Product Sheet

Key Message for the Visitor:

Doctor, how are you? My name is _____ from Biogen. Today, I would like to talk to you about Spinal Muscular Atrophy (SMA), a severe, disabling, and potentially fatal neuromuscular disease. Although rare among neuromuscular diseases, it is one of the first conditions you should suspect and rule out, as it can be treated with disease-modifying therapies like Spinraza (Nusinersen). This treatment can change the natural history of the disease and provide a longer life expectancy and better quality of life for your patient. SMA has a broad clinical spectrum and is classified into 5 phenotypes based on the age of onset of symptoms and the motor function achieved. Signs and symptoms affecting the psychomotor development and health of the patient begin within the first months or years of life. The earlier the onset, the faster and more severe the disease progression. Patients often present with a delay or regression in motor development or symptoms of muscle weakness. If there are any difficulties or delays in achieving motor milestones, do not wait, doctor. Examine your patient for the following symptoms:

- Peripheral hypotonia
- Generalized muscle weakness with more significant proximal involvement
- Hypo/areflexia
- Tongue fasciculations or distal tremors
- Bulbar or respiratory involvement
- No cognitive or sensory impairment

This is a patient with a high clinical suspicion of Spinal Muscular Atrophy, and the diagnosis can be confirmed with a Genetic Study (MLPA) for the SMN1 and SMN2 genes. Biogen offers a diagnostic program that supports these tests free of charge. Remember, doctor, time is critical in SMA. Early diagnosis and treatment can change the course of the disease. The patient will progressively lose all motor function and experience severe respiratory, nutritional, and orthopedic complications. In the most severe cases, life expectancy is no more than 2 years. Today, doctor, you can change the prognosis of SMA for your patients and their families. The first step is to suspect and diagnose the disease. I am here to help you with this process.

Tips for the Visitor:

Always ask for complete information about patients suspected of Spinal Muscular Atrophy (SMA). If the suspected patient has symptoms very similar to SMA, suggest the doctor conduct the "Diagnostic Test for Spinal Muscular Atrophy" to confirm if the patient has SMA.

Frequently Asked Questions:

What is Spinal Muscular Atrophy (SMA)? Spinal Muscular Atrophy (SMA) is a rare orphan disease with a high impact on the life expectancy and quality of life of those affected. It is a

neuromuscular disorder caused by a mutation/deletion in the SMN1 gene, which produces the SMN protein (survival of motor neurons). People with SMA do not produce enough SMN protein, leading to the degeneration of motor neurons in the anterior horn of the spinal cord and progressive muscle weakness and atrophy. Although there is no cure, there is treatment available. The disease has an incidence of 1 in every 10,000 live births. The prevalence of SMA is 1–2 patients per 100,000 individuals. It is the leading genetic cause of infant mortality. SMA has a broad clinical spectrum and is classified into 5 phenotypes based on the age of onset of symptoms and the motor function achieved. The patient's quality and life expectancy can vary depending on the SMA phenotype. SMA is an autosomal recessive disease, meaning both parents must carry the gene, and each pregnancy has a 25% chance of resulting in a child with SMA. It is estimated that the carrier rate is 1 in 50 individuals. We educate about SMA 5Q, which is the most common form (95% of cases) and is named after the location of the gene mutation. However, other non-5Q SMAs (5%) do not have pharmacological treatment options.

When should I suspect the disease? Spinal Muscular Atrophy has three cardinal signs: hypotonia, weakness, and hypo/areflexia. The earlier the onset, the more rapid and severe the symptoms. There are two main pathways for initial diagnosis based on the severity and progression of SMA symptoms and comorbidities (phenotype):

1. **Respiratory complications:** More common in early-onset patients due to significant respiratory involvement caused by chest muscle weakness. Although the initial signs may have been hypotonia, weakness, and hypo/areflexia, these may have gone unnoticed by the physician, leading to rapid respiratory complications that can result in a critical acute event requiring emergency care. In this context, the physician should evaluate these symptoms and suspect SMA. This pathway is critical because it may be too late for the patient to recover from the respiratory crisis and may result in death. Therefore, early suspicion of cardinal signs is crucial to prevent rapid disease progression and low therapeutic opportunities.

