



Shriners Hospitals
for Children™

Portland
Pediatric Specialty Care

Orthopaedics

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July 21, 2017

P&T Committee
Oregon Health Plan

Re: Approval of Deflazacort as a Treatment for patients with
Duchenne Muscular Dystrophy

Dear Committee Members:

I am writing to support the use of Deflazacort for patients with Duchenne Muscular Dystrophy (DMD). I am a Pediatric Orthopedic Surgeon and have been heavily involved with patients with neuromuscular disease since I began my practice at the University of Virginia in 1976. When I arrived at the Shriners Hospitals for Children in Portland, Oregon in 1992 as Chief of Staff one of my first initiatives was to establish a multi-discipline clinic for patients with progressive neuromuscular disease; which ultimately became a fully sanctioned clinic in association with the Muscular Dystrophy Association of America. This was the first such clinic in the Shriners Hospitals for Children system.

I have had quite a deep interest in patients with DMD and have authored on two occasions, most recently this current year a chapter on Orthopedic Treatment of Neuromuscular Diseases for the American Academy of Orthopedic Surgeons (AAOS) *Orthopedic Knowledge Update* for Pediatric Orthopedics (copy enclosed). I have also lectured widely including throughout Europe and the Middle East on this topic.

It is quite clear that corticosteroids provide significant benefit to patients with DMD. This has been clearly stated in the practice parameter from the American Academy of Neurology on which I was co-author (Practice Parameter: Corticosteroid Treatment of Duchenne Muscular Dystrophy RT Moxley, S Ashwal, et al. (including M Sussman) ; *Neurology* 2005;64:13-20, 2005). However, it seems like the best outcomes are from the series of patients treated in Toronto who had greatest prolongation of walking, the greatest reduction in scoliosis and many of these boys, according to Dr. Biggar, the senior author of the study, with whom I have spoken with over the years, are still surviving with some function into their third and fourth decade (Long-term benefits of Deflazacort treatment for boys with DMD in their second decade; *Neuromuscular Disorders* 16:249-255, 2006).

Although corticosteroid has a tremendous benefit in maintaining pulmonary function, walking ability, upper extremity function and extending life span, the side effects are significant. One of these side effects is obesity, since these boys have weak muscles the more weight they carry clearly will reduce their ability to walk. Deflazacort has been shown in several studies including Reference 8 in the OHSU Review by Griggs, et al. and a smaller study published in



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Muscle & Nerve in 2000 by Bonifati, et al. Much of this difference in weight gain occurs during the first six months of treatment so that if all patients are subjected to a six month trial of prednisone then they will incur more weight gain than they would have with Deflazacort, and this difference will not be equalized over time. Of course, not all patients who are put on corticosteroids gain weight, but a significant number of them do. (One may not recognize this if you just look at mean values, but there is certainly a subset of patients who begin on the thin side and remain thin and seem do not seem to be subject to the weight gain side effects of corticosteroid.)

It should also be noticed that on Page 2 of the comprehensive Review from the OSU Drug Use Research and Management Program, it stated that “only 25% of patients remain ambulatory by age 16”. I’m not sure where this data came from, but essentially all studies show that patients who are not treated with corticosteroids lose the ability to walk by their 12th birthday. It is difficult to write such a review without having personal experience with the patient group under study.

Clearly there is an increased incidence of cataracts in the patients treated with Deflazacort versus prednisone. However, these are cataracts that are detected on slit lamp examination, and it is very rare that they progress to the degree that treatment is necessary. In our program, I don’t think that any of our patients have had cataract surgery. So, that although this is a finding, it is not clinically relevant.

Another issue is behavior. Anecdotally, I have had several patients in whom the institution of prednisone resulted in very serious acting out behaviors which necessitated removal from classrooms and mal-treatment of siblings. One mother described this as flipping a switch and changing his behavior. Several of these patients were switched to Deflazacort and these behaviors became much more controllable. Myself, and associates here at Shriners, initiated a 9 year longitudinal study of boys with DMD wherein one of the components assessed was behavior. (PLOS Currents Muscular Dystrophy <http://currents.plos.org/md/article/prednisone-and-deflazacort-in-duchenne-muscular-dystrophy-do-they-play-a-different-role-in-child-behavior-and-perceived-quality-of-life>, June 17, 2016). We found that the patients on Deflazacort still had mood problems, but the aggressive externalizing behaviors were less frequent, when compared to prednisone. The inability of these patients to be in school and interact positively with their siblings and classmates is quite overwhelming.

