week 24 (**-3.32 mm**)<sup>7</sup> is comparable to the proptosis reduction achieved with orbital decompression surgery<sup>12</sup>. Moreover, the efficacy of TEPEZZA in reducing proptosis comes without surgical trauma to orbital tissue and does not expose patients to the pain and risks associated with invasive orbital surgeries. Also, the proptosis response number needed to treat in the Phase 3 study was 1.36<sup>7</sup>. In other words, only 1.36 patients are required to be treated for an additional positive response.

The most common adverse reactions ( $\geq 5\%$ ) that occurred at greater incidence in the TEPEZZA group were muscle spasms, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, and dry skin<sup>3,6,7</sup>. The majority of the events were mild to moderate and noted by the FDA to be of "limited duration and were able to be managed without interruption of therapy".<sup>9</sup>

As proposed, three of the 11 prior authorization criteria present serious concerns, which we summarize here and request changes to help ensure medically necessary access. It appears that some of the "draft" prior authorization criteria for TEPEZZA were derived from the clinical trial Inclusion and Exclusion criteria. Applying the clinical trial's Inclusion and Exclusion Criteria to real-world use may inadvertently and severely restrict access to the drug. Further, the selected criteria below are not in product labeling.

#### 1. Proposed Approval Criteria #4. Requiring Clinical Activity Score (CAS) of 4 or Higher on 7-Point Scale

The Clinical Activity Score (CAS) represents the number of inflammatory symptoms/signs present in the patient. Under proposed approval criteria #4, a patient must have Active TED, which the proposed criteria defines as an individual having a CAS of 4 or higher on the 7-point CAS scale within the past three months. There are several concerns regarding this draft criteria, both regarding TED and TEPEZZA. Most notably:

- **A CAS of  $\geq 4$  on the 7-point scale is not considered Active TED.** On the 7-point scale, a CAS score of 3 or higher – rather than 4 or higher – is considered active disease.
- **The CAS is not clinically meaningful and is not a primary or secondary endpoint.** For TED, the primary hallmark of patient symptoms and concerns is proptosis. Accordingly, the FDA clinical review team's accepted primary efficacy measure is the proptosis responder rate. Further, the FDA clinical review team determined that a CAS score is not clinically meaningful. The CAS score is a composite with equal weighting of a number of factors. Since these factors are not of equal weight either to the patients or physicians treating these patients, the FDA clinical team explicitly rejected the use of Clinical Activity Score as an endpoint.<sup>5</sup>

Therefore, the FDA review and approval of TEPEZZA were based on the proptosis responder rate as the measure of clinical efficacy.

**We request removing the baseline CAS score requirement, as there is no prerequisite for a CAS in the FDA-approved product labeling.<sup>3</sup> The FDA does not consider CAS as clinically meaningful. Furthermore, a CAS  $\geq 4$  on the 7-point scale is not accepted as Active TED. Despite this, should the Committee still consider CAS as mandatory for determining patients with significant activity, we suggest changing the wording to reflect the requirement for significant inflammation upon follow-up. According to CAS methodology, this would be based on a score of 4 or greater on the 10-point scale (not the 7-point scale).**

## 2. Proposed Approval Criteria #5. Severity Criteria

Under proposed approval criteria #5, a TED patient must be assessed for severity based on all of the clinical features outlined in the Graves' Orbitopathy Severity Assessment. However, TED is a heterogeneous disorder and patients progress through varied symptomatology over the course of their disease. **We request that this criterion be revised to match the severity criteria mentioned explicitly in the clinical trial protocol. Given the heterogeneity of TED, the clinical trial protocol used the following criteria: Patient has one or more of the following: lid retraction, moderate or severe soft tissue involvement, proptosis, and/or diplopia or double vision.**<sup>12</sup>

## 3. Proposed Approval Criteria #7. Use of corticosteroids

Proposed approval criteria #7 would apply an elaborate step therapy requirement involving corticosteroids. This raises many serious clinical concerns. Specifically:

- **Oral or IV corticosteroids are not FDA-approved treatments for TED and have not been shown to be effective in improving either proptosis or diplopia.**<sup>1,13</sup> In lieu of an FDA-approved therapy, glucocorticoids are used off-label. There is only one placebo-controlled clinical trial using intravenous glucocorticoid monotherapy for TED that was published in 2008 by Van Geest, RJ, et al.<sup>14</sup> The authors reported no significant improvement in the most serious progressive outcomes of the disease (proptosis and diplopia) both of which are significantly improved with TEPEZZA.
- **As FDA states in the TEPEZZA approval benefit-risk assessment, "corticosteroids ... have been used with generally poor results."**<sup>4</sup>
- **Unlike TEPEZZA, corticosteroids carry significant adverse event risks, including liver failure, diabetes, insomnia, psychological changes, and even death, together with associated medical and social costs.**
- **Given the safety and efficacy issues with corticosteroids, there were no corticosteroid requirements in the clinical trial program.** The clinical benefits of TEPEZZA were demonstrated independent of corticosteroids, and there are no steroid-related requirements in FDA-approved labeling.

**We therefore request the removal of criteria #7. For the reasons stated above and given the availability of an FDA-approved therapy for the treatment of TED, requiring corticosteroid use/failure is insupportable on safety and efficacy grounds.** Requiring corticosteroids prior to receiving TEPEZZA effectively forces the use of a medicine that is neither approved nor effective in managing TED, and will delay the use of a safe and effective approved therapy.

Regarding the note that reads "teprotumumab is associated with hyperglycemia which may necessitate diabetic medication changes and may not be an appropriate alternative when avoiding steroids in patients with uncontrolled diabetes mellitus", this assumption is not consistent with the FDA-approved Prescribing Information<sup>3</sup>. Hyperglycemia has been reported in 10% of patients in the TEPEZZA<sup>3</sup> cohort, and none of the patients with hyperglycemia experienced complications such as ketoacidosis or had to withdraw from the studies<sup>5</sup>. In the clinical trials, hyperglycemia in non-diabetics was controlled with diet modification and oral anti-hyperglycemic agents<sup>5</sup>. In the Prescribing Information<sup>1</sup>, hyperglycemia is discussed under Warnings and Precautions, but not as a contraindication.

In summary, TEPEZZA is the only FDA-approved treatment for TED. Furthermore, TEPEZZA is the only therapeutic option with data to support dramatic improvements in all aspects of TED, including proptosis, double vision (diplopia), inflammatory changes of the eye, and patient's quality of life in both function and appearance.

## References:

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October 27, 2020

Oregon Pharmacy & Therapeutics Committee  
Oregon Health Authority  
4070 27th Ct. SE  
Salem, OR 97302

Re: New Drug Evaluation: Risdiplam (Evrysdi™) oral solution

Dear Oregon Pharmacy & Therapeutics Committee Members:

On behalf of Oregon residents with a neuromuscular disease known as spinal muscular atrophy (SMA), **Cure SMA urges the Oregon Pharmacy & Therapeutics Committee to approve and allow full access to Evrysdi, a new SMA treatment, for all eligible Oregon residents with SMA according to the FDA label.** As we wrote in our August 12, 2020 Evrysdi coverage letter to Oregon Medicaid (attached), we advocate that **no one impacted by SMA should be denied access to a potentially life-saving treatment.**

SMA is a progressive neurodegenerative disease that can significantly impact an individual's ability to walk, swallow, and—in the most severe cases—even breathe. In Oregon, an estimated 4 babies with SMA are born each year and more than 83,000 Oregon residents are carriers of the SMA genetic mutation.<sup>i</sup>

Cure SMA is the leading national organization dedicated to finding a cure and treatments for SMA. Cure SMA and our Oregon supporters, including the Grabham family and the Miller family, both of Portland, are focused on improving lives and removing barriers for Oregon residents with SMA and their families. The Grabham's 14-year-old daughter, Wren, was diagnosed in 2008 with SMA Type 3. The Miller's 5-year old daughter, Magdalene, was diagnosed in 2015 with SMA Type 1. Wren and Magdalene have both benefited from accessing SMA treatments and care that was appropriate for them.