2. **Delays or regressions in motor development:** The main reasons for consultation for an infant with SMA are: "My child hardly moves, is very calm, doesn't cry," "The child's head droops," "He doesn't take his bottle or breast milk," "His voice is very soft," "He doesn't sit," "He doesn't crawl," "He hasn't started to crawl or stand"... If the child is older: "He hasn't started to walk," "He started walking and falls a lot or can't walk anymore," "He's very lazy, doesn't exercise," "He can't climb stairs properly," "He falls frequently," "He struggles to get out of bed or a chair"... Sometimes doctors dismiss these signs of motor development difficulties or tell parents to wait because it's normal for the child to take time to reach motor milestones. This is a mistake that can delay the diagnosis for years. The physician should evaluate these cardinal signs during a clinical consultation and, if present, conduct a more in-depth examination of the symptoms associated with the disease with a neurological evaluation. There are motor function evaluation scales associated with the patient's age, and the WHO has established ages for reaching motor milestones.

How do I differentiate SMA from other neuromuscular diseases? The three cardinal signs are a key differentiator of SMA from other neuromuscular diseases. The patient should exhibit

all three signs, although one may be more or less pronounced. Peripheral hypotonia and greater proximal to distal weakness are notable features. The absence or reduction of osteotendinous reflexes is a significant differentiator, and tongue fasciculations (in younger patients) or hand polyclonus (in older patients) should always be checked. A crucial differentiator for SMA patients compared to other neuromuscular diseases is that SMA patients have intact cognition and sensory perception. These patients have full mental capacity and cognitive abilities appropriate for their age. SMA can be confused with other neuromuscular diseases:

- Congenital or hypomyelinating neuropathies
- Hereditary sensory and motor neuropathies
- Congenital myopathies
- Myotonic or muscular dystrophies
- Mitochondrial or metabolic myopathies
- Myasthenias
- Congenital myasthenic syndromes
- Botulism
- Duchenne/Becker Muscular Dystrophy
- Pompe Disease
- Charcot-Marie-Tooth Disease
- Guillain-Barré Syndrome
- Amyotrophic Lateral Sclerosis (ALS)
- Non-5q SMA

A detailed clinical analysis and specific medical tests, such as CK transaminases or EMG, can help the physician differentiate SMA from other neuromuscular diseases by identifying whether the damage originates in the muscle (e.g., DMD), the neuromuscular junction (e.g., myasthenias), the peripheral nerve (e.g., neuropathies), or the motor neuron (as in SMA). It is recommended that the physician conducts a thorough semiological evaluation of the patient. If there is a high suspicion of SMA due to the presence of several symptoms (and possibly a genetic background, such as consanguinity or living in a highly endogamous area), the genetic test should be ordered to confirm the diagnosis. Among genetic neuromuscular diseases, SMA is one of the most "common" and has treatment options that change the natural course of the disease. Therefore, the physician should consider SMA one of the first conditions to suspect and diagnose when encountering such a clinical picture.

How do I diagnose SMA? Once clinical suspicion is established, the physician should request a diagnostic genetic test. The gold standard is the MLPA Genetic Study (Deletions/Duplications) for the SMN1 and SMN2 genes. This test can be requested through

Biogen, with the RDAE guiding the physician through the request and sample collection process with the testing laboratory in each country. This test is free, and the physician will receive the patient's results directly 3 to 4 weeks after the sample is taken.

In Mexico, the physician can request a saliva or blood sample collection kit, collect the sample themselves, and schedule sample collection. In Colombia, the physician issues an order for the patient to have the sample taken at the institution's laboratory (which has the kit) or another center, or the sample can be taken at home. The laboratory coordinates directly with the patient for sample collection. In both Colombia and Mexico, the physician can also request the genetic test through the health system or with a competitor.

Why should I diagnose SMA? SMA is a chronic, progressive, highly disabling, and potentially fatal disease. Early diagnosis provides a greater therapeutic opportunity for the patient and a better prognosis for the disease. The physician is in a race against time to prevent further loss of motor neurons and greater irreversible physical impairment. A patient with SMA Type 1, which accounts for 60% of cases, will not be able to sit independently and will die before the age of two. Early diagnosis and treatment can save the patient's life and prevent outcomes such as tracheostomy and gastrostomy. A patient with SMA Type 2 or Type 3, which accounts for 35% of cases, may have a longer life expectancy and reach adulthood but will rapidly lose acquired motor skills (sitting (SMA 2) or walking (SMA 3)). This significantly reduces quality of life and independence. Early diagnosis can prevent the patient from being bedridden or confined to a wheelchair, limiting personal, professional, and social development opportunities, as well as the multisystem complications associated with the condition. A patient with SMA Type 4 (<5%) will progressively lose motor function, limiting mobility and independence, and impacting the patient's psychosocial well-being. Therefore, it is crucial not to overlook this disease early, as it is treatable.