I recognize that the cost of Deflazacort is exceedingly high particularly when patients used to be able to obtain this through internet pharmacies for \$50-\$60 a month. I cannot explain why the cost of the new formulation is so high, but the benefits of Deflazacort I feel are significant. The two major benefits are the decreased weight gain and the lower frequency of the aggressive behaviors. The behavioral effects are the most frequent reason, in my experience, for parents discontinuing corticosteroid. I hope you will consider approving Deflazacort for treatment of boys with Duchenne Muscular Dystrophy.

Sincerely,

Michael D. Sussman, MD
Orthopedic Surgeon



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July 21, 2017

P&T Committee of the Oregon Health Plan

Re: Concerning Intrathecal Spinraza (Nusinersen) for Patients with Spinal Muscular Atrophy (SMA)

Dear Committee Members:

I am writing in support of the use of Spinraza (Nusinersen) for patients with Spinal Muscular Atrophy (SMA). I am a Pediatric Orthopedic Surgeon and have been heavily involved with patients with neuromuscular disease since I began my practice at the University of Virginia in 1976. When I arrived at the Shriners Hospitals for Children in Portland, Oregon in 1992 as Chief of Staff, one of my first initiatives was to establish a multi-discipline clinic for patients with progressive neuromuscular disease, which ultimately became a fully sanctioned clinic in association with the Muscular Dystrophy Association of America. This was the first such clinic in the Shriners Hospitals for Children system.

I have had quite a deep interest in patients with SMA and have authored on two occasions, most recently this current year, a chapter on Orthopedic Treatment of Neuromuscular Diseases for the American Academy of Orthopedic Surgeons (AAOS) *Orthopedic Knowledge Update for Pediatric Orthopedics* (copy enclosed). I have also lectured widely, including throughout Europe and the Middle East on this topic.

In spite of its high cost, Spinraza provides almost miraculous benefits to patients with SMA. One must understand that patients with SMA Type I, once the onset of the disease becomes apparent, have progressive loss of motor skills and 80% die by age 2 of respiratory failure due to profound muscle weakness. However, patients under treatment are gaining motor skills. Therefore, even small gains represent not only gains, but a lack of the inevitable progression which occurs in untreated patients by preserving the motor neurons. Although there are some complications which have been reported, none of these are significantly life threatening and are far outweighed by the huge benefits which have been demonstrated in not only just the patients with SMA Type I, but also in patients with Types II and III. This data has been presented at the National meetings, although not yet published in peer-reviewed journals. As opposed to the otherwise thorough and well-done report from the OSU Drug Research and Management Program, where it is stated on the second page that patients have “marginal clinical benefit” I would disagree with this assessment and say that patients have a remarkable and highly significant clinical benefit. In addition to improvement in motor skills and in some cases

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acquisition of the ability to stand and walk, it is likely, although data is not yet available, that this may reduce the incidence of hip dislocation which is almost universal in SMA Types I and II as well as scoliosis.

Although published studies are not yet available for SMA types II and III, the dramatic response of the type I patients is a clear proof of principle that this drug will also be efficacious for types II and III also, as current data indicates, and I would urge the committee to also approve the drug for all SMA patients. Since there is progressive loss of motor neurons over time, the longer the delay in treatment the more motor neurons and associated function will be lost. This loss is not recoverable.

With regard to the approval criteria I have several comments:

Criteria #3 states that patients whose gestational age is less than 37 weeks and more than 42 weeks are excluded. I am not sure of the relevance of this, although I speculate that the goal is to exclude patients with motor disability based on central nervous system problems such as: Cerebral Palsy (CP). I think that it would be inappropriate to exclude patients with mild CP who have the potential to walk. Therefore, an assessment to demonstrate the presence of CP could be done by a Developmental Pediatrician and might include a brain MRI Study if there is a suspicion of CP. The exclusion of patients greater than 42 weeks gestation, is unclear.

Criteria #4 is unclear why patients greater than 7 months of age should be excluded. Although most patients with SMA I will present prior to the age of 7 months, there are occasional patients with SMA I who may present later. In addition, patients with SMA II whose clinical course is usually milder but may overlap SMA I patients, should also be included in the treatment protocol as should some patients with SMA Type III in order to maintain their motor function.

Criteria #5 some patients with SMA Type I may have three copies of the SMN2 gene, so if you are going to limit approval for patients with SMA I it should be two or three copies.

Summary: Having worked with patients and families with SMA for the past 40 years with only supportive care available to help maintain their function, the introduction of this antisense oligonucleotide drug to increase production of the SMN protein is truly miraculous. These families now have hope that their children may have vastly more functional lives with far less disability than in the past. From the purely financial standpoint, support of a ventilator dependent patient with SMA I over a lifetime (which may go over several decades with proper pulmonary management) is likely to be significantly expensive and therefore maintaining their function with these medications may in the long run reduce this cost. I would urge you to strongly consider approval of Spinraza, not only for patients with SMA Type I, but also patients with Type II and Type III SMA.

From: Mariam Ischander
Sent: Friday, June 23, 2017 7:51:47 PM
To: Pharmacy Drug Information
Subject: Nusinersen

Nusinersen gave a hope to a fatal disease which is spinal muscular atrophy, so far we have given to few patients in our institution without seeing any bleeding or renal toxicity/proteinuria or low platelets. I think SMA patients should be given the chance for Nusinersen and the outcome to be evaluated separately for every individual patient. it is an FDA approved medication and so patient has the right for access to the medication especially for a fatal disease.

From: Coral Hamill
Sent: Tuesday, June 27, 2017 9:14:19 AM
To: Pharmacy Drug Information
Subject: Dmd

I believe it is unfair to not allow this boys who can benefit from this medication to not be allowed to have it. If it can change the lifes of few to many it is worth it!

Coral hamill

From: Chafic Karam
Sent: Wednesday, June 21, 2017 2:37:38 PM
To: Pharmacy Drug Information
Subject: Spinraza

June 21, 2017

Dear Oregon Drug Use Review / Pharmacy & Therapeutics Committee:

It is with great concern that I learned about the change in Oregon Medicaid policy to restrict access to Spinraza (Nusinersen) to Type 1 SMA patients only. Although I understand the rationale behind the change in policy, I cannot agree with it for several reasons.

First of all, it is essential to consider the mechanisms of action of Spinraza. As you know, SMA is caused by the loss of the SMN1 gene, resulting in low SMN protein levels. The human genome has an additional SMN2 gene that produces low levels of full-length SMN but cannot adequately compensate for the loss of SMN1 due to an aberrant splicing. Spinraza is a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide which promotes SMN2 exon 7 retention in the mature SMN2 transcripts, increasing SMN protein expression in SMA cells. Thus, all patients with SMA would benefit from Spinraza regardless whether they are type 1, 2, 3 or 4.

Second, there are increasing reports in the neuromuscular community of patients with SMA other than type 1 who have already benefited objectively from the treatment outside of trials. For example one patient in Texas with type 2 SMA who could not sit, is now sitting after 3 doses. Another patient in Arizona with type 3 SMA has after 3 doses regained the ability to walk on his knees, and they are removing the trunk lateral supports from his power wheelchair because he no longer needs it.

Third, many of my patients are still working despite being disabled. They are productive members of society and their families depend on them. They rely on their last working muscles, especially those that control fingers functions to be able to carry their work, control their motorized wheelchair, feed themselves and remain partially independent. Losing those critical functions will be devastating for our patients and their families.

For those reasons, I urge the committee to consider the impact of their decisions on the life of Oregonians with SMA, and to change the policy back to include treatment for all SMA patients as it was originally approved by the FDA and the European Medicines Agency.

