March 20, 2017

Oregon Health Authority
Oregon Drug Use Review/Pharmacy & Therapeutics Committee
RE: Exondys 51

To Whom it May Concern:

As the three providers in the state of Oregon with the most expertise in the care of children with Duchenne muscular dystrophy (DMD), we urge the Oregon Health Authority to provide access to eteplirsen (Exondys 51) to those patients who are amenable to exon 51 skipping. Exondys 51 received accelerated approval from the FDA based on evidence that it treats the underlying cause of the disease, which is absence of dystrophin production.

Duchenne muscular dystrophy is a severe genetic condition leading to progressive muscle weakness over time. DMD is caused by mutations in the dystrophin gene. DMD is the most common muscular dystrophy in childhood, affecting one in 5000 live male births. Patients are typically diagnosed around age 5 with motor delays and muscle weakness which is progressive leading to wheelchair dependence in the early teens and limited life expectancy with death in the 2nd to 3rd decade. Advances in medical management have improved life expectancy and quality of life for males with DMD through a multidisciplinary approach to symptom management. In addition, the off label use of corticosteroids beginning in early childhood has pushed the age at loss of ambulation to around 13 years old. However, corticosteroids do not treat the underlying cause of the disease.

Our Neuromuscular clinic at Shriners Hospital Portland provides healthcare to the vast majority of Oregon residents under 21 years of age with the diagnosis of Duchenne muscular dystrophy. We currently care for approximately 75 patients with DMD. Only about 13% of patients with DMD have genetic mutations which would be amenable to correction with Exondys51. At this time in Oregon, I am aware of ten patients living with exon-51 skipping amenable mutations. Not all patients will be deemed appropriate for therapy given severe end-stage disease or other medical issues. Currently, at least two patients have expressed interest in pursuing this treatment.

Exondys 51 is the first Duchenne specific medication targeted at the underlying genetic defect. It is intended to allow for production of an internally truncated but functional dystrophin protein. In a double-blind placebo-controlled study, treated patients showed dystrophin-positive fibers had increased to 23% of normal at 24 weeks; no increases were detected in placebo-treated patients (p_0.002). Even greater increases occurred at week 48 (52% and 43% in the 30 and 50 mg/kg cohorts, respectively), suggesting that dystrophin increases with longer treatment (Mendell et al, Ann Neurol 2013;74:637–647). Further, functional data generated from studies to date show that at 36 months of treatment, Exondys 51-treated patients (n = 12) demonstrated a statistically significant advantage of 151 meters ($p < 0.01$) on the 6 minute walk test (6MWT) and experienced a lower incidence of loss of ambulation in comparison to matched historical controls (n = 13) amenable to exon 51 skipping (Mendell et al, Ann Neurol 2016;79:257–271). Our institution is currently a clinical trial site for the ongoing phase 3 clinical study of this medication, so we can attest to the rigor and encouraging outcomes that continue to be published about this medication.

Oregon is not the first state to consider Medicaid coverage for this newly emerging medical treatment. California's Medicaid program recently reviewed this same information and approved its use

in this specified patient group. Duchenne-experts (Doctors Craig McDonald of UC Davis, Perry Shieh of UCLA and John Dey of Stanford) recorded their explanation of this data and the context of prescribing in their much larger state. Their recording is available at this YouTube site: https://www.youtube.com/watch?v=FCgypchATn4. The recording includes information about the disease progression, how studies were conducted and considerations for prescribing and monitoring in the clinical setting.

In summary, studies to date support the suggestion that relatively low levels of dystrophin can be functionally significant to patients and reasonably likely to predict clinical benefit. The males treated with this drug in clinical trials showed prolonged and longer distance walking compared to natural history studies, as well as in controls in enrolled in the study. As stated above, longer walking (which is highly desirable by itself) is associated with positive outcomes of improved pulmonary function later in the disease. Based on the functional measures and biopsy data, we believe Exondys 51 supplied to our patients will help to preserve muscle, delaying loss of function.

If you have any further questions, please contact us at 503-221-3424.

Sincerely,

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