**Every person with SMA in Oregon should be able to access the treatment of their choice, based on their individualized needs and in consultation with their health care provider.** As we wrote in our August 12, 2020 letter to Oregon Medicaid, the U.S. Food and Drug Administration (FDA) approved Evrysdi for the treatment of SMA in all individuals with SMA who are 2 months of age and older.

**FDA Prescribing Information for EVRYSDI (August 2020)<sup>ii</sup>**

*EVRYSDI is a survival of motor neuron 2 (SMN2) splicing modifier indicated for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older.*

The FDA's approval and broad label were based on clinical trials that demonstrated Evrysdi's effectiveness in all individuals with SMA who are 2 months of age and older. In our August 12, 2020 letter, Cure SMA highlighted the key data from the FIREFISH (Part 1

& 2), SUNFISH, and JEWELFISH trials. Together, these studies showed individuals with SMA who received Evrysdi achieved unprecedented developmental gains and milestones (i.e., swallowing, sitting, standing) and required fewer hospitalizations and reduced need for permanent ventilation and feeding support. In addition to the efficacy, the FDA thoroughly reviewed the SMA treatment for safety and concluded that the clinical trials data established that Evrysdi was safe for the treatment of SMA.<sup>ii</sup>

**Cure SMA respectfully asks that this distinguished committee of health care experts approves Medicaid coverage of Evrysdi for all Oregon Medicaid beneficiaries with SMA who are 2 months of age and older, as recommended by the FDA.** We are pleased that the Evrysdi policy under consideration attempts to match much of the FDA label. We do have concerns with the criteria related to use with other SMA treatments and the length of authorization.<sup>iii</sup> Covering Evrysdi without restrictions, based on the FDA label, will allow individuals with SMA to experience a higher quality of life and greater longevity – leading to better outcomes. **All Oregon residents with SMA should be able to access an SMA treatment based on their individual choice and circumstance.**

Thank you for considering Cure SMA's recommendation for full coverage of Evrysdi. Please do not hesitate to contact Cure SMA if you have questions or need additional information. Cure SMA can be reached through Maynard Friesz, Vice President for Policy and Advocacy at Cure SMA, at [maynard.friesz@curesma.org](mailto:maynard.friesz@curesma.org) or 202-871-8004. Thank you for your consideration.

Sincerely,



Kenneth Hobby  
President



Mary Schroth, M.D  
Chief Medical Officer



Jill Jarecki, PhD  
Chief Scientific Officer

**Enclosure: August 12, 2020 Oregon Medicaid Letter Seeking Coverage of Evrysdi**

<sup>i</sup> Cure SMA Oregon Fact Sheet, 2020 [https://www.curesma.org/wp-content/uploads/2020/09/SMA-State-Fact-Sheet\\_Aug2020\\_OR\\_v2.pdf](https://www.curesma.org/wp-content/uploads/2020/09/SMA-State-Fact-Sheet_Aug2020_OR_v2.pdf)

<sup>ii</sup> U.S. Food and Drug Administration, Evrysdi Prescribing Information, 2020, (Page 2), [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/213535s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213535s000lbl.pdf)

<sup>iii</sup> Oregon New Drug Evaluation" Risdiplam (Evrysdi) Oral Solution, [https://www.orpd.org/durm/meetings/meetingdocs/2020\\_12\\_03/drafts/Risdiplam\\_Evrysdi\\_NDE.pdf](https://www.orpd.org/durm/meetings/meetingdocs/2020_12_03/drafts/Risdiplam_Evrysdi_NDE.pdf)



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August 12, 2020

Lori Coyner  
Medicaid Director  
State of Oregon, Oregon Health Authority  
500 Summer Street, NE E49  
Salem, OR 97301

RE: Evrysdi (risdiplam) for Medicaid Beneficiaries with Spinal Muscular Atrophy

Dear Director Coyner,

On behalf of the largest organization dedicated to finding treatments and a cure for Spinal Muscular Atrophy (SMA), **we are writing to respectfully request that you provide coverage and access to Evrysdi (risdiplam) for Medicaid beneficiaries as indicated by the drug's label.** The U.S. Food and Drug Administration (FDA) approved Evrysdi for the treatment of SMA on August 7, 2020. The treatment was approved for daily oral/enteral route of administration in all individuals with SMA who are two months of age and older. We urge you to ensure that this drug is covered without restriction for all people with SMA over two months old.

SMA is a progressive neurodegenerative disease that impacts 1 in 11,000 births in the US among all races, ethnicities, and genders. An estimated 1 in 50 Americans are genetic carriers. SMA robs people of physical strength by affecting the motor nerve cells in the spinal cord, impeding their ability to walk, swallow, and in the most severe cases, the ability to breathe. The disease is an autosomal recessive genetic disease caused by a mutation in the survival motor neuron gene 1 (SMN1).

As an oral treatment for SMA, the burden of administration is decreased, giving more patients potential access to SMA treatment. Covering this treatment without restrictions will allow individuals with SMA to experience a higher quality of life and greater longevity – leading to better outcomes. At the current time approximately 60% of all US patients are not yet treated. There are ongoing urgent unmet needs in our community, especially for our older patients, which this treatment will meet.

Historically, individuals with SMA have required aggressive medical care to survive, especially as the disease progressed and weakness increased with further loss of function. Because of the complexities of the disease, patients traditionally have needed a multi-disciplinary team of healthcare professionals to provide them with care and support. Without treatment, patients with SMA type 1 require permanent ventilation and feeding tubes, and costly, intensive, around the clock care. Those with type 2 and 3 may also require some of these interventions. All of these services place a tremendous financial burden on both families and insurers.

Evrysdi modifies splicing of the backup gene SMN2 to produce more functional full length SMN protein, a protein that is deficient in SMA and is necessary for motor neuron function and survival. Evrysdi is designed to increase and sustain SMN protein levels both throughout the central nervous system and in the peripheral tissues of the body. Evrysdi is a liquid oral treatment that is given daily at home.



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**Clinical trials have demonstrated Evrysdi's effectiveness.** In the FIREFISH trial Part 1, a pivotal global study evaluating Evrysdi safety and efficacy in infants aged 2-7 months with symptomatic SMA type 1, the study showed that 41% of infants (7/17) sat without support for 5 seconds by month 12, as assessed by the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development Third Edition (BSID-III). No infants achieved this milestone in the natural history of SMA type 1.<sup>1</sup> In addition, after 12 months of treatment with Evrysdi, 90% (19/21) of patients were alive without permanent ventilation. After a minimum of 23 months of treatment with Evrysdi, 81% (17/21) of patients were alive without permanent ventilation and reached an age of 28 months or older compared to average age of 13.5 months for death or permanent ventilation in a natural history study.<sup>1</sup> In this cohort, 88% (15/17) of infants were able to feed by mouth and swallow; 13/17 fed exclusively by mouth. In a natural history study, all infants over 12 months of age with SMA type 1 required feeding support.<sup>1</sup> Motor milestone assessment with the Hammersmith Infant Neurological Exam Module 2 (HINE-2) showed 77% (13/17) of infants had more milestones improve versus decline.

In the FIREFISH trial Part 2, a pivotal global study evaluating Evrysdi in infants aged 2-7 months old with symptomatic SMA type 1, the study met its primary endpoint with 29% of infants (12/41;  $p < 0.0001$ ) sitting without support for 5 seconds by month 12, as assessed by the BSID-III. No infants achieve this milestone in the natural history of SMA type 1. In addition, 44% (18/41) of infants were able to hold their head upright, 32% (13/41) were able to roll to the side and 5% (2/41) were able to stand with support, as measured by the HINE-2. Approximately 90% (37/41) had a Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score increase of at least 4 points, with 56% (23/41) achieving a score above 40; the median increase was 20 points. Without treatment, infants with SMA type 1 show a decrease in CHOP-INTEND scores over time. Almost half of the infants (49%) treated with Evrysdi did not require hospitalization up to month 12 compared to up to 7.6 hospitalizations per year for untreated patients with SMA type 1.<sup>2</sup> In addition, 93% were alive at month 12 compared to average age of 13.5 months for death or permanent ventilation in a natural history study.<sup>1</sup> Of the surviving infants, swallowing was maintained in 95% (36/38) and the ability to feed by mouth was maintained in 89% (34/38) compared to natural history.<sup>1</sup>

SUNFISH, a two-part, double-blind, placebo-controlled pivotal study in patients aged 2-25 years with SMA type 2 or type 3. Part 1 (n=51), determined the dose for the confirmatory Part 2 study. Part 2 (n=180) evaluated motor function using total score of Motor Function Measure 32 (MFM-32) at 12 months of treatment in non-ambulatory patients with type 2 or type 3. MFM-32 is a validated scale used to evaluate fine and gross motor function in people with neurological disorders including SMA. The study met its primary endpoint and showed that the MFM-32 change from placebo was significant in people treated with Evrysdi (1.55 point mean difference;  $p = 0.0156$ ). The Revised Upper Limb Module (RULM), a key secondary endpoint, also showed improvement (1.59 point difference;  $p = 0.0028$ ) compared to placebo. As anticipated, exploratory subgroup analyses showed that the strongest responses in MFM-32 versus placebo were observed in the youngest age group (2-5 years) with 78.1% vs. 52.9% achieving  $\geq 3$  point increase. Importantly, disease stabilization was observed in the 18-25 years age group (57.1% vs. 37.5%, with stabilization defined as a  $\geq 0$  point increase), which is the goal of treatment for those with more established disease.

The exploratory efficacy analysis of SUNFISH study Part 1 assessed motor function, using the MFM-32 scale. In a weighted analysis comparing the data with a robust natural history comparator cohort, MFM-32 change from placebo at month 24 was greater in patients receiving Evrysdi (3.99 point difference [95% CI: 2.34, 5.65]  $p < 0.0001$ ). Even small changes in motor function can result in meaningful



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differences in daily living. Results also showed that treatment with Evrysdi led to a median two-fold increase in blood SMN protein levels after four weeks, which was sustained for at least 24 months. This is consistent with previously reported results through 12 months of treatment. SMN protein is found throughout the body and is critical for maintaining healthy motor neurons, which transmit movement signals from the central nervous system to the muscles.

JEWELFISH is an open-label study, assessing safety and pharmacodynamic data in people with SMA aged 6 months-60 years who have previously received other SMA-directed treatments and who currently are receiving Evrysdi. Among the patients who completed 12 months of treatment with Evrysdi, a median two-fold increase in SMN protein versus baseline was observed (n=18), consistent with treatment naïve patients. An early assessment of safety showed a consistent safety profile compared to treatment-naïve patients. No patients had drug related adverse events that led to Evrysdi withdrawal.

As individuals with SMA are life-long patients and regular consumers of significant health care resources, treatment with Evrysdi will very likely reduce their need for other health care services, such as inpatient and outpatient visits, emergency care, physical therapy, occupational therapy, and other related care and services. Participants in the clinical trials have already shown less need for costly, invasive interventions and services. In addition, the caregiver burden is dramatically reduced as patients gain or maintain independence.

**Therefore, we ask that this life-changing treatment be covered with no restrictions for Medicaid beneficiaries for whom it has been approved.** Decisions about care should be made by patients, their families, and their expert clinical care providers, based on what works best for that individual, not on financial or insurance concerns. We believe that no one impacted by SMA should be denied access to a potentially life-saving therapy, intervention, or expert care provider. To that end, we are eager to work with you to ensure that the forthcoming coverage and reimbursement policies associated with Evrysdi adequately address the needs of the eligible SMA community.

