Product Monograph

Including Patient Medication Information

PrZOLGENSMA®

onasemnogene abeparvovec

Recombinant adeno-associated virus serotype 9 (AAV9) containing the human survival motor neuron (SMN) gene

Solution for intravenous infusion

2×10^{13} vector genomes/mL

Other drugs for disorders of the musculo-skeletal system

Novartis Pharmaceuticals Canada Inc.

700 Saint-Hubert St., Suite 100
Montreal, Quebec
H2Y 0C1

Date of Authorization:
2025-11-21

Control Number: 291209

Recent Major Label Changes

1 Indications, 1.1 Pediatrics	2024-11
4 Dosage and Administration, 4.1 Dosing Considerations	2025-11
7 Warnings and Precautions, General	2025-04
7 Warnings and Precautions, Cardiovascular	2025-11
7 Warnings and Precautions, Immune	2025-03
7 Warnings and Precautions, 7.1.3 Pediatrics	2024-11

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. Indications

Zolgensma® (onasemnogene abeparvovec) is indicated for the treatment of pediatric patients with 5q spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene and:

- 3 or fewer copies of SMN2 gene; or
- infantile-onset SMA.

The efficacy and safety data supporting the use of Zolgensma in treating pediatric patients with SMA are derived from completed and ongoing open-label, single-arm, clinical trials in patients with:

- infantile-onset SMA and 2 copies of SMN2 gene; and
- presymptomatic genetically diagnosed SMA and 2 or 3 copies of SMN2 gene (see 14 Clinical Trials).

Zolgensma is an adeno-associated virus (AAV) vector-based gene therapy. Knowledge of the disease natural history and the use of management strategies that assist the patient in coping with the manifestations of SMA, which can include decline in motor function, serious respiratory complications, and feeding difficulties, remain necessary for the overall management of the disease. Administration of Zolgensma should only be performed by healthcare professionals who are experienced in the screening, diagnosis, and management of SMA and trained in the delivery of gene therapy.

1.1. Pediatrics

Pediatrics (≥ 8 months of age): The efficacy of Zolgensma in pediatric patients 8 months of age and older at the time of infusion has not been established in clinical trials. There is limited safety information in patients aged 1.5 to 9 years (see 8.2 Clinical Trial Adverse Reactions).

1.2. Geriatrics

Geriatrics: Zolgensma is not authorized for geriatric use.

2. Contraindications

Zolgensma is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition, and Packaging.

3. Serious Warnings and Precautions Box

- Hepatotoxicity (acute liver failure, acute liver injury and elevated liver aminotransferases) can occur with Zolgensma. Cases of acute liver failure with fatal outcomes have been reported (see 7 Warnings and Precautions and 8 Adverse Reactions).
    - Patients with pre-existing liver impairment or hepatic viral infection may be at higher risk.
    - Before infusion, assess liver function by clinical examination and by laboratory testing in all patients. Before and after infusion, administer corticosteroid (oral prednisolone or

equivalent) to all patients. Do not stop systemic corticosteroids abruptly. Continue to monitor liver function for at least 3 months after infusion, and at other times as clinically indicated (see 4.1 Dosing Considerations).

- Thrombotic microangiopathy (TMA) can occur with Zolgensma. Cases of TMA have been reported to occur after Zolgensma infusion in the post-market setting. Prompt attention to signs and symptoms of TMA is advised, as TMA can result in life-threatening or fatal outcomes (see 7 Warnings and Precautions and 8 Adverse Reactions).
    - Before infusion, assess kidney function by laboratory testing in all patients. Monitor all patients for signs and symptoms of TMA (see 4.1 Dosing Considerations and 7 Warnings and Precautions).

4. Dosage and Administration

4.1. Dosing Considerations

Zolgensma should only be infused by a healthcare professional trained in the delivery of gene therapy.

To improve the traceability of biological medicinal products, the name and batch number of the administered product should be clearly recorded.

Zolgensma is for a single treatment only. An immune response to the adeno-associated viral vector serotype 9 (AAV9) capsid will occur after infusion of Zolgensma. Patients should not be re-dosed with Zolgensma.

Overall Health Status

Due to the increased risk of serious systemic immune response, patients must be clinically stable in their overall health status (e.g., hydration and nutritional status, absence of infection) prior to Zolgensma infusion. Postpone Zolgensma in patients with infections until the infection has resolved (including the completion of any treatment for the infection [e.g., antibiotics, etc.]) and the patient is clinically stable. Clinical signs or symptoms of infection should not be evident at the time of Zolgensma infusion (see 7 Warnings and Precautions, Immune).

Laboratory Testing and Monitoring to Assess Safety

Liver function

To manage possible liver injury, including increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin, treat all patients with corticosteroid (oral prednisolone or equivalent) before and after Zolgensma infusion and monitor liver function (see 3 Serious Warnings and Precautions Box and 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic).

Before Zolgensma Infusion

- Clinically assess the patient's liver function, including aminotransferase and synthetic function testing (AST and ALT, total bilirubin, albumin, prothrombin time, partial thromboplastin time [PTT] and international normalized ratio [INR]).
- On the day before Zolgensma infusion, pre-treat the patient with oral prednisolone at a dose of 1 mg/kg body weight/day (or equivalent if another corticosteroid is used).

Day of Zolgensma Infusion and After Zolgensma Infusion

- Continue prednisolone treatment daily at 1 mg/kg body weight/day (or equivalent if another corticosteroid is used) including the day of Zolgensma infusion, for 30 days.
- During infusion, and immediately following infusion, monitor patient closely for infusion-related hypersensitivity/anaphylactic reactions. If a reaction occurs the infusion should be interrupted and treatment should be provided as needed (see 7 Warnings and Precautions and 8 Adverse Reactions, 8.5 Post-Market Adverse Reactions).
- Liver function should be monitored regularly for at least 3 months, and at other times as clinically indicated. During the first 30 days, monitor AST, ALT, total bilirubin and the clinical signs of liver injury weekly. Promptly clinically assess and closely monitor patients with worsening liver function test results and/or signs or symptoms of acute illness. If hepatic injury is suspected, further testing is recommended (albumin, prothrombin time, PTT and INR).
- After 30 days, assess liver function by clinical examination and by measuring ALT, AST, and total bilirubin:
    - For patients with unremarkable liver function findings (*i.e.*, normal clinical exam, total bilirubin, and ALT and AST levels below 2 × ULN), gradually taper the corticosteroid dose over the next 28 days with careful monitoring, performed at least weekly. Do not stop systemic corticosteroids abruptly. If the patient is clinically stable with unremarkable findings at the end of the corticosteroid tapering period, continue monitoring every other week for another month.
    - For patients with new or persistent liver function abnormalities, continue systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg body weight/day) until AST and ALT values are both below 2 × ULN and all other assessments return to within the normal range. Gradually taper the corticosteroid dose over the next 28 days with careful monitoring, performed at least weekly. Do not stop systemic corticosteroids abruptly. If the patient is clinically stable with unremarkable findings at the end of the corticosteroid tapering period, continue monitoring every other week for another month.
- If a patient does not respond adequately to the equivalent of 1 mg/kg body weight/day of oral prednisolone, and/or if acute serious liver injury/acute liver failure is suspected, promptly consult with one or more specialists (*e.g.*, pediatric gastroenterologist/hepatologist). Consider increasing the daily dose of corticosteroid, and/or increasing the duration of corticosteroid treatment, and/or using a more gradual taper. If oral corticosteroid therapy is not tolerated or not effective, intravenous corticosteroid may be considered as clinically indicated.

Educational materials related to the risks of hepatotoxicity for healthcare professionals and caregivers are available through the manufacturer.

Creatinine

Measure creatinine level before Zolgensma infusion.

Complete blood count

A complete blood count (including hemoglobin and platelet count) should be obtained before Zolgensma infusion.

Platelet count

Monitor platelet counts at least weekly for the first month and every other week for the second and third months. Continue monitoring until platelet count results are unremarkable (see 7 Warnings and Precautions, Hematologic).

Troponin-I

Increases in cardiac troponin-I levels may occur following Zolgensma infusion (see 7 Warnings and Precautions, Cardiovascular). Consider troponin-I measurement before and after Zolgensma infusion, as well as cardiac evaluation after Zolgensma infusion. Consult a cardiologist as needed.

Anti-AAV Antibodies

Measure anti-AAV9 antibodies before Zolgensma infusion. Patients with titers higher than 1:50 should not be treated with Zolgensma (see 7 Warnings and Precautions, Immune).

4.2. Recommended Dose and Dosage Adjustment

The recommended dose of Zolgensma is 1.1×10^{14} vector genomes (vg)/kg patient body weight (Table 1).

Table 1 – Recommended Zolgensma Dose by Patient Body Weight

Patient weight range (kg)	Dose (vg)	Total volume of dose[a] (mL)
2.6 – 3.0	3.3×10^{14}	16.5
3.1 – 3.5	3.9×10^{14}	19.3
3.6 – 4.0	4.4×10^{14}	22.0
4.1 – 4.5	5.0×10^{14}	24.8
4.6 – 5.0	5.5×10^{14}	27.5
5.1 – 5.5	6.1×10^{14}	30.3
5.6 – 6.0	6.6×10^{14}	33.0
6.1 – 6.5	7.2×10^{14}	35.8
6.6 – 7.0	7.7×10^{14}	38.5
7.1 – 7.5	8.3×10^{14}	41.3
7.6 – 8.0	8.8×10^{14}	44.0
8.1 – 8.5	9.4×10^{14}	46.8
8.6 – 9.0	9.9×10^{14}	49.5
9.1 – 9.5	1.05×10^{15}	52.3
9.6 – 10.0	1.10×10^{15}	55.0
10.1 – 10.5	1.16×10^{15}	57.8
10.6 – 11.0	1.21×10^{15}	60.5
11.1 – 11.5	1.27×10^{15}	63.3

Patient weight range (kg)	Dose (vg)	Total volume of dose[a] (mL)
11.6 – 12.0	1.32×10^{15}	66.0
12.1 – 12.5	1.38×10^{15}	68.8
12.6 – 13.0	1.43×10^{15}	71.5
13.1 – 13.5	1.49×10^{15}	74.3
13.6 – 14.0	1.54×10^{15}	77.0
14.1 – 14.5	1.60×10^{15}	79.8
14.6 – 15.0	1.65×10^{15}	82.5
15.1 – 15.5	1.71×10^{15}	85.3
15.6 – 16.0	1.76×10^{15}	88.0
16.1 – 16.5	1.82×10^{15}	90.8
16.6 – 17.0	1.87×10^{15}	93.5
17.1 – 17.5	1.93×10^{15}	96.3
17.6 – 18.0	1.98×10^{15}	99.0
18.1 – 18.5	2.04×10^{15}	101.8
18.6 – 19.0	2.09×10^{15}	104.5
19.1 – 19.5	2.15×10^{15}	107.3
19.6 – 20.0	2.20×10^{15}	110.0
20.1 – 20.5	2.26×10^{15}	112.8
20.6 – 21.0	2.31×10^{15}	115.5

[a] NOTE: Volume of dose is calculated using the upper limit of the Patient Weight Range.

Special populations

Renal impairment

The efficacy and safety of Zolgensma have not been established in patients with renal impairment.

Hepatic impairment

The efficacy and safety of Zolgensma have not been established in patients with hepatic impairment; however, a risk of hepatotoxicity has been identified in patients after Zolgensma infusion (see 3 Serious Warnings and Precautions Box and 7 Warnings and Precautions, Hepatic/Biliary/ Pancreatic).

Educational materials for healthcare professionals and caregivers related to the risks of hepatotoxicity are available through the manufacturer.

Pediatric patients

The efficacy and safety of Zolgensma in neonates who have not reached full-term gestational age have not been established.

The efficacy and safety of Zolgensma in pediatric patients 8 months of age and older at the time of infusion have not been established in clinical trials.

4.4. Administration

Zolgensma is for single-dose intravenous infusion only.

Preparation of Zolgensma:

- Zolgensma should be prepared aseptically.
- Thaw Zolgensma in the refrigerator (2°C to 8°C) for approximately 16 hours, or at room temperature (20°C to 25°C) for approximately 6 hours.
- Do not use Zolgensma unless thawed.
- When thawed, Zolgensma is a clear to slightly opaque, colourless to faint white liquid, free of particles. Visually inspect vials for particulate matter and discolouration prior to infusion. Do not use vials if particulates or discolouration are present.
- DO NOT SHAKE.
- Immediately prior to dosing, draw the prescribed dose volume from all vials into the syringe, remove air from syringe, cap syringe, and deliver filled syringe to patient infusion location.
- Once dose is drawn into the syringe, it must be used within 8 hours.
- DO NOT REFREEZE.

Intravenous Infusion Instructions:

- Place a primary catheter in a peripheral vein (generally in the arm or leg).
- Insertion of a secondary catheter is recommended.
- Program syringe pump for saline priming, or prime tubing manually with saline.
- Administer Zolgensma as a slow infusion over 60 minutes. Do not infuse as a rapid intravenous injection or bolus.
- Following completion of the infusion, flush line with saline.
- Seal used Zolgensma vials in a biohazard bag and discard in biohazard waste containers according to institutional biohazard guidelines (see 11 Storage, Stability, and Disposal).

4.5. Missed Dose

Not applicable. Zolgensma is to be administered only once.

5. Overdose

No data from clinical studies are available regarding overdose of Zolgensma. Adjustment of the dose of prednisolone, close clinical observation and monitoring of laboratory parameters (including clinical chemistry and hematology) for systemic immune response are recommended (see 4.1 Dosing Considerations and 7 Warnings and Precautions).

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

To help ensure the traceability of biologic products, healthcare professionals should record both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 2 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Intravenous	Solution for infusion / 2.0×10^{13} vector genome (vg)/mL	Hydrochloric Acid (for pH adjustment), magnesium chloride, poloxamer 188, sodium chloride, tromethamine, water for injection

Description

Zolgensma is a solution for intravenous infusion supplied as single use vials. When thawed, Zolgensma is a clear to slightly opaque, colorless to faint white solution.

Each mL contains onasemnogene abeparvovec with a nominal concentration of 2×10^{13} vector genomes (vg).

Zolgensma is supplied in a vial (10 mL polymer crystal zenith) with stopper (20 mm chlorobutyl rubber) and seal (aluminum, flip-off) with a coloured cap (plastic), in two different vial fill volume sizes, either 5.5 mL or 8.3 mL.

The total number of vials and combination of fill volumes in each finished pack will be customized to meet dosing requirements for individual patients depending on their weight (Table 3).

Table 3 – Zolgensma kit configuration

Patient weight (kg)	5.5 mL vial[a]	8.3 mL vial[b]	Total vials per kit
2.6 – 3.0	0	2	2
3.1 – 3.5	2	1	3
3.6 – 4.0	1	2	3
4.1 – 4.5	0	3	3
4.6 – 5.0	2	2	4
5.1 – 5.5	1	3	4
5.6 – 6.0	0	4	4
6.1 – 6.5	2	3	5

Patient weight (kg)	5.5 mL vial[a]	8.3 mL vial[b]	Total vials per kit
6.6 – 7.0	1	4	5
7.1 – 7.5	0	5	5
7.6 – 8.0	2	4	6
8.1 – 8.5	1	5	6
8.6 – 9.0	0	6	6
9.1 – 9.5	2	5	7
9.6 – 10.0	1	6	7
10.1 – 10.5	0	7	7
10.6 – 11.0	2	6	8
11.1 – 11.5	1	7	8
11.6 – 12.0	0	8	8
12.1 – 12.5	2	7	9
12.6 – 13.0	1	8	9
13.1 – 13.5	0	9	9
13.6 – 14.0	2	8	10
14.1 – 14.5	1	9	10
14.6 – 15.0	0	10	10
15.1 – 15.5	2	9	11
15.6 – 16.0	1	10	11
16.1 – 16.5	0	11	11
16.6 – 17.0	2	10	12
17.1 – 17.5	1	11	12
17.6 – 18.0	0	12	12
18.1 – 18.5	2	11	13
18.6 – 19.0	1	12	13
19.1 – 19.5	0	13	13
19.6 – 20.0	2	12	14
20.1 – 20.5	1	13	14
20.6 – 21.0	0	14	14

[a] Vial nominal concentration is 2.0×10^{13} vg/mL and contains an extractable volume of not less than 5.5 mL.

[b] Vial nominal concentration is 2.0×10^{13} vg/mL and contains an extractable volume of not less than 8.3 mL.

7. Warnings and Precautions

See 3 Serious Warnings and Precautions Box.

General

Advanced SMA

Since SMA results in progressive and non-reversible damage to motor neurons, the benefit of Zolgensma in symptomatic patients depends on the degree of disease burden at the time of treatment, with earlier treatment resulting in potential greater benefit.

Progressive motor neuron loss is irreversible. The treating healthcare professional should consider that the benefits and risks have not been established in patients with profound muscle weakness and respiratory failure, patients on permanent ventilation, and patients unable to swallow.

Blood and Tissue Donation

Patients treated with Zolgensma should not donate blood, organs, tissues or cells for transplantation.

Vector Shedding

Temporary vector shedding of Zolgensma occurs primarily through bodily waste (see 10 Clinical Pharmacology, Pharmacokinetics). Advise caregivers on the precautionary handling of patient feces (see 11 Storage, Stability and Disposal, Special Precautions for Disposal).

AAV vector DNA integration and risk of tumourigenicity

There is a theoretical risk of tumourigenicity due to integration of AAV vector DNA into the genome. The clinical relevance of individual integration events is unknown, but it is acknowledged that these events could potentially contribute to a risk of tumourigenicity.

Zolgensma is composed of a recombinant non-replicating AAV9 vector whose DNA persists largely in episomal form. Cases of tumour have been reported in patients treated with Zolgensma, and random integration of recombinant AAV9 vector DNA has been reported in patient tumour tissues following Zolgensma treatment. A causal relationship with Zolgensma has not been established based on tumour analyses performed to date; however, in some cases the available information was limited due to incomplete/inconclusive analyses. If a patient treated with Zolgensma develops a tumour, healthcare professionals should report the case to Novartis Pharmaceuticals Canada Inc., at 1-877-631-6775.

Cardiovascular

Troponin-I

Increases in cardiac troponin-I levels (up to 0.2 mcg/L) following infusion with Zolgensma have been observed in clinical trials (see 8 Adverse Reactions). Elevated troponin-I levels may indicate potential myocardial tissue injury; however, the clinical importance of these findings has not been established. Cardiac toxicity following onasemnogene abeparvovec treatment was observed in animal studies (see 16 Non-Clinical Toxicology). Consider troponin-I measurement before and after Zolgensma infusion, as well as cardiac evaluation after Zolgensma infusion. Consult a cardiologist as needed.

Hematologic

Thrombocytopenia

Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were

typically observed within the first two weeks after Zolgensma infusion (see 8 Adverse Reactions). Thrombocytopenia requiring platelet transfusion has been reported in patients with and without thrombotic microangiopathy in the post-market setting (see section below and 8.5 Post-Market Adverse Reactions). Measure platelet count before Zolgensma infusion and closely monitor for significant decreases within the first two weeks following infusion and on a regular basis afterwards; at least weekly for the first month and every other week for the second and third months. Continue monitoring until platelet count results are unremarkable.

Educational materials for healthcare professionals and caregivers related to the risks of thrombocytopenia are available through the manufacturer.

