

CADTH Reimbursement Review

Onasemnogene Abepravovec (Zolgensma)

Sponsor: Novartis Pharmaceuticals Canada Inc.

Indication: For the treatment of pediatric patients with 5q spinal muscular atrophy (SMA) with biallelic mutations in the survival motor neuron 1 (*SMN1*) gene and:

- 3 or fewer copies of the *SMN2* gene or
- infantile-onset SMA

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Background

In the March 2021 [CADTH Canadian Drug Expert Committee Recommendation](#) for onasemnogene abeparvovec, the CADTH Canadian Drug Expert Committee recommended that onasemnogene abeparvovec be reimbursed for the treatment of pediatric patients with 5q spinal muscular atrophy (SMA) with biallelic mutations in the survival motor neuron 1 (*SMN1*) gene, only if the following conditions are met.

Conditions for Reimbursement

Initiation criteria

1. Genetic documentation of 5q spinal muscular atrophy with biallelic mutations in the *SMN1* gene.
2. Patients who are:
 - 2.1. symptomatic or pre-symptomatic with 1 to 3 copies of the *SMN2* gene
 - 2.2. 180 days of age or younger
 - 2.3. not currently requiring permanent feeding or ventilatory support (either invasive or non-invasive).

Prescribing conditions

1. Patient must be under the care of a specialist with experience in the diagnosis and management of spinal muscular atrophy.
2. Reimbursement is limited to 1 lifetime administration of onasemnogene abeparvovec.

Pricing conditions

1. A reduction in price.

The CDEC recommendation notes that the genetic testing required to confirm the presence of biallelic mutations in the *SMN1* gene (i.e., newborn screening) is not currently available in all jurisdictions. Given the absence of newborn screening in some jurisdictions, it is anticipated

Table 1: Drug Details

Criteria	Description
Drug	Onasemnogene abeparvovec (Zolgensma), given as a single-dose IV infusion of 1.1×10^{14} vector genomes/kg
Indication	For the treatment of pediatric patients with 5q SMA with biallelic mutations in the survival motor neuron 1 (<i>SMN1</i>) gene and: <ul style="list-style-type: none"> • 3 or fewer copies of the <i>SMN2</i> gene or • infantile-onset SMA
Dosage form	IV infusion
NOC date	December 15, 2020
Manufacturer	Novartis Pharmaceuticals Canada Inc.

NOC = Notice of Compliance; SMA = spinal muscular atrophy.

that many patients will be diagnosed upon presentation of SMA symptoms, which could occur at an age after 180 days.

A request was received from the pan-Canadian Pricing Alliance and CADTH participating drug plans to develop clinical criteria that could be used to identify SMA patients older than 180 days who are most likely to benefit from treatment with onasemnogene abeparvec. These criteria may be used on a case-by-case basis until such time that newborn screening is available in all jurisdictions.

Implementation Advice Request

For SMA patients with 1 to 3 *SMN2* gene copies who are between the ages of 180 days and 2 years, what characteristics could be used to identify those patients who are most likely to benefit from treatment with onasemnogene abeparvec? Specifically addressing the following elements:

- **Objective clinical criteria:** What objective clinical criteria can be used to identify patients most likely to respond?
- **Prior therapy:** Provide guidance regarding the use of onasemnogene abeparvec in patients who have received prior therapy with a drug approved in Canada for use in the treatment of SMA.
- **Exclusion criteria:** Provide guidance on exclusion criteria for those patients between the ages of 180 days and 2 years who should not be treated with onasemnogene abeparvec.
- **Response criteria:** Provide guidance on how response to onasemnogene abeparvec should be evaluated.

At the request of the participating drug programs, CADTH reviewed the available evidence and input received from Canadian clinical experts as part of the review of onasemnogene abeparvec to provide advice to address the outstanding issues noted in the implementation advice request.

Consultation Process and Objectives

The clinical expert panel comprised 4 Canadian specialists with expertise in the diagnosis and management of patients with SMA. The objective of the panel was to provide advice to the participating drug programs regarding the outstanding issues noted in the Implementation Advice Request section. A consensus-based approach was used, and input was sought using surveys, questionnaires, and/or panel meetings (as required).

The advice presented in this report is not necessarily evidence-based, but it has been developed based on the experience and expertise of the implementation advice panel members and, as such, represents experience-informed opinion.

Implementation Advice

Implementation Issues

The implementation advice from the clinical experts is summarized in Table 2. For each issue, a summary of the relevant input is also provided for additional context.

Objective Clinical Criteria

- Provide advice on objective clinical criteria to identify SMA patients with 1 to 3 *SMN2* gene copies between the ages of 180 days and 2 years who are most likely to respond to treatment with onasemnogene abeparvovec.

