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College of Pharmacy
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Attn: Oregon Pharmacy and Therapeutics Committee
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November 27th , 2017

Dear Pharmacy and Therapeutics Committee Members

The Multiple Sclerosis Association of America is a national 501(c)(3) patient advocacy organization that serves the more than 400,000 US residents diagnosed with multiple sclerosis. Founded 46 years ago, MSAA has established an excellent record of reasoned, fair and balanced public positions on various MS issues focusing on the needs of the patient. As a leading resource for the entire MS community, improving lives through vital services and support, we are strong advocates for patient access to all needed and appropriate treatments.

**It has come to MSAA's attention that this honorable committee is currently evaluating the addition of Ocrevus (ocrelizumab) for coverage for patients with Relapsing Remitting MS (RRMS)**. MSAA's position on MS treatment is heavily dependent on FDA guidance, and we strongly support the principle that all FDA approved treatments that benefit people with MS should be made fully available to them. Furthermore, since the needs and circumstances of no two MS patients are alike, the decision to have full access to any specific medication at any time after diagnosis is the primary responsibility of the patient and the physician. **As such, MSAA kindly requests that the Pharmacy and Therapeutics Committee make this needed addition to the Prescription Drug List and continue to allow physicians the flexibility to choose any of the FDA approved MS agents they feel best fits the disease state of the individual patient.**

**Additionally, MSAA would like to urge the members of this committee to recommend that the Health Evidence Review Commission add Primary Progressive Multiple Sclerosis (PPMS) to the diagnoses list enabling beneficiaries with this devastating form of the disease the ability to secure treatment as prescribed by their physician. Currently, Oregon Medicaid patients with PPMS are the only MS patients in the nation whose state Medicaid plan does not cover treatment specific to their disease course.**

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Currently, no MS medication is curative with efficacy varying from one individual to another and for any given individual at different points in time. In addition, people with MS differ in their tolerance for different routes of administration and side effects, and clinicians and patients vary in their tolerance for risk, with risk tolerance undergoing potential shifts as the disease progresses. As such, access to a full range of options of MS Disease Modifying Therapies (DMTs) is essential in order to optimize the ability of people with MS to effectively manage their own disease course, and for their physicians to make the most optimal treatment decisions.

As with the majority of MS medications currently available, which primarily target inflammation, the optimal window for impacting long-term disability is during the early relapsing phase of the disease, with an end-goal of decreasing relapses and preventing disability from unresolved relapses and disease progression. Any potential withholding of a physician and patient's preferred treatment risks the potential of non-response from a medication that will prove ineffective and increases the likelihood of recurrent disease activity. Additionally, that potential for increased disease progression also correlates with higher emergency services utilization among MS patients.

I would be happy to provide further insight in to our concerns about the positive impact that this addition might have on MS patients' access to care. I can be reached at (800) 532-7667, x160 or kpinion@mymsaa.org. Thank you in advance for your attention to this matter.

Respectfully,

Kyle Pinion

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***Brief Outline***

- Background and overview of DMD impact
- Deflazacort is the first and only approved corticosteroid for the treatment of DMD. AAN guidelines recommend early use of corticosteroids for DMD
- Pivotal Studies 1 and 2 summaries
- Emerging data shows benefits deflazacort versus prednisone in well-designed, independent studies
- ACT-DMD Results further confirm benefit of deflazacort over prednisone
- Meta-analysis from 2 independent Phase 3 studies corroborates the benefit of deflazacort versus prednisone
- Deflazacort may Result in a Number of Benefits, based on these data and Natural History Studies
- Adverse events were consistent with those of corticosteroids
- Implications for Managed Care/Medicaid

***Background and overview of DMD impact[1-8]:***

- Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder affecting 1:5000 live male births in the US and is the most common and severe form of muscular dystrophy among children.[1-3] Mutations in the DMD gene result in a lack of functional dystrophin protein, which leads to the replacement of muscle fibers with fibrofatty connective tissue.[1,4,5]
- DMD is a rapidly progressing disease, with developmental delays evident between the ages of 2 and 5 years, as patients struggle to walk or climb stairs.[1]
- Untreated, most patients lose significant strength and function by ages 6 and 7 years, and lose the ability to walk by approximately 12 years of age.[1,4] Respiratory, orthopedic, and cardiac complications emerge as the disease progresses; without treatment life expectancy is around 19 years.[1,4-8]

***Deflazacort is the first and only approved corticosteroid for the treatment of DMD. AAN guidelines recommend early use of corticosteroids for DMD[1,9]:***