Thrombotic Microangiopathy

Cases of thrombotic microangiopathy (TMA), also known as atypical hemolytic uremic syndrome (aHUS) have been reported to occur generally within the first two weeks after Zolgensma infusion in the post-market setting (see 8.5 Post Market Adverse Reactions). Concurrent/recent immune system activation (e.g. infections, vaccinations) was identified as a possible contributing factor in some cases. TMA is characterized by thrombocytopenia, fever, hypertension, microangiopathic hemolytic anemia, and acute kidney injury.

Prompt attention to signs and symptoms of TMA is advised, as TMA can result in life-threatening or fatal outcomes. Advise caregivers about the importance of promptly identifying and reporting signs and symptoms of TMA following Zolgensma infusion.

Since thrombocytopenia is a key feature of TMA, closely monitor platelet count for significant decreases within the first two weeks following infusion and on a regular basis afterwards (see sub-section Thrombocytopenia above). In addition, monitor all patients for the signs and symptoms of TMA, including hypertension, increased bruising, seizures, or decreased urine output. In case these signs and symptoms occur in the presence of thrombocytopenia, promptly undertake further diagnostic evaluation for hemolytic anemia and renal dysfunction. If clinical signs, symptoms and/or laboratory findings consistent with TMA occur, immediately consult a pediatric hematologist and/or pediatric nephrologist to manage TMA as clinically indicated.

Educational materials for healthcare professionals and caregivers related to the risks of thrombotic microangiopathy are available through the manufacturer.

Hepatic/Biliary/Pancreatic

Acute Liver Failure/Liver Injury and Elevated Aminotransferases

Hepatotoxicity (acute liver failure, acute liver injury and elevated aminotransferases) can occur with Zolgensma (see 8 Adverse Reactions). Cases of acute liver failure with fatal outcomes have been reported. Patients with pre-existing liver impairment or hepatic viral infection may be at higher risk of acute liver failure/liver injury. The efficacy and safety of Zolgensma in patients with ALT, AST, or total bilirubin levels (except due to neonatal jaundice) > 2 × ULN have not been established. Before Zolgensma infusion, assess liver function by clinical examination and by testing AST, ALT, total bilirubin, albumin, prothrombin time, PTT and INR in all patients. Continue to monitor liver function (ALT, AST, total bilirubin) for at least 3 months after infusion, and at other times as clinically indicated (see 4.1 Dosing Considerations). Promptly clinically assess and closely monitor patients with worsening liver function test results and/or signs or symptoms of acute illness. In case hepatic injury is suspected, further testing is recommended (e.g., albumin, prothrombin time, PTT and INR).

Before and after infusion, administer corticosteroid (oral prednisolone or equivalent) to all patients. Do not stop systemic corticosteroids abruptly. Promptly consult with a specialist (pediatric gastroenterologist/hepatologist) if the patient does not adequately respond to prednisolone adjustments (see 4.1 Dosing Considerations).

Educational materials for healthcare professionals and caregivers related to the risks of hepatotoxicity are available through the manufacturer.

Immune

Systemic Immune Response and Concomitant Infections

Patients with infection were excluded from participation in Zolgensma clinical trials. In some post-market cases, patients with potential underlying acute (e.g. respiratory) or chronic uncontrolled infection who were treated with Zolgensma had severe clinical courses of the infection reported. A systemic immune response following Zolgensma infusion concomitantly with an infection could lead to serious/severe outcomes. Poor health status (e.g. nutrition, hydration) may also be a contributory factor.

Prior to Zolgensma infusion, patients must be clinically stable in their overall health status (e.g., hydration and nutritional status, absence of infection, etc.). Postpone Zolgensma infusion in patients with infections until the infection has resolved (including the completion of treatment for the infection [e.g. antibiotics, etc.]) and the patient is clinically stable. Clinical signs or symptoms of infection should not be evident at the time of Zolgensma infusion (see 4.1 Dosing Considerations).

Increased vigilance in the prevention, monitoring, and management of infection is recommended before and after Zolgensma infusion. Advise caregivers about infection prevention and the importance of promptly identifying and reporting signs and symptoms of infection before and after Zolgensma infusion.

Immunogenicity

In clinical trials, patients were required to have anti-AAV9 antibody titers at or below 1:50 as measured with an enzyme-linked immunosorbent assay (ELISA) before Zolgensma infusion. The efficacy and safety of Zolgensma has not been established in patients with anti-AAV9-antibody titers above 1:50 before infusion. Test patients for the presence of anti-AAV9 antibodies before Zolgensma infusion (see 4.1 Dosing Considerations). Retesting may be performed if anti-AAV9 antibody titers are reported as above 1:50 (see 10.4 Immunogenicity).

Infusion-related reactions

Serious infusion-related reactions, including hypersensitivity reactions and anaphylaxis, have occurred during, and/or shortly after, infusion of Zolgensma (see 8.5 Post Market Adverse Reactions). Signs and symptoms of these reactions may include, but are not limited to, rash, urticaria, vomiting, dyspnea, flushing, swelling of face/mouth/throat, chills, wheezing, oxygen desaturation, and/or alterations in heart rate and blood pressure. Closely monitor patients for signs and symptoms of infusion reactions during the infusion period and immediately following the end of the infusion. If a reaction occurs, the infusion should be interrupted and treatment should be provided as needed. Based on clinical evaluation and standard practices, administration may be cautiously resumed.

Reproductive Health

- **Fertility**

  There are no data on the effect of Zolgensma on fertility available. The effects of onasemnogene abeparvovec on male and female fertility have not been evaluated in animal studies (see 16 Non-Clinical Toxicology, Reproductive and Developmental Toxicology).

- **Germline integration**

  The potential for the germline transmission or integration of the onasemnogene abeparvovec vector genome has not been evaluated in animal studies (see 16 Non-Clinical Toxicology, Reproductive and Developmental Toxicology).

7.1. Special Populations

7.1.1. Pregnancy

There are no available data regarding Zolgensma use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with onasemnogene abeparvovec (see 16 Non-Clinical Toxicology, Reproductive and Developmental Toxicology).

7.1.2. Breastfeeding

There is no information available on the presence of Zolgensma in human milk, the effects on the breastfed infant or the effects on milk production.

7.1.3. Pediatrics

The efficacy and safety of Zolgensma in premature neonates who have not reached full-term gestational age have not been established.

The efficacy of Zolgensma in pediatric patients 8 months of age and older at the time of infusion has not been established in clinical trials. There is limited safety information in patients aged 1.5 to 9 years (see 8.2 Clinical Trial Adverse Reactions).

7.1.4. Geriatrics

No data are available for this population.

8. Adverse Reactions

8.1. Adverse Reaction Overview

The most frequently reported adverse events following Zolgensma infusion in the 4 open-label clinical studies described in section 8.2 below are fever/pyrexia (51%) liver function enzyme elevations (33%; 6.2% serious) and decreased platelet count/thrombocytopenia (6.2%) (see 3 Serious Warnings and Precautions Box, 4.1 Dosing Considerations, 7 Warnings and Precautions and 8.2 Clinical Trial Adverse Reactions, Descriptions of Selected Adverse Reactions).

Adverse drug reactions identified in the post-market setting are described below in 8.5 Post-Market Adverse Drug Reactions.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

The safety of Zolgensma was evaluated in 97 patients who received Zolgensma at the recommended dose (1.1×10^{14} vg/kg) from 4 open-label clinical studies (CL-101, CL-303, CL-302, CL-304). The patients ranged in age from 0.3 months to 7.9 months at the time of Zolgensma administration (weight range: 3.0 kg to 8.4 kg). The duration of follow-up ranged from 1.8 months to 24 months post-infusion.

The treatment-emergent adverse events identified in patients treated with Zolgensma by intravenous infusion (frequencies ≥ 5%) from the 4 open-label clinical studies are presented in Table 4.

Table 4 - Treatment-emergent adverse events reported in clinical trials (studies CL-101, CL-303, CL-302, CL-304) (frequencies ≥ 5%)

System Organ Class Preferred Term	**Zolgensma 1.1×10^{14} vg/kg (N=97) n (%)**
Infections and infestations	
Upper respiratory tract infection[a]	48 (49.5)
Lower respiratory tract infection[b]	28 (29.9)
Respiratory tract infection[c]	20 (20.6)
Gastroenteritis	16 (16.5)
Urinary tract infection[d]	11 (11.3)
Otitis media[e]	9 (9.3)
Fungal infection[f]	8 (8.2)
Conjunctivitis	8 (8.2)
Ear infection	7 (7.2)
Gastrointestinal disorders	
Constipation	25 (25.8)
Vomiting	24 (24.7)
Gastrooesophageal reflux disease	17 (17.5)
Diarrhoea	15 (15.5)
Teething	10 (10.3)
General disorders and administration site conditions	
Pyrexia[g]	49 (50.5)

System Organ Class Preferred Term	Zolgensma 1.1 x 10^{14} vg/kg (N=97) n (%)
Respiratory, thoracic and mediastinal disorders	
Cough[h]	21 (21.6)
Nasal congestion	12 (12.4)
Respiratory distress	9 (9.3)
Hypoxia[i]	7 (7.2)
Respiratory failure[j]	7 (7.2)
Use of accessory respiratory muscles	6 (6.2)
Aspiration[k]	5 (5.2)
Atelectasis	5 (5.2)
Respiration abnormal	5 (5.2)
Rhinorrhoea	5 (5.2)
Tachypnoea	5 (5.2)
Investigations	
Liver function test increased[l]	32 (33.0)
Skin and subcutaneous tissue disorders	
Rash[m]	17 (17.5)
Dermatitis[n]	12 (12.4)
Injury, poisoning and procedural complications	
Contusion	6 (6.2)
Musculoskeletal and connective tissue disorders	
Scoliosis[o]	13 (13.4)
Nervous system disorders	
Muscle contractions involuntary	6 (6.2)
Blood and lymphatic system disorders	
Anaemia[p]	6 (6.2)
Thrombocytopenia[q]	6 (6.2)
Cardiac disorders	
Tachycardia	5 (5.2)
Psychiatric disorders	

System Organ Class Preferred Term	**Zolgensma 1.1 x 10^{14} vg/kg** **(N=97)** **n (%)**
Irritability	5 (5.2)
Vascular disorders	
Hypertension[r]	8 (8.2)

[a] *Grouped with Influenza, Nasopharyngitis, Pharyngitis streptococcal, Bacterial tracheitis, Rhinitis, Laryngitis, Viral upper respiratory tract infection, Pharyngitis, Croup infectious, Tonsillitis*
[b] *Grouped with Pneumonia, Pneumonia viral, Metapneumovirus infection, Pneumonia bacterial, Pneumonia parainfluenzae viral, Pneumonia respiratory syncytial viral, Bronchiolitis, Respiratory syncytial virus bronchiolitis, Bronchitis*
[c] *Grouped with Rhinovirus infection, Parainfluenzae virus infection, Respiratory tract infection viral, Respiratory syncytial virus infection*
[d] *Grouped with Urinary tract infection bacterial, Bacteriuria, Cystitis, Pyelonephritis*
[e] *Grouped with Otitis media acute*
[f] *Grouped with Candida infection, Candida nappy rash, Fungal skin infection, Oral candidiasis*
[g] *Grouped with Body temperature increased*
[h] *Grouped with Productive cough*
[i] *Grouped with Oxygen saturation decreased*
[j] *Grouped with Acute respiratory failure*
[k] *Grouped with Pneumonia aspiration*
[l] *Grouped with Hypertransaminasaemia, Hepatic enzyme increased, Transaminases increased, Aspartate aminotransferase increased, Alanine aminotransferase increased, Gamma-glutamyltransferase increased*
[m] *Grouped with Rash macular, Rash generalised, Genital rash*
[n] *"Dermatitis" was not reported but was chosen to group the following events: Dermatitis diaper, Dermatitis atopic, Dermatitis allergic, Dermatitis contact, Dermatitis infected, Catheter site dermatitis*
[o] *Grouped with Deformity thorax, Kyphosis, Kyphoscoliosis*
[p] *Grouped with Haemoglobin decreased, Microcytic anaemia, Iron deficiency anaemia*
[q] *Grouped with Platelet count decreased*
[r] *Grouped with Blood pressure systolic increased, Diastolic hypertension*

Description of Selected Adverse Drug Reactions

Acute Liver Failure/Liver Injury and Elevated Aminotransferases

In the 4 open-label clinical trials, elevations in liver function enzymes were reported as adverse events in 32 (33%) patients, of which 6 (6.2%) patients reported serious adverse events. In the patients experiencing serious adverse events, the duration of prednisolone treatment ranged from 51 to 181 days.

Some patients have experienced AST and ALT elevations of greater than 20 times ULN and have been symptomatic (e.g. vomiting, jaundice), which required the use of corticosteroids, sometimes with prolonged duration and/or a higher dose (see 3 Serious Warnings and Precautions Box, 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic, 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data, and 8.5 Post-Market Adverse Reactions).

Thrombocytopenia

In clinical trials, transient decreases from baseline in mean platelet count, some of which met the criteria for thrombocytopenia, were observed at multiple time points after Zolgensma infusion. Thrombocytopenia was reported in the 4 open-label clinical trials in 6/97 (6.2%) patients (see 7 Warnings and Precautions, Hematologic, 8.4 Abnormal Laboratory Findings: Hematologic, Clinical

Chemistry and Other Quantitative Data, and 8.5 Post-Market Adverse Reactions).

Increased troponin-I levels

In the 4 open-label clinical trials, increases in cardiac troponin-I levels up to 0.2 mcg/L were reported in 3/97 (3.1%) patients after Zolgensma infusion (see 7 Warnings and Precautions, Cardiovascular and 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data).

Other special populations

Body weight ≥ 8.5 kg to ≤ 21 kg

The safety of Zolgensma was evaluated in a post-authorization clinical study (COAV101A12306) in 24 patients weighing ≥ 8.5 kg to ≤ 21 kg (median weight: 15.8 kg). The patients ranged in age from approximately 1.5 to 9 years at the time of administration. 1 of the 24 patients was under the age of 2 at the time of administration (median age: 4.9 years). Before treatment with Zolgensma, 21 patients discontinued their previous treatment with nusinersen or risdiplam. The types of adverse reactions observed were consistent with that of the 4 open-label studies.

Liver enzyme increases in this study occurred at a higher frequency compared with the previous 4 studies. AST or ALT elevations > 2 × ULN were observed in the majority of patients (23/24), including 21 patients with ALT elevations > 3 × ULN and 5 patients with ALT elevations > 20 × ULN. These patients were clinically asymptomatic and there were no elevations of bilirubin. The AST and ALT elevations were managed with the use of corticosteroids, typically with prolonged duration and/or a higher dose (see 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic).

Transient decreases in platelet counts, which met the criteria for thrombocytopenia were observed in 20 out of 24 patients. Four patients had platelet counts below 50,000 per µL (see Thrombocytopenia above).

8.3. Less Common Clinical Trial Adverse Reactions

Serious or severe treatment-emergent adverse events that were reported in clinical trials with a frequency less than 5% were:

Cardiac Disorders: bradycardia, cyanosis

Gastrointestinal disorders: dysphagia, duodenal ulcer, inguinal hernia

Infections and infestations: enterovirus infection, viral infection, adenovirus infection, device related infection, exanthema subitum, postoperative wound infection, sepsis, staphylococcal bacteraemia

Injury, poisoning, and procedural complications: lower limb fracture[a], post procedural haemorrhage

Investigations: human rhinovirus test positive, enterovirus test positive, blood alkaline phosphatase increased, coagulation test abnormal, human metapneumovirus test positive, norovirus test positive, respiratory syncytial virus test positive, sleep study

Metabolism and nutrition disorders: feeding disorder, dehydration, abnormal weight gain, failure to thrive, hypercalcaemia, hypernatraemia, hyperphosphatasaemia, hypokalaemia

Nervous System disorders: lethargy, hydrocephalus, hypoxic-ischaemic encephalopathy, loss of consciousness

Product issues: device malfunction

Psychiatric disorders: anxiety[b]

Respiratory, thoracic, and mediastinal disorders: sleep apnoea syndrome, upper respiratory tract congestion[c], adenoidal hypertrophy, increased bronchial secretion, respiratory arrest, tonsillar hypertrophy

Skin and subcutaneous tissue disorders: decubitus ulcer

Surgical and medical procedures: gastrostomy, hospitalisation

Vascular disorders: hypotension[d]

[a] *"Lower limb fracture" was not reported but was chosen to group Femur fracture and Tibia fracture*
[b] *Grouped with Nervousness*
[c] *Grouped with Influenza, Nasopharyngitis, Pharyngitis streptococcal, Bacterial tracheitis, Rhinitis, Laryngitis, Viral upper respiratory tract infection, Pharyngitis, Croup infectious, Tonsillitis*
[d] *Grouped with Blood pressure diastolic decreased*

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

Clinical Trial Findings

In clinical trials, laboratory parameters and other quantitative data were evaluated independent of adverse events and are presented in Table 5 and Table 6 below.

Table 5 - Summary of Patients Meeting Criteria for Potentially Clinically Significant Hematology Values*

Parameter	n/N (%)
Platelets	7/96 (7.3)
Neutrophils	37/96 (38.5)

*Criteria for potentially clinically significant values:
Platelets: $<75x10^9$/L
Neutrophils: Subjects 0-14 days and >180 days: $<1.5 x10^9$/L; Subjects 15-179 days: $<1x10^9$/L

Table 6 - Summary of Patients Meeting Criteria for Potentially Clinically Significant Chemistry Values*

Parameter	n/N (%)
Alanine Aminotransferase (ALT)	15/97 (15.5)
Aspartate Aminotransferase (AST)	15/97 (15.5)
Alkaline Phosphatase	6/96 (6.3)
Bilirubin	13/97 (13.4)
Troponin I	5/32 (15.6)

*Criteria for potentially clinically significant values:
ALT: >150 U/L
AST: >180 U/L
Alkaline Phosphatase: >675 U/L
Bilirubin: >33.4 µmol/L
Troponin I: >50 ng/L

8.5. Post-Market Adverse Reactions

The following adverse drug reactions have been derived from post-market experience with Zolgensma, including spontaneous case reports and literature cases. Because these reactions are reported voluntarily, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

Table 7 - Adverse drug reaction from post-marketing experience (frequency not known)

Blood and lymphatic system disorders
Thrombotic microangiopathy
Hepatobiliary Disorders
Acute liver failure[a]/liver injury
General disorders and administration site conditions
Infusion-related reactions, including hypersensitivity and anaphylaxis[b]

[a] Includes fatal cases

[b] Infusion-related reactions included signs and symptoms that occurred during, and/or shortly after, infusion (e.g. rash, urticaria, vomiting, dyspnea, wheezing, throat/mouth/face swelling, chills, oxygen desaturation, flushing, blood pressure and heart rate changes).

Acute liver failure/liver injury

Cases of acute liver failure with fatal outcome and of liver injury have been reported in the post-market setting. In some cases, patients required hospitalization, exhibited signs and symptoms associated with liver dysfunction (e.g., jaundice, coagulopathy, elevated ammonia levels), and required the use of corticosteroids (see 3 Serious Warnings and Precautions Box).

Educational materials for healthcare professionals and caregivers related to the risks of hepatotoxicity are available through the manufacturer.

Thrombotic microangiopathy

Thrombotic microangiopathy (TMA) has been reported following Zolgensma infusion in the post-market setting (see 7 Warnings and Precautions, Hematologic). TMA is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury. Reported cases occurred generally within the first two weeks after Zolgensma infusion. Hospitalization and platelet transfusions were required in some cases.

Educational materials for healthcare professionals and caregivers related to the risks of thrombotic microangiopathy are available through the manufacturer.

9. Drug Interactions

9.2. Drug Interactions Overview

No interaction studies have been performed.

