

▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – ZOLGENSMA® (ONASEMNOGENE ABEