Pharmacy Focus: Spinal Muscular Atrophy (SMA) Treatment

SMA Overview

In the United States, Spinal Muscular Atrophy (SMA) affects approximately 9,000 individuals, with 400 babies being born with SMA each year. SMA is a genetic disorder that results in motor neuron loss in the spinal cord. For people without SMA or those who carry only one SMA gene, the SMN1 gene produces adequate amounts of SMN protein for the body. For those diagnosed with SMA, not enough SMN protein is produced, so toxic byproducts accumulate and cause motor neuron loss, which makes the brain unable to stimulate the spinal cord. This ultimately progresses into muscle weakness and wasting in areas of the body that include the arms, legs, neck and trunk, creating reduced or total inability to sit or stand, and even eating and/or breathing can be difficult without mechanical support.

SMA is an autosomal recessive disorder, meaning that the affected gene has to be inherited from both parents for the disease to be expressed. There are several different types of SMA, and they are defined by the genetic mutation of both SMN1 gene copies and the number of SMN2 "backup" genes located on chromosome 5. Since the SMN2 gene only produces 10 percent to 15 percent of the SMN proteins compared to SMN1 genes, the severity of SMA is determined by the number of copies of the SMN2 gene. When three or more copies are present, the disease symptoms may be less severe and have a later onset of symptoms.

Traditional SMA treatment involves managing the patient's symptoms through physical therapy, breathing exercises and chest physiotherapy. As the disease progresses, use of mechanical ventilation and feeding tubes often is inevitable. Today, three highly specialized pharmaceuticals have become options for potentially helping to slow the progression of severe forms of SMA – Zolgensma®, Spinraza® and Evrysdi®.

SMA Treatment Plan Considerations

- 60 percent of the identified cases are SMA type I
- There is a 25 percent chance siblings of the same biologic parents will express the gene
- Because SMA genetic testing is still positive AFTER receipt of Zolgensma®, it is plausible that an infant born onto a plan could receive Zolgensma®, Spinraza® and Evrysdi® all in one plan year, especially if the policy is based on a genetic test
- Policyholders should know the health plan's criteria for use of pharmaceuticals, considering the following:
  - Spinraza® and Zolgensma® are billed under medical benefits, and Evrysdi® is billed under pharmacy benefits; it's necessary to understand the health plan's medical and pharmacy policies for all of these products
  - For patients not be eligible for Zolgensma®, there are trials reviewing concomitant use of Spinraza® and Evrysdi®
  - Concomitant use of Zolgensma® with Spinraza® is currently investigational in most medical policies due to lack of strong clinical evidence, but Spinraza® may be started/restarted for disease progression after Zolgensma® since the mutated SMN1 genes are still present

SMA Pharmaceuticals Can Come with Multimillion-Dollar Costs

- Average cost of Spinraza® can reach $850,000 (first year) and up to $400,000 (every year after for life)
- Estimated baseline cost of Zolgensma® is $2,125,000 for the one-time therapy
- Evrysdi® costs can be $370,000 to 400,000 per year, indefinitely
- In certain instances, treatments can be used in combination, further escalating costs

Notifying HM Insurance Group of a member diagnosed with SMA is required and helps to ensure engagement with up-to-date knowledge and resources for proactive cost containment opportunities.

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Treatment Option Details

	Spinraza® (nusinersen)	**Evrysdi®** (risdiplam)	**Zolgensma®** (onasemnogene abeparvovec-xioi)
FDA Approved Uses	FDA approved for children and adults	FDA approved for persons 2 months and older	FDA approved for pediatric patients up to 2 years of age
Cost and Medical Benefit	$850,000 first year; $400,000 every year thereafter*	$370,000 to 400,000 per year, indefinitely*	>$2,125,000 once in a lifetime*
Payment Structures	Medical Benefit HCPCS: J2326	Prescription Benefit NDC 50242-175-07	Medical Benefit HCPCS: J3399

**Prices are estimates and subject to change; the prices listed do not include any ancillary charges or additional costs that may be incurred when therapy is in use.*

Types of SMA and Treatment Options by Type

Type of SMA	**Typical Number of SMN2 Proteins**	**Disease Description**	**Most Medical Policies**		
			Spinraza®	**Evrysdi®**	**Zolgensma®**
Type 0	1	• Most severe form • Begins before birth • Lifespan: Approximately 2-6 months			
Type I (Most Common)	1 to 3	• Werdnig-Hoffmann disease – weakness at <6 months old • Feeding difficulty • Survival is largely dependent on respiratory function • Lifespan: <2 years without intervention or >20 years with intervention	**X**	**X**	**X**
Type II	2 to 3	• Intermediate or chronic SMA • Symptoms start around 6 to 12 months of age • Highest motor function attained is sitting independently, and this milestone often is lost by mid-teens • Lifespan: Usually normal	**X**	**X**	**X**
Type III	3 to 4	• Kugelberg-Welander syndrome • Disease starts at >12 months; subtype 3a onset <3 years; subtype 3b onset >3 years • Symptoms of muscle weakness occur after walking milestones have been achieved • Lifespan: Usually normal	**X**	**X**	
Type IV	≥4	• Adult onset • Least severe form • Many are able to walk into their 60s • Lifespan: Usually normal			

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Zolgensma® FDA Timeline

With advancements, especially those being touted as "curative," come challenges – and questions. The information shared below provides a timeline regarding the data provided by the manufacturer of Zolgensma® and the FDA response. Of particular note is the delay in approval for Zolgensma® use in children over two years of age that came to light in September 2020 and is elaborated on below.

May 2019

The FDA approves Zolgensma®, an AveXis/Novartis product for SMA patients <2 years old meeting additional criteria.

June 2019

AveXis/Novartis informs the FDA of data manipulation around animal testing that was submitted to the FDA with regard to Zolgensma®.

August 2019

The FDA revealed notification by Novartis in June that the company submitted manipulated preclinical animal data in the original application, and the FDA indicated that it is carefully assessing and believes Zolgensma® should remain in the U.S. market.

October 2019

The FDA partially suspended the STRONG trial, placing a safety hold on the high dose formulation of the intrathecal (spinal) injection after concerns of neurologic damage in primates.

March 2020

The FDA investigatory team completed the review on data manipulation and took no further action.

September 2020

The FDA requests a new clinical trial to support the findings of the STRONG trial for intrathecal administration in SMA patients >2 years old; this trial cannot begin until the FDA lifts the clinical hold from 2019.

2023

The earliest that Zolgensma® use would likely be expanded.

Pharmacy Focus provides valuable information about pharmaceutical industry developments and their associated costs that can impact the growing claims trend in the self-funded insurance market. Be aware of influences and gain insight into approaches that may help to contain costs. Please share topic suggestions or feedback with **HMPharmacyServices@hmig.com**.

References: Rare Disease Database-Spinal Muscular Atrophy, NORD, https://rarediseases.org/rare-diseases/spinal-muscular-atrophy/, accessed August 11, 2020; SMN1 gene, Genetics Home Reference, https://ghr.nlm.nih.gov/gene/SMN1#:~:text=The%20SMN1%20gene%20provides%20instructions%20for%20making%20the,maintenance%20of%20specialized%20nerve%20cells%20called%20motor%20neurons, August 14, 2020; Spinal Muscular Atrophy, GARD, https://rarediseases.info.nih.gov/diseases/7674/spinal-muscular-atrophy, accessed August 11, 2020; Spinal Muscular Atrophy 1, GARD, https://rarediseases.info.nih.gov/diseases/7883/spinal-muscular-atrophy-1, accessed August 11, 2020; Spinal Muscular Atrophy type 2, GARD, https://rarediseases.info.nih.gov/diseases/4945/spinal-muscular-atrophy-type-2, accessed August 11, 2020; Spinal Muscular Atrophy type 3, GARD, https://rarediseases.info.nih.gov/diseases/198/spinal-muscular-atrophy-type-3, accessed August 11, 2020; Spinal Muscular Atrophy - A devastating disease now has 2 approved breakthrough treatments available, Practical Neurology, https://practicalneurology.com/articles/2019-aug-july/spinal-muscular-atrophy, accessed August 14, 2020; EVRYSDI™ (risdiplam) [prescribing information], Genentech, https://www.gene.com/download/pdf/evrysdi_prescribing.pdf, accessed August 11, 2020; Spinraza [prescribing information], Biogen, https://www.spinraza.com/content/dam/commercial/spinraza/caregiver/en_us/pdf/spinraza-prescribing-information.pdf, accessed August 11, 2020; Zolgensma [prescribing information], AveXis, https://www.avexis.com/us/Content/pdf/prescribing_information.pdf, accessed August 11, 2020; Risdiplam Raising SMN Levels in Older Patients in Ways That Seem Durable, Researcher Says of Early Trial Data, SMA News Today, https://smanewstoday.com/2019/07/19/risdiplam-raising-smn-protein-levels-in-durable-ways-in-older-patients-researcher-says-in-interview/, accessed August 11, 2020; Evrysdi [prescribing information] https://www.gene.com/download/pdf/evrysdi_prescribing.pdf, accessed August 17, 2020.

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