9.4. Drug-Drug Interactions

No interaction studies have been performed.

Vaccinations

Live vaccines should not be administered to patients taking an immunosuppressive corticosteroid dose. Where feasible, adjust the patient's vaccination schedule to accommodate prednisolone (or equivalent) treatment before and after Zolgensma infusion (see 4.1 Dosing Considerations). Seasonal Respiratory Syncytial Virus (RSV) prophylaxis is not precluded.

5q SMA Targeting Agents

The efficacy and safety of the use of Zolgensma with other 5q SMA targeting agents have not been established.

9.5. Drug-Food Interactions

Interactions with food have not been established.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

Onasemnogene abeparvovec is a gene therapy designed to introduce a functional copy of the survival motor neuron gene (SMN1) in the transduced cells to address the monogenic root cause of spinal muscular atrophy (SMA). By providing an alternative source of SMN protein expression in motor neurons, it is expected to promote the survival and function of transduced motor neurons.

Onasemnogene abeparvovec is a non-replicating recombinant AAV vector that utilizes AAV9 capsid to deliver a stable, fully functional human SMN1 transgene. The SMN1 gene present in onasemnogene abeparvovec is designed to reside as episomal DNA in the nucleus of transduced cells and is expected to be stably expressed for an extended period of time in post-mitotic cells. The transgene is introduced to target cells as a self-complementary double stranded molecule. Expression of the transgene is driven by a constitutive promoter (cytomegalovirus enhanced chicken β actin hybrid), which is expected to result in continuous and sustained SMN protein expression.

10.2. Pharmacodynamics

There are no clinically relevant pharmacodynamics data for onasemnogene abeparvovec.

10.3. Pharmacokinetics

Vector Shedding: Onasemnogene abeparvovec vector shedding analysis, which assessed the amount of vector eliminated from the body through saliva, urine, and feces, were performed on samples from 5 patients with Type 1 SMA in a Phase 1 study.

Onasemnogene abeparvovec was shed in saliva, urine, and stool post-infusion of onasemnogene abeparvovec. Clearance of onasemnogene abeparvovec was primarily via feces and the majority is cleared within 30 days after dose administration. Onasemnogene abeparvovec concentrations in urine

and saliva were highest at day 1 post-infusion and dropped thereafter.

Biodistribution: Biodistribution was evaluated in two patients who died 5.7 months and 1.7 months, respectively, after infusion of onasemnogene abeparvovec at the dose of 1.1 x 10^{14} vg/kg. Both cases showed that the highest levels of vector DNA were found in the liver. Vector DNA was also detected in the spleen, heart, pancreas, inguinal lymph node, skeletal muscles, peripheral nerves, kidney, lung, intestines, gonads (male and female), spinal cord, brain, and thymus. Immunostaining for SMN protein showed generalized SMN expression in spinal motor neurons, neuronal and glial cells of the brain, and in the heart, liver, skeletal muscles, and other tissues evaluated.

10.4. Immunogenicity

All therapeutic proteins have the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medicinal products and underlying disease. For these reasons, comparison of incidence of antibodies in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

In clinical trials, patients were required to have anti-AAV9 antibody titers at or below 1:50 as measured with an enzyme-linked immunosorbent assay (ELISA) before Zolgensma infusion. Mean increases from baseline in anti-AAV9 antibody titer were observed in all patients. Titers reached at least 1:102,400 in all patients tested (n=15) and exceeded 1:819,200 in most patients (73%).

11. Storage, Stability, and Disposal

- Zolgensma is shipped and delivered frozen (≤ -60 °C) in clear vials.
- Immediately place the kit in a refrigerator at 2°C to 8°C upon receipt.
- Zolgensma is stable for 14 days from receipt when stored at 2°C to 8°C.
- DO NOT REFREEZE.
- Must use within 14 days of receipt.

Once the prescribed dose volume is drawn into the syringe, Zolgensma must be infused within 8 hours (see 4.4 Administration). Following infusion, or after 8 hours if prepared Zolgensma is not infused, dispose the vector-containing syringe in accordance with institutional guidelines for biohazard waste (see Special Precautions for Disposal below).

Zolgensma must be kept out of the reach and sight of children.

Special Precautions for Disposal

Unused Zolgensma and waste material containing or exposed to Zolgensma must be disposed of in accordance with institutional guidelines for biohazardous waste (see 12 Special Handling Instructions).

12. Special Handling Instructions

Incompatibilities

Zolgensma must not be mixed with other medicinal products.

Instructions for use and handling

Each vial is for single use only.

Follow appropriate precautions for the handling and disposal of Zolgensma:

- Handle Zolgensma aseptically.
- Wear personal protective equipment (i.e., gloves, safety goggles, laboratory coat and sleeves) while handling or administering Zolgensma. Healthcare professionals should not handle or administer Zolgensma if they are at risk of exposure through cut or scratched skin.
- Wipe all spills of Zolgensma with absorbent gauze pads and disinfect the spill area. Dispose of all clean-up materials in accordance with institutional guidelines for biohazard waste.
- Dispose of all materials that have or may have come into contact with Zolgensma (e.g., vial, syringe, needles, gauze, wipes, gloves, and drapes) in accordance with institutional guidelines for biohazard waste.

Handling of Patient Waste

Vector shedding of Zolgensma occurs primarily through body waste. Advise caregivers about the proper handling of patient feces. Protective gloves and good hand hygiene are required when in contact with patient body waste for a minimum of 1 month after Zolgensma infusion. Disposable diapers should be sealed in disposable trash bags and discarded in regular trash. Reusable diapers should not be used within the first month after Zolgensma infusion.

Accidental Exposure

Avoid accidental exposure to Zolgensma.

If skin is accidentally exposed to Zolgensma, wash the affected area thoroughly with soap and water for at least 15 minutes. In the case of eye exposure, flush affected eye(s) thoroughly with water for at least 15 minutes. In case of accidental needle stick exposure, refer to institutional biosafety guidelines and contact site health unit as required.

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

Proper name: Onasemnogene abeparvovec

Chemical name: DNA (synthetic adeno-associated virus 9 vector scAAV9.CB.hSMN human survival motor neuron protein-specifying)

Structure: Onasemnogene abeparvovec is a non-replicating, recombinant adeno-associated virus serotype 9 (AAV9) containing the human survival motor neuron (SMN) gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). One of the two adeno-associated vector (AAV) inverted terminal repeats (ITRs) has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription.

Physicochemical properties: Clear to slightly opaque, colorless to faint white solution.
pH value: 7.7 – 8.3

Product Characteristics:

Onasemnogene abeparvovec is a non-replicating recombinant AAV vector that utilizes AAV9 capsid to deliver a stable, fully functional human SMN transgene.

14. Clinical Trials

14.1. Clinical Trials by Indication

Spinal muscular atrophy

The efficacy of Zolgensma in patients less than 8 months of age with spinal muscular atrophy (SMA) was demonstrated based on three open-label, single-arm, single-dose clinical trials.

Table 8 - Summary of patient demographics for clinical trials in SMA

Study #	Study design	Dosage, route of administration, and duration	Study Subjects (n)	Age (range)	Sex
AVXS-101-CL-303 (Completed)	Open-label, single-arm, single dose, multicentre trial.	1.1×10^{14} vg/kg Single-dose intravenous administration End of study at 18 months of age	n = 22	3.7 months (0.5 - 5.9 months)	Male: 45.5%; Female: 54.5%

AVXS-101-CL-101 (Completed)	Open-label, single-arm, ascending-dose, single centre trial.	Cohort 1: 6.7 x 10^{13} vg/kg[a] Cohort 2: 1.1 × 10^{14} vg/kg[b] Single-dose intravenous administration End of study at 2 years post-dose	n = 15 Cohort 1: n=3 Cohort 2: n=12	4.0 months (0.9-7.9 months)	Male: 40.0%; Female: 60.0%
AVXS-101-CL-304 (Ongoing)	Open-label, single-arm, single-dose, multicentre trial.	1.1 × 10^{14} vg/kg Single-dose intravenous administration End of study at 18 months of age (subjects with 2 copies SMN2) or 24 months of age (subjects with 3 copies SMN2)	n = 29 Cohort 1 (2 copies SMN2): n=14 Cohort 2 (3 copies SMN2): n=15	Subjects with 2 copies SMN2: 20.6 days (8 to 34 days) Subjects with 3 copies SMN2: 28.7 days (9 to 43 days)	Subjects with 2 copies SMN2: Male: 28.6%; Female: 71.4% Subjects with 3 copies SMN2: Male: 40%; Female: 60%

[a] *Low dose as measured by quantitative PCR (qPCR)*

[b] *Proposed therapeutic dose as directly measured by validated droplet digital PCR (ddPCR)*

AVXS-101-CL-303 Phase 3 Study in Subjects with Type 1 SMA with two copies of SMN2

Study CL-303 was a phase 3, open-label, single-arm, single-dose, multi-centre trial that assessed the efficacy and safety of intravenous administration of Zolgensma (1.1 × 10^{14} vg/kg) in subjects (n=22) with symptomatic SMA Type 1 with bi-allelic deletion of the survival motor neuron 1 (SMN1) gene and 2 copies of SMN2 gene without the SMN2 gene modifier mutation (c.859G>C). At the time of administration, the age and weight of subjects varied from 0.5 to 5.9 months and 3.9 to 7.5 kg, respectively.