For SMA patients with 1 to 3 *SMN2* gene copies and between the ages of 180 days and 2 years, there is currently insufficient evidence available to identify which patients are most likely to benefit from treatment with onasemnogene abeparvovec or to inform treatment and reimbursement decisions in this age group. Evidence for the efficacy of onasemnogene abeparvovec from the STR1VE-US, STR1VE-EU, and START studies represents patients with SMA who are up to 6 months of age, have 2 copies of *SMN2*, do not require mechanical support for nutrition, and receive invasive or non-invasive ventilation for less than 12 hours daily. The SPR1NT study provides evidence of efficacy of onasemnogene abeparvovec in children with pre-symptomatic SMA and treated within 6 weeks after birth. The clinical experts indicated that, given the mechanism of action of onasemnogene abeparvovec and the considerable heterogeneity in disease presentation and progression with SMA, extrapolating the available evidence beyond patients with SMA type I and the populations enrolled in the onasemnogene abeparvovec trials is not appropriate.

By 6 months of age, patients with SMA type I are typically severely affected with irreversible neurological injury if untreated with a SMN upregulator. Although a diagnosis may be delayed for some patients, children with severe disease are less likely to improve with treatment. Due to the lack of evidence-based guidelines, case-by-case decision-making may be based on anecdotal evidence, which can be highly divisive, according to the clinical experts. There is a need for additional clinical trials to evaluate the use of onasemnogene abeparvovec in SMA patients with 1 to 3 *SMN2* gene copies who are older than 6 months.

Table 2: Summary of Advice for Addressing Implementation Issues

Issue	Advice
Objective clinical criteria	The experts were unable to provide definitive guidance on reimbursement criteria for onasemnogene abeparvovec for children between 180 days and 2 years of age due to insufficient evidence on the efficacy and safety of onasemnogene abeparvovec in this age group; factors related to the disease, such as the irreversible loss of motor neurons; and the large heterogeneity in disease presentation and progression beyond SMA type I.
Prior therapy	Unable to provide guidance.
Exclusion criteria	Patients requiring permanent ventilatory support. ^a
Response criteria	Response would depend on the patient’s baseline motor function and age. Motor function is the primary outcome to assess; other important outcomes include respiratory function, bulbar function, and survival.

^aThe general definition of “permanent ventilation” in the onasemnogene abeparvovec studies was the need for a tracheostomy or requirement of 16 hours or more of respiratory assistance per day (via non-invasive ventilatory support) for 14 or more consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation.

The clinical experts noted that there are 2 drugs approved in Canada for patients with SMA who are older than 6 months, and these drugs have evidence of efficacy and safety in this age group. Thus, there are treatments available for infants not eligible to receive onasemnogene abeparvovec.

One clinical expert advised that children in this age group could be considered for case-by-case reimbursement of treatment with onasemnogene abeparvovec if they had received treatment with another SMN upregulator before 6 months of age and were not receiving permanent ventilation. It was noted that there is insufficient evidence to support this approach (see Criteria Based on Response to Prior Therapy).

The clinical experts were unable to provide further guidance on reimbursement criteria for onasemnogene abeparvovec in children between 180 days and 2 years of age.

Prior Therapy

- Provide guidance regarding the use of onasemnogene abeparvovec in patients who have received prior therapy with a drug approved in Canada for use in the treatment of SMA, including those who are currently responding to treatment, have an inadequate response, or have demonstrated an initial response but have subsequently declined and are no longer responding.

There is no robust clinical data available on the efficacy of onasemnogene abeparvovec in patients who have previously been treated with nusinersen or risdiplam. The experts stated that because onasemnogene abeparvovec and nusinersen both increase the amount of the SMN protein, and due to the lack of robust clinical data, there is nothing to suggest that non-responders to nusinersen would respond to onasemnogene abeparvovec. Further benefit from sequential therapies is not supported by sufficient evidence and may not be realistic depending on the stage of disease (i.e., if patients have incurred irreversible damage).

Exclusion Criteria

- Provide guidance on exclusion criteria for those patients between the ages of 180 days and 2 years who should not be treated with onasemnogene abeparvovec.

Patients requiring permanent ventilatory support should be excluded. One expert suggested that children in this age group with 2 copies of the *SMN2* gene or fewer who have not been previously treated with another SMN upregulator should be excluded.

Response Criteria

- Provide guidance on how response to onasemnogene abeparvovec should be evaluated.

The experts stated that assessment of response would depend on the patient's baseline motor function and age. Outcome measures may include the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), the Hammersmith Infant Neurological Exam (HINE) (SMA type I), the Revised Hammersmith Scale or Hammersmith Functional Motor Scale Expanded (HFMSSE) (SMA type II or III), the 4-stair climb, the Get-Up-and-Go Test, the Revised Upper Limb Module, and nerve conduction studies. Motor function is the primary outcome to assess; other important outcomes include respiratory function, bulbar function, and survival. Pre-symptomatic patients would be expected to achieve their developmental milestones within the expected age range of healthy infants; for patients with a more advanced stage of disease, stability would be clinically meaningful.

The experts also indicated that some of the outcome measures, such as the CHOP INTEND and the HFMSE, are designed and intended for clinical trials, require specialized training and expertise in their administration, and are typically not feasible for use in clinical practice settings.

Compilation of these outcome measures may be useful as part of real-world evidence generation; however, given that onasemnogene abeparvovec is a single treatment, response measures would not help inform ongoing therapy for an individual patient.