- Corticosteroids are the backbone/standard of treatment for DMD. Both the Centers for Disease Control (CDC) and American Academy of Neurology (AAN) guidelines support the use of corticosteroids in patients with DMD, as they have been shown to slow the decline in muscle strength, improve motor function, reduce the risk of scoliosis and need for scoliosis surgery, and delay the onset of cardiomyopathy and loss of independent ambulation.[1,9] The AAN has found that deflazacort may be offered for improving strength and timed motor function and delaying age at loss of ambulation by 1.4–2.5 years (Level C). Deflazacort may be offered for improving pulmonary

function, reducing the need for scoliosis surgery, delaying cardiomyopathy onset, and increasing survival at 5–15 years of follow-up (Level C for each).[9]

***Pivotal Studies 1 and 2 summaries[10,11]:***

- Additional analyses in the publication of Pivotal Study 1 showed that patients randomized to 0.9 mg/kg/day of deflazacort had significant improvements at week 12 in muscle strength and time to climb 4 stairs compared to patients randomized to prednisone, and numerical improvements on time to stand from supine and time to run or walk 30 feet.[10]

- Analyses of Pivotal Study 2 showed that patients randomized to deflazacort had an approximately 30-month delay in median loss of ambulation relative to patients randomized to placebo.[11]

***Emerging data shows benefits deflazacort versus prednisone in well-designed, independent studies[12,13]:***

- The Cooperative International Neuromuscular Research Group (CINRG) natural history study of 340 DMD patients found daily deflazacort maintained independent ambulation significantly longer than any dosing regimen of prednisone, with an additional 2 years of independent ambulation relative to daily prednisone.[12]

- Similarly, DuchenneConnect, an online registry of over 1,000 DMD patients found that current use of corticosteroids was the most significant predictor of improved wheelchair-free survival, and when they compared deflazacort to prednisone users, patients taking deflazacort had significantly longer wheelchair-free survival by 1 year compared to prednisone.[13]

***ACT-DMD Results further confirm benefit of deflazacort over prednisone[15]:***

- Results from the placebo arm of an independent phase 3 trial assessing the efficacy and safety of ataluren were analyzed. Patients in the placebo arm received standard of care and were either on deflazacort (n=53) or prednisone/prednisolone (n=62).[14]
    - Deflazacort may extend ambulation by 3.8 years when compared to prednisone/prednisolone.
    - Over 48 weeks, patients showed a 39-meter decline compared to a 70.6-meter decline in the deflazacort and prednisone/prednisolone arms, respectively (p=0.0484) in 6-minute walk distance (6MWD).
    - Deflazacort significantly improved the time to climb 4 stairs and stand from supine compared to prednisone/prednisolone. Deflazacort also demonstrated numerical improvements in the time to descend 4 stairs and walk/run 10 meters.

***Meta-analysis from 2 independent Phase 3 studies corroborates the benefit of deflazacort versus prednisone[14]:***

- Trial 1 Overview:
    - The tadalafil trial was a randomized, double-blind, placebo-controlled phase 3 trial of tadalafil in 116 ambulatory males with DMD, aged 7-14 years who had a baseline six-minute walk distance (6MWD) between 200-400 meters.
- Trial 2 Overview:

- ACT-DMD was a randomized, double-blind, placebo-controlled phase 3 trial of ataluren in 115 ambulatory males aged 7-16 years with nonsense mutation DMD who had a baseline 6MWD of >150 meters.
- Fixed effects meta-analysis results:
  - Compared with patients receiving prednisone/prednisolone, patients receiving deflazacort experienced significantly slower declines:
    - 28.3 meters in 6MWD (p=0.01 vs. prednisone)
    - 2.9 seconds in rise from supine (p<0.01 vs. prednisone)
    - 2.3 seconds in 4 stair climb (p=0.01 vs. prednisone)
    - 1.2 points on the North Star Ambulatory Assessment total score (p=0.05 vs. prednisone)

***Deflazacort may Result in a Number of Benefits, based on these data and Natural History Studies***

- Preserve functional parameters (demonstrated through reduced change in 6MWD and TFTs)[15,16,17]
- Reduce the risk of developing scoliosis and delay the need for spinal surgery
- Delay loss of ambulation and preserve pulmonary function[12,13,15,17]
- Prolong survival in the second decade of life[17]

***Deflazacort was associated with a favorable safety profile compared to prednisone[10]:***

- Adverse events were consistent with the corticosteroid class. In clinical trials, patients treated with deflazacort had more subclinical cataracts and less weight gain relative to prednisone; at week 52 patients treated with deflazacort had gained significantly less weight than those treated with prednisone.

**Implications for Managed Care/Medicaid[19]**

- Deflazacort dosing is not linear and does not increase when patient weight increases (EAP with 860 patients).
  - Clinicians tend to maintain the dose to when patient initiated therapy vs. increasing as patient naturally increases in weight with age.
- Incremental pharmacy cost for an Emflaza patient is approximately $0.009 over three years for a Medicaid program excluding any cost offset calculations for delaying disease progression milestones.
  - Based on a budget impact model with 1 million members per year.

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