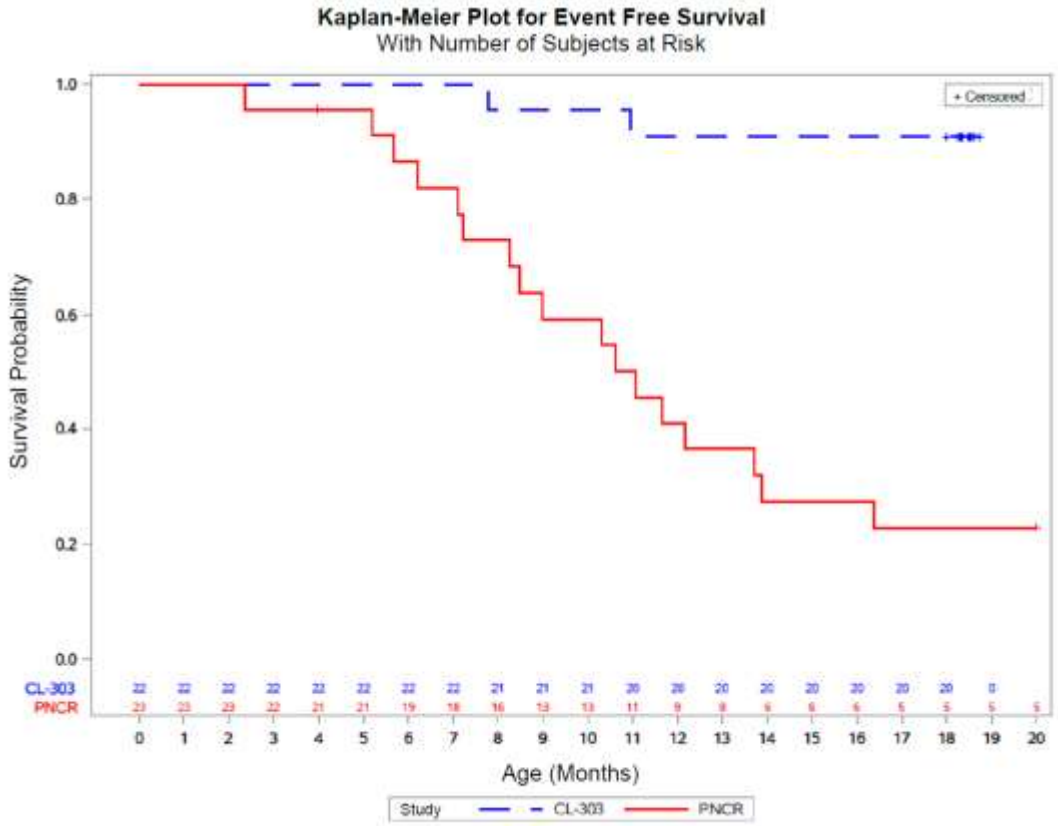
The co-primary efficacy endpoints were: i) the proportion of subjects that achieved functional independent sitting for at least 30 seconds at the 18 months of age study visit; and ii) survival at 14 months of age. Independent sitting was defined as sitting up straight with the head erect for at least 30 seconds as per the Bayley Scales of Infant and Toddler Development (ver. 3) and confirmed by video recording. Survival was defined as the avoidance of death or permanent ventilation (i.e., tracheostomy or requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation).

The co-secondary efficacy endpoints were: i) the proportion of subjects maintaining the ability to thrive; and ii) the proportion of subjects who were independent of ventilatory support at 18 months of age. Ability to thrive was defined as the ability to tolerate thin liquids and to maintain weight (> third percentile based on WHO Child Growth Standards for age and gender) without need of gastrostomy or other mechanical or non-oral nutritional support at 18 months of age.

Twenty subjects (90.9%) demonstrated event-free survival (alive without permanent ventilation) at 14 months of age (Figure 1). Three subjects did not complete the study, of which two subjects had an event (death or permanent ventilation). One subject died at age 7.8 months due to disease progression, and one subject required permanent ventilation prior to discontinuation at age 11.9

months. The other subject who did not complete the study discontinued at the age of 18 months due to an adverse event.

Figure 1 - Time to death or permanent ventilation in Study CL-303



PNCR = Pediatric Neuromuscular Clinical Research natural history cohort

Thirteen subjects (59.1%) confirmed the milestone of independent sitting for at least 30 seconds at the Month 18 visit; one additional subject achieved the milestone of sitting independently for 30 seconds at 16 months of age, but this milestone was not confirmed at the Month 18 visit. For the 14 subjects (64%) that achieved the milestone of independent sitting for at least 30 seconds, the median age when this milestone was first demonstrated was 12.6 months (min 9.2, max 18.6).

The video-confirmed developmental milestones for subjects in Study CL-303 are summarized in Table 9.

Table 9 - Median time to achievement of other motor milestones in Study CL-303

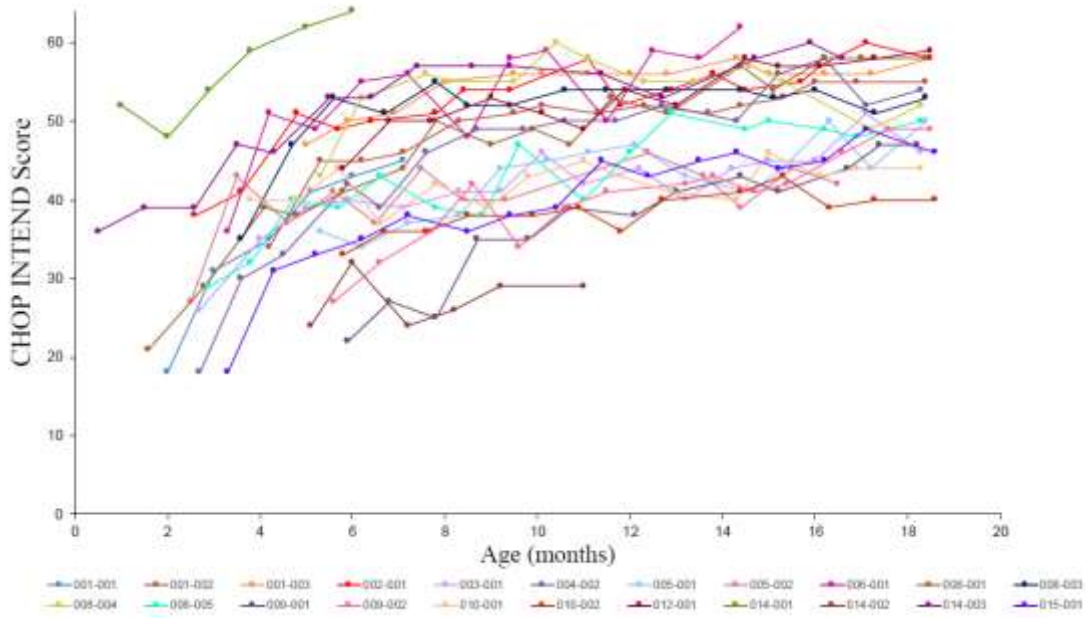
Video documented milestone	Number of subjects achieving milestone n/N (%)	Median age to the milestone achievement (Months)
Head control	17/20* (85)	6.8
Rolls from back to sides	13/22 (59)	11.5
Sitting without support for at least 10 seconds‡	14/22 (64)	13.9

* 2 subjects were reported to have 'head control' by clinician assessment at baseline.
‡ WHO (World Health Organization) definition

One subject (4.5%) walked with assistance at 12.9 months. Based on the natural history of the disease, subjects who met the study entry criteria would not be expected to attain the ability to sit without support. Additionally, only approximately 25% of these subjects would be expected to survive (i.e., being alive without permanent ventilation) beyond 14 months of age.

Motor function improvements relative to baseline were also observed as measured by the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) (Figure 2). Twenty-one subjects (95.5%) achieved a CHOP-INTEND score ≥ 40; subjects with untreated SMA Type 1 do not typically achieve a CHOP-INTEND score ≥ 40. Among these subjects, 14 (64%) achieved a CHOP-INTEND score ≥ 50, including five (23%) who achieved a CHOP-INTEND score ≥ 60.

Figure 2 - CHOP-INTEND Motor Function Scores in Study CL-303



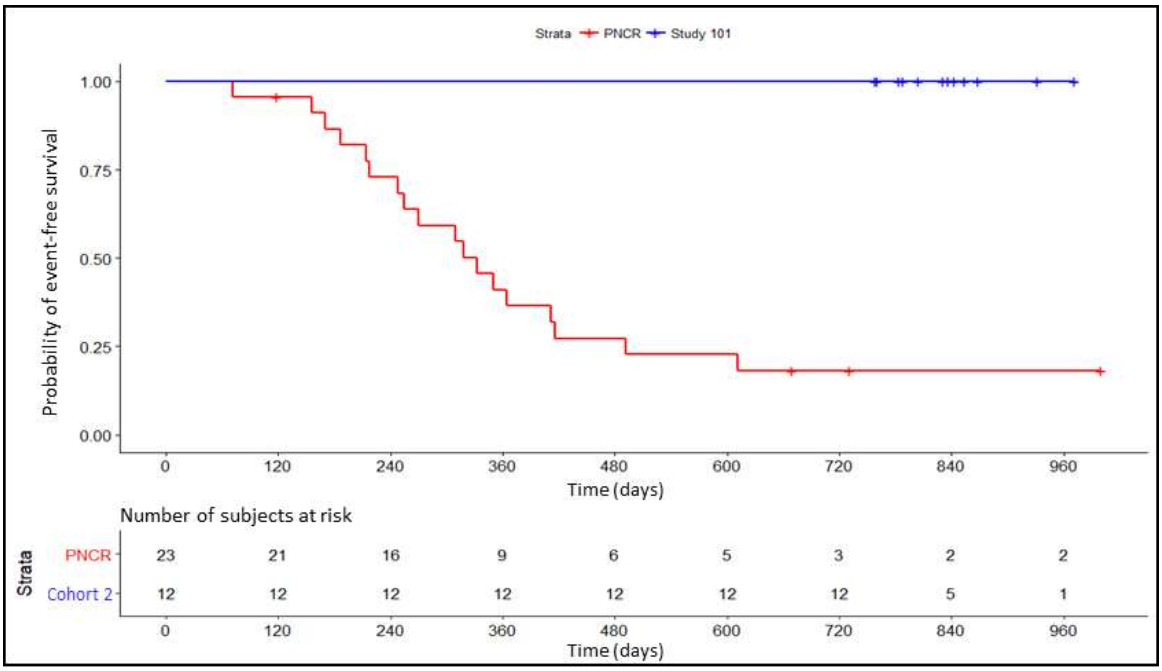
AVXS-101-CL-101 Phase 1 Study in Subjects with Type 1 SMA

Study CL-101 was a phase 1 open-label, single-arm, ascending dose, single-centre trial that assessed the safety and efficacy of intravenous administration of Zolgensma in subjects (n=12, cohort 2) with symptomatic SMA Type 1 with bi-allelic deletion of SMN1 gene and 2 copies of SMN2 gene without the SMN2 gene modifier mutation (c.859G>C). At the time of administration, the mean age of subjects was 3.4 (min 0.9, max 7.9) months.