For more information, please contact Maynard Friesz, Vice President for Policy and Advocacy at Cure SMA at [maynard.friesz@curesma.org](mailto:maynard.friesz@curesma.org) or 202.871.8004.

Sincerely,

Kenneth Hobby  
President

Jill Jarecki, PhD  
Chief Scientific Officer

Mary Schroth, M.D.  
Chief Medical Officer

References:

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Doernbecher Children's Hospital

Division of Pediatric Neurology

Mail code CDRCP
707 SW Gaines Street
Portland, OR 97239-3098
Phone 503-494-5856
Fax 503 494-2370

Yoon-Jae Cho, MD
Chief, Pediatric Neurology
Professor of Neurology & Pediatrics

Stephen Back, MD, PhD
Professor of Neurology & Pediatrics

Barry Russman, MD FAAP, FAAN
Professor of Neurology & Pediatrics

Jason Coryell, MD
Associate Professor of Neurology & Pediatrics

Carter Wray, MD
Associate Professor of Neurology & Pediatrics

Erika Finanger, MD, MS, FAAP
Associate Professor of Neurology & Pediatrics

Colin Roberts, MD
Associate Professor of Neurology & Pediatrics

Michael Narus, DO
Adjunct Associate Professor of Neurology & Pediatrics

Juan Piantino, MD
Assistant Professor of Neurology & Pediatrics

Jenny Wilson, MD
Assistant Professor of Neurology & Pediatrics

Ittai Bushlin, MD, PhD
Assistant Professor of Neurology & Pediatrics

Kaitlin Greene, MD
Assistant Professor of Neurology & Pediatrics

Andrea Frank, CPNP
Pediatric Nurse Practitioner

Meganne Leach, CPNP
Pediatric Nurse Practitioner

Wendy Herrick, DNP, CPNP-AC/PC
Pediatric Nurse Practitioner

October 27, 2020

Oregon Health Authority
P&T Committee

RE: Risdiplam for Spinal Muscular Atrophy

To Whom It May Concern:

We are the Neuromuscular clinicians in the only Muscular Dystrophy Association supported pediatric multidisciplinary neuromuscular clinic in Oregon. Dr. Finanger, the program director, has fellowship training in Neuromuscular Medicine and is board certified in Neurology and Neuromuscular Medicine. Both Dr. Finanger and Ms. Leach each have more than 15 years of experience caring for individuals with Spinal Muscular Atrophy (SMA).

We are excited to see the recommendation for inclusion of risdiplam on the OHA preferred drug list for the treatment of SMA.

We would like to recommend revision of the renewal criteria which currently states that motor function must demonstrate "improvement from baseline motor function score documented within one month of renewal request AND more areas of motor function improved than worsened OR documentation of clinically significant improvement in SMA-associated signs and symptoms...compared to the predicted natural history" (Appendix 2, Renewal criteria #2).

As we have discussed at previous meetings regarding other SMA directed therapies, it would be clinically appropriate to modify these criteria to allow for evidence of drug efficacy by any of the three measures listed in the criteria above. Specifically, given the progressive nature of SMA, stabilization of motor decline itself would be a clinically significant improvement from predicted natural history. In addition, we would recommend the inclusion of other potential clinically meaningful outcomes including respiratory function measures, increased independence and/or the ability to self-care.

Thank you for the opportunity to share our clinical experience and your continued partnership to provide excellent care for pediatric neuromuscular patients in Oregon.

Sincerely,

[Handwritten signature of Erika Finanger]

[Handwritten signature of Meganne Leach]

Erika Finanger, MD MS
Associate Professor of Neurology and Pediatrics
Director, Muscular Dystrophy Association Clinic at Shriners Hospital Portland
Oregon Health & Science University

Meganne Leach, MSN PPCNP-BC
Instructor of Neurology and Pediatrics
Oregon Health & Science University