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From: Carrie Grant
Sent: Tuesday, June 27, 2017 10:44:24 AM
To: Pharmacy Drug Information
Subject: eteplirsen

An article published in the [New York Times](#) this week showcases the problems many Duchenne muscular dystrophy (DMD) patients are having in acquiring access to the recently approved Exondys 51 (eteplirsen).

DMD, a progressive, degenerative muscle disorder, is caused by a lack of functional dystrophin, and symptoms typically begin in early childhood. By the time a boy is in his early teens, he is often wheelchair bound. As the disease progresses, the patient's muscles will continue to deteriorate and most will die in their 20s.

Exondys 51 treats boys with DMD amenable to exon 51 skipping therapy.

The primary issue that payors have regarding the drug is that it was approved based on data that was very conclusive based on the patients' testimonials, but somewhat questionable from a statistically perspective. The drug was given an Accelerated Approval by the FDA last year, which means the company developing it, Sarepta, is currently conducting a Phase 3 study to confirm that the drug is effective.

The accelerated approval along with the statistical uncertainty of the drug's efficacy, means that while the drug is approved, some insurance companies would prefer to wait until more data is available before paying for it.

PLEASE RECONSIDER!!!

From: Helen Kim
Sent: Thursday, July 13, 2017 12:00:29 PM
To: Pharmacy Drug Information
Subject: Written Testimony Submission

My name is Helen Kim, PharmD and I am a Medical Science Liaison with Synergy Pharmaceuticals, a biopharmaceutical company focused on the development and commercialization of novel gastrointestinal (GI) therapies. On January 19, 2017, TRULANCE™ (plecanatide) was approved for the treatment of adults with chronic idiopathic constipation (CIC), dosed at 3mg once daily, taken with or without food. CIC is one of the most common functional GI disorders in the United States, affecting approximately 33 million adults and studies consistently demonstrate impaired quality of life for those affected. Insufficient fluid levels in the gut lumen may lead to constipation and many patients attempt to manage their symptoms with improved diet, over-the-counter (OTC) laxatives, and currently available prescription medications. However, these options may fail to provide relief and/or may be associated with poor tolerability. Thus there remains a significant need for new treatment options.

TRULANCE is a 16 amino-acid peptide structurally identical to human uroguanylin, with the exception of a single amino acid. Uroguanylin is a naturally-occurring GI peptide that plays an important role in supporting normal bowel function by regulating fluid and electrolyte secretion into the GI tract. It is an endogenous agonist that binds and activates guanylate cyclase-C (GC-C) receptors expressed on the epithelial lining of the GI mucosa, and it does so in a pH-sensitive manner. This enables uroguanylin to have greatest activity primarily in the proximal small intestine, the site of normal physiological fluid secretion. Activation of the GC-C receptors results in elevation of intracellular cyclic guanosine monophosphate. This, in turn, stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the cystic fibrosis transmembrane conductance regulator ion channels. The resulting ionic gradient promotes fluid secretion that serves to hydrate stool and facilitate bowel movements. Like uroguanylin, TRULANCE activates GC-C receptors, and only TRULANCE is thought to replicate the pH sensitivity of naturally occurring uroguanylin.

The efficacy and safety of TRULANCE for CIC was established in two large Phase 3, 12 week, randomized, double-blind, placebo-controlled trials. The primary endpoint was met in both studies, in which TRULANCE significantly increased the percentage of patients who were efficacy responders compared to placebo ($p < 0.001$), with improvements noted within one week and sustained throughout treatment. Significant improvements in bowel movement frequency, stool consistency and straining were also observed. The safety results demonstrated that TRULANCE was well tolerated, and resulted in a low overall incidence of adverse events and discontinuations. Diarrhea was the most common adverse event and was reported in 5% of patients randomized to TRULANCE vs 1% of patients randomized to placebo. TRULANCE is contraindicated in patients less than 6 years of age due to the risk of serious dehydration and in patients with known or suspected mechanical gastrointestinal obstruction. The use of TRULANCE should be avoided in patients 6 years to less than 18 years of age.

In summary, the approved dosing regimen for TRULANCE is 3 mg taken orally, once daily, with or without food. TRULANCE offers patients with CIC a new treatment option with proven efficacy and safety, and we hope you consider adding TRULANCE to the formulary.