The primary efficacy endpoint was event-free survival; survival was defined consistent with study CL-303. A key secondary efficacy endpoint was the achievement of clinically meaningful developmental milestones.

In cohort 2, all subjects demonstrated event-free survival at 14 months of age. At the end of the trial (24 months post dose), all subjects continued to demonstrate event-free survival (Figure 3).

Figure 3 - Time to death or permanent ventilation in Study CL-101



PNCR = Pediatric Neuromuscular Clinical Research natural history cohort.

At 24 months of follow-up post dose, 10 subjects (83.3%) were able to sit without support for ≥ 10 seconds, 9 subjects (75.0%) were able to sit without support for ≥ 30 seconds and 2 subjects (16.7%) were able to stand and walk without assistance.

AVXS-101-CL-304 Phase 3 Study in pre-symptomatic Subjects expected to develop SMA

Study CL-304 is an ongoing, phase 3, open-label, single-arm, single-dose, multi-centre trial that is assessing the efficacy and safety of intravenous Zolgensma (1.1×10^{14} vg/kg) in pre-symptomatic newborn subjects up to 6 weeks of age who are expected to develop infantile onset SMA. All subjects have bi-allelic deletion of SMN1 gene and either 2 copies (n=14; cohort 1) or 3 copies (n=15; cohort 2) of SMN2 gene. Data are limited to the most recent study visit prior to the data cut-off on 31 December 2019, At that time, subjects in cohort 1 were between 6 months and 18.6 months of age, and had been in the trial for a mean of 10.5 (min 5.1, max 18.0) months; subjects in cohort 2 were between 3.3 and 15.1 months of age and had been in the trial for a mean of 8.7 (min 2, max 13.9) months.

The primary efficacy endpoint in cohort 1 is the proportion of subjects achieving the development milestone of functional independent sitting for at least 30 seconds at any visit up to 18 months of age. The primary efficacy endpoint in cohort 2 is the proportion of subjects achieving the ability to stand without support for at least 3 seconds at any visit up to 24 months of age.

A key secondary efficacy endpoint in cohort 1 is the proportion of subjects that have survived to 14 months of age, without need for permanent ventilation (i.e., tracheostomy or requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation). A key secondary efficacy endpoint in cohort 2 is the proportion of subjects demonstrating the ability to walk alone, defined as the ability to take at least five steps independently displaying coordination and balance at any visit up to 24 months of age.

As of the data cut-off, all subjects had demonstrated event-free survival (i.e., alive without permanent ventilation). In cohort 1, eight subjects (57.1%) had achieved the milestone of sitting for at least 30 seconds. This milestone was achieved between 5.7 to 11.8 months of age. Six subjects (42.9%) who had not achieved this milestone were less than 9.2 months of age. Additionally, 12 subjects (85.7%) had achieved CHOP-INTEND scores ≥ 60. In cohort 2, four subjects (26.7%) had achieved the developmental milestone of the ability to stand without support for at least 3 seconds. This milestone was achieved between 9.5 and 12.4 months of age. Eleven subjects (73.3%) who had not achieved this milestone were less than 12.5 months of age. Additionally, two subjects (13.3%) achieved the milestone of able to walk at least five steps independently; 13 subjects (86.7%) who had not achieved this milestone were 3.3 to 12.5 months of age. Additionally, 10 subjects (66.7%) were able to sit without support for at least 30 seconds; this milestone was achieved between 6.1 and 12 months of age. Five subjects (33.3%) who had not achieved this milestone were between 3.3 and 9.6 months of age.

16. Non-Clinical Toxicology

Biodistribution: Biodistribution of onasemnogene abeparvovec in mice was evaluated at 3, 6, and 12 weeks following a single-dose administration of up to 3 X 10^{14} vg/kg by IV injection. Onasemnogene abeparvovec transduced target tissues such as neurons of the spinal cord and the brain, as well as many non-target organs, including the liver, lungs, spleen, adrenal gland, thymus, skeletal muscle, cardiac muscle, and reproductive organs as determined by the presence of vector genome and/or SMN mRNA. Onasemnogene abeparvovec showed a similar biodistribution in monkeys.

General Toxicology: In the mouse single-dose toxicity studies, the doses tested across the studies ranged from 7.9×10^{13} to 3.91×10^{14} vg/kg by IV injection, and the main target organs of toxicity identified were the heart and liver. Onasemnogene abeparvovec-related findings in the ventricles of the heart were comprised of dose-related inflammation, edema, and fibrosis. In the atria of the heart, inflammation, thrombosis, myocardial degeneration/necrosis, and fibroplasia were observed. Liver findings were comprised of hepatocellular hypertrophy, Kupffer cell activation, and scattered hepatocellular necrosis. Inflammation was reported in the lungs. Treatment-related mortality attributable to atrial thrombosis occurred at doses ≥2.4×10^{14} vg/kg. Onasemnogene abeparvovec-related findings in the ventricular myocardium were present at all doses studied and a No Observed Adverse Effect Level (NOAEL) could not be identified.

In a 6-month toxicology study conducted in juvenile cynomolgus monkeys, administration of a single dose of onasemnogene abeparvovec at the clinically recommended intravenous dose (1.1 x 10^{14} vg/kg), with or without corticosteroid treatment (oral prednisolone), resulted in oval cell hyperplasia in the liver. Monkeys also developed acute, mononuclear cell inflammation and neuronal degeneration in the dorsal root ganglia (DRG) and trigeminal ganglia (TG), as well as axonal degeneration and/or gliosis in the spinal cord. At 6 months, these findings showed decreased incidence and/or severity in the TG, DRG, spinal cord and liver. A NOAEL could not be determined for this study.

Carcinogenicity: Studies have not been conducted to evaluate the carcinogenic potential of onasemnogene abeparvovec.

Genotoxicity: Studies have not been conducted to evaluate the genotoxic potential of onasemnogene abeparvovec. Studies evaluating the potential for onasemnogene abeparvovec to integrate into the host genome have not been conducted.

Reproductive and Developmental Toxicology: Studies have not been conducted to evaluate the reproductive and developmental toxicity of onasemnogene abeparvovec.

Studies evaluating the potential for onasemnogene abeparvovec to integrate into the germline have also not been conducted. It is noted that vector DNA sequences and SMN mRNA were detected in the ovaries and testes of mice 3, 6, and 12 weeks following IV injection of onasemnogene abeparvovec at doses up to 3 X 10^{14} vg/kg. SMN mRNA were also detected in the testes of monkeys 12 months following IT injection of onasemnogene abeparvovec at a dose of 2 X10^{13} vg/kg.

Female monkeys were administered scAAV9 viral vector containing the gene for green fluorescent protein marker (i.e., not the SMN gene) under control of the CB promoter at doses of 1 X 10^{13} and 3 X 10^{13} vg/animal by intrathecal or intracisterna magna injection. The scAAV9 viral vector, which is utilized in onasemnogene abeparvovec, was shown to transduce oocytes.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrZOLGENSMA®

Onasemnogene abeparvovec

This Patient Medication Information is written for your child who will be receiving **Zolgensma®**. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **Zolgensma**, talk to a healthcare professional.

What Zolgensma is used for:

Zolgensma is a type of medicine called a 'gene therapy'. It contains the active ingredient onasemnogene abeparvovec, which contains human genetic material.

Zolgensma is used to treat babies and young children who have a rare, serious inherited condition called 'spinal muscular atrophy' (SMA).

How Zolgensma works:

Zolgensma supplies a fully functioning copy of the survival motor neuron 1 (SMN1) gene, which helps cells produce SMN protein necessary for the survival of nerves that control muscles (motor neurons). Patients treated with Zolgensma showed improvements relative to the usual progress of SMA. These improvements included the avoidance of death or permanent need for breathing help, and achievement of developmental motor milestones (e.g., head control, sitting, and standing).

The ingredients in Zolgensma are:

Medicinal ingredient: onasemnogene abeparvovec.

Non-medicinal ingredients: hydrochloric acid (for pH adjustment), magnesium chloride, poloxamer 188, sodium chloride, tromethamine, and water for injection.

Zolgensma comes in the following dosage forms:

Zolgensma is a clear to slightly cloudy solution for infusion. Each vial of Zolgensma contains onasemnogene abeparvovec at a nominal concentration of 2×10^{13} vg/mL.

Do not use Zolgensma if:

Your child is allergic to onasemnogene abeparvovec or any of the other ingredients of this medicine listed in this leaflet.

To help avoid side effects and ensure proper use, talk to your healthcare professional before your child is given Zolgensma. Talk about any health conditions or problems your child may have.

Warnings you should know about:

Your child's healthcare professional will test your child's blood for antibodies against part of this medicine to help decide if this medicine is suitable for your child.

Liver problems

If your child has had any problems with his/her liver, talk to your child's healthcare professional before your child is treated with this medicine. Zolgensma can cause an immune response that could damage the liver. Injury to the liver can lead to serious outcomes, including liver failure and death. Possible signs you need to look out for after your child is given this medicine include vomiting, jaundice (yellowing of the skin or of the whites of the eyes) or reduced alertness (see **Possible side effects from using Zolgensma** for more information). Tell your child's healthcare professional immediately if you notice your child develops any symptoms suggestive of injury to the liver. Your child will have a blood test to check liver function before starting treatment with Zolgensma. He/she will also have regular blood tests for at least 3 months after being treated with Zolgensma to check for increases in liver enzymes.

Educational materials for caregivers related to the risks of liver problems are available through the manufacturer.

Infections

If your child develops an infection (such as cold, flu, or bronchiolitis) before or after being treated with Zolgensma, this could lead to more serious problems, which could be life-threatening. Caregivers and close contacts with the patient should follow infection prevention practices (e.g., hand hygiene, respiratory/cough etiquette, limit potential contacts). Signs of a possible infection that you need to check for in your child include coughing, wheezing, sneezing, runny nose, sore throat, or fever. Tell your child's healthcare professional immediately if you notice that your child develops any signs suggestive of infection **before** or **after** Zolgensma treatment.

Risk of bleeding and blood clotting problems

Zolgensma can lower the number of a certain type of cell in the blood, called blood-platelets (a condition called thrombocytopenia). This has been observed to generally occur within the first two weeks after Zolgensma treatment. Possible signs of a low blood-platelet count you need to check for after your child is treated with Zolgensma include abnormal bruising, blood in urine or feces, or nosebleeds (see **Possible side effects from using Zolgensma** for more information).

Blood clotting problems in small blood vessels (a serious and potentially life-threatening condition called thrombotic microangiopathy) have been reported in some patients usually within the first two weeks after treatment with Zolgensma. This happened at the same time as a decrease in red blood cells and a decrease in cells involved in clotting (blood-platelets). These blood clots could damage your child's kidneys. Before starting treatment with Zolgensma, your child will have a blood test to check the amount of blood cells (including red blood cells and platelets) as well as creatinine level, which is an indicator of how the kidneys are working. Following Zolgensma treatment, your child's healthcare professional may want to check your child's blood cells (platelet counts) and blood pressure. Seek urgent medical attention if your child starts to bruise easily, has seizures (fits), develops a fever, or passes less urine than usual after Zolgensma treatment (see **Possible side effects from using Zolgensma** for more information).

Educational materials for caregivers related to the risks of thrombocytopenia and thrombotic microangiopathy are available through the manufacturer.

Heart problems

Zolgensma may cause raised levels in the blood of a protein specific to the heart called 'troponin-I'. Increased levels may indicate damage to the heart. Possible signs you need to look out for after your child is given Zolgensma include pale grey/blue skin colour, difficulty in breathing (e.g. rapid breathing, shortness of breath) at rest or with activity, tiring easily or sweating during feeding, and swelling of the arm/legs or abdomen. Tell your child's doctor right away if you notice your child develops any of the above symptoms, which are signs of potential heart problems. (See **Possible side effects from using Zolgensma** for more information.)

Infusion-related side effects

Life-threatening infusion-related side effects, including serious allergic (anaphylactic) reactions have occurred during, and/or shortly after, Zolgensma infusion. Signs and symptoms of these reactions may include rash, hives, vomiting, flushing, chills, mouth/tongue/face swelling, difficulty breathing, shortness of breath, and changes in heart rate and blood pressure. Tell your child's doctor or healthcare provider immediately if your child experiences these or any other new signs and symptoms during or shortly after infusion. Your child may be given additional medication to treat the signs and symptoms of this side effect. Before your child is discharged, the doctor will provide you with information on what to do in case your child experiences new side effects or side effects which come back once you leave the medical facility.

Risk of tumours associated with potential insertion of gene therapy DNA into the patient's DNA

Zolgensma DNA has been shown to insert into the DNA of patient's body cells. As a consequence, Zolgensma could contribute to a risk of tumours. Some patients treated with Zolgensma have developed tumours, but it is not certain at this time if Zolgensma was the cause of those tumours. You should discuss this with your child's doctor. In the event of a tumour, your child's doctor may take a sample for further evaluation.

Additional information for parents/caregiver

Regular blood tests

Your child will have a blood test to check liver function before starting treatment with Zolgensma. He/she will also have regular blood tests for at least 3 months after being treated with Zolgensma to check for increases in liver enzymes.

Before starting treatment with Zolgensma, your child will have blood tests to check the amount of blood cells (including red blood cells and platelets), as well as creatinine levels. Your child will also have regular blood tests for at least three months after treatment with Zolgensma to check for possible changes in blood-platelets. Troponin-I levels may also be checked.

Advanced SMA

Zolgensma can save living motor neurons, but does not rescue dead motor neurons. Children with less severe symptoms of SMA (such as absent reflexes or reduced muscle tone) may have enough live motor neurons to receive meaningful benefit from Zolgensma. Zolgensma may not work as well in children with severe muscle weakness or paralysis, with breathing problems, who are unable to swallow, or with critical malformation (such as heart defects). These signs suggest less potential for improvement from treatment with Zolgensma. Your child's healthcare professional will decide if your child should be treated with Zolgensma.

Hygiene care

The active substance in Zolgensma will be passed from your child's body in their waste. As parents/caregivers, you must follow additional hygiene practices for at least one month after your child is treated with Zolgensma. Wear protective gloves when coming into direct contact with your child's bodily fluids or waste and wash hands thoroughly afterward with soap and warm running water, or an alcohol-based hand sanitizer. Double bags should be used to dispose of soiled diapers and other waste. Disposable diapers may still be disposed of in household waste. Reusable diapers should not be used during the first month after Zolgensma treatment.

Talk to your child's doctor or nurse if you have any questions.

Tell your child's healthcare professional about all the medicines your child is taking, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

At this time, there are no known medicines that interact with Zolgensma.

Prednisolone

Your child will also be treated with a medicine called 'prednisolone' (see **How Zolgensma is given**) before and after his/her treatment with Zolgensma. Prednisolone is a type of medicine called a 'corticosteroid' which will help manage any potential liver damage that your child could develop after Zolgensma treatment. Your child's healthcare professional will decide if your child should be treated with prednisolone or a different corticosteroid.

Vaccinations

As corticosteroids can affect the body's immune system, **your child's healthcare professional may decide to delay giving some vaccinations** to your child while he/she is treated with prednisolone/corticosteroid. Talk to your child's healthcare professional if you have any questions.

How Zolgensma is given:

Zolgensma is given to your child by a healthcare professional trained in the delivery of gene therapy and in the management of SMA.

Zolgensma is given intravenously (into a vein) to your child by a single infusion (drip) over a period of 1 hour.

Usual dose:

The amount of Zolgensma your child will be given will be calculated based on their weight. The dose is measured in units called vector genomes.

The recommended dose is 1.1×10^{14} vector genomes per kilogram (kg) of body weight.

Zolgensma will be given to your child ONCE only.

Starting 24 hours before treated with Zolgensma, your child will also be given treatment with prednisolone (or another corticosteroid) by mouth. The dose of prednisolone will depend on your child's weight. The recommended dose of prednisolone is 1 mg per kg body weight daily. Your child's healthcare professional will calculate the correct total dose.

After treatment with Zolgensma, your child will be treated with prednisolone every day for approximately 2 months until your child's increased liver enzymes decrease to an acceptable level. Your

child's dose of prednisolone will be slowly reduced until treatment can be fully stopped. **The prednisolone treatment must not be stopped suddenly.** Your child's healthcare professional will explain when and how they will stop this treatment for your child.

If you have any further questions on the use of Zolgensma or prednisolone, ask your child's healthcare professional.

Overdose:

There is no experience of overdose with Zolgensma.

If you think your child has been given too much Zolgensma, contact your child's healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If your child is unable to be treated with Zolgensma as planned, talk to your healthcare professional to ensure that Zolgensma can be given as soon as possible.

Possible side effects from using Zolgensma:

Like all medicines, Zolgensma can cause side effects, although not everybody gets them.

Talk to your child's doctor or nurse if your child develops any side effects. These can include:

Very common (may affect more than 1 in 10 people)

- increases in liver enzymes (aminotransferases) seen in blood tests
- fever

Common (may affect up to 1 in 10 people):

- vomiting
- decreases in blood-platelets, seen in blood tests
- increases in troponin-I (a heart protein) seen in blood tests

These are not all the possible side effects your child may feel when taking Zolgensma. If your child experiences any side effects not listed here, contact your child's healthcare professional.

Serious side effects and what to do about them			
Frequency/Side Effect/Symptom	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Thrombocytopenia (low blood-platelet count): Bruising or bleeding for longer than usual if your child has been hurt, blood in urine or feces, nosebleeds			√
Heart problems: Pale grey or blue skin colour, difficulty in breathing (e.g., rapid breathing, shortness of			√

Serious side effects and what to do about them			
Frequency/Side Effect/Symptom	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
breath), swelling of the arm/legs or abdomen			
FREQUENCY NOT KNOWN			
Thrombotic microangiopathy (abnormal clotting of blood in small blood vessels): Bruising easily, seizures (fits), decrease in urine output			√
Liver injury/failure: Vomiting, yellowish skin or eyes, irritability/fussiness, swollen abdomen, sleeping more than normal			√
Infusion-related reaction: Rash, hives, vomiting, flushing, mouth/throat/face swelling, difficulty breathing, shortness of breath and/or changes in heart rate and blood pressure during, and/or shortly after, infusion			√

If your child has a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with their daily activities, talk to your child's healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Zolgensma will be managed and stored by healthcare professionals. Below are some of the guidelines for storing Zolgensma:

- Vials will be transported frozen (at or below -60°C).
- Upon receipt vials should be refrigerated at 2°C to 8°C immediately, and in the original carton.

Zolgensma therapy should be initiated within 14 days of receipt of vials.
- Do not use this medicine after the expiry date which is stated on the vial label and carton after EXP. The expiry date refers to the last day of that month.
- Keep out of reach and sight of children.

If you want more information about Zolgensma:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (Drug Product Database: Access the database); the manufacturer's website www.novartis.ca, or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

Date of Authorization: 2025-11-21

ZOLGENSMA is a registered trademark