What should I do with my patient diagnosed with SMA? Once diagnosed, the patient should be evaluated for the therapeutic window for pharmacological treatment with Spinraza (validate the indication in the country) and set therapeutic goals over time. Rapid initiation of treatment ensures less time for disease progression and generally better outcomes with therapy. To do this, the patient should be referred to a multidisciplinary team to assess the current disease state and establish clinical goals with therapy and comprehensive management focused on:

- **Motor function:** Physical rehabilitation is the main pillar of treatment to provide the patient with a better quality of life and independence. It is crucial to evaluate the patient's motor function with a specific SMA scale that establishes the baseline score (objective) to assess disease progression and/or treatment outcomes over time. This scale can be administered by a rehabilitation therapist, physiatrist, or pediatric neurologist. Different scales apply depending on the type and age:
    - SMA TYPE 1: HINE-2, CHOP INTEND.
    - SMA TYPE 2, 3, and 4: HFMSE, RULM, and 6MWT (the latter for ambulatory patients).

- **Respiratory and nutritional function:** The goal is to prevent the progression of respiratory complications that could lead to permanent ventilation (or tracheostomy) and bulbar complications that may require assisted feeding (nasogastric tube or gastrostomy). Proactive rehabilitation therapy and nutritional support are essential to prevent malnutrition or obesity in the patient.
- **Orthopedic management:** Due to muscle weakness, the patient may develop contractures or scoliosis. Proactive management with devices, therapy, or surgery can reduce these comorbidities.
- **Others:** The patient will also require psychological support, genetic counseling (for the family), and management from other specialties such as endocrinology.

What is the therapeutic opportunity for SMA with Spinraza (Nusinersen)? Spinraza (Nusinersen) is the first disease-modifying therapy for SMA that has demonstrated a change in the natural history of the disease for all phenotypes and ages of SMA patients. It acts directly on the disease's origin by helping produce the missing SMN protein in the body, halting or delaying disease progression. The best results have been seen with earlier diagnosis and treatment. Pharmacological treatment with Spinraza should be part of a comprehensive management plan for the patient, involving a multidisciplinary team. Therapeutic goals should be set according to the patient's baseline function and phenotype, focusing primarily on stabilizing the disease, maintaining and/or gaining mobility, and preventing health complications over time. The aim is to ensure the patient's well-being, independence, and social inclusion.

Common Objections: "It's a fatal disease, and there's nothing we can do. The patient will soon die, so it's not worth diagnosing and causing that emotional burden to the family." I understand your concern about the emotional impact that an SMA diagnosis can have on families. However, early diagnosis opens the door to disease-modifying treatments like Spinraza (Nusinersen), which have been shown to significantly improve patients' quality of life and life expectancy. Not diagnosing means missing the opportunity to offer hope and tangible support to affected families.

"It's a very rare disease that will never come to my office." Although SMA is a rare disease, the impact of an early diagnosis on patients who do have it is profound. As healthcare professionals, we must be prepared for all possibilities, especially when effective interventions are available. Additionally, diagnosing even a single case can completely change that patient's and family's life.

"The therapeutic opportunity is not significant. It's better not to treat the patient and let the disease progress and lose motor function." Recent advances in therapies for SMA have dramatically changed the prognosis for many patients. These therapies can slow and even stop disease progression, allowing patients to maintain mobility and motor function longer than previously possible. Refusing to explore these options denies patients the possibility of a better quality of life.

"It's very difficult to order the genetic test, and the results take too long. The patient is lost." I understand that obtaining genetic tests can seem daunting. However, support programs like

the one offered by Biogen facilitate this process free of charge for patients and their families. These programs are designed to ensure patients are not lost in the system and that results are delivered promptly, allowing for rapid diagnosis and treatment.

"Since I'm not going to treat the disease, I can't do anything for the patient. It's better to refer them to another specialist who can order the test." Even if you do not personally treat SMA, your role in early diagnosis is crucial. Referring a patient to a specialist without a preliminary diagnosis can significantly delay access to vital treatments. By identifying and suspecting SMA and facilitating the initial diagnosis, you play a vital role in the patient's path to treatment. Additionally, collaborating with specialists from the outset can improve care coordination and support for the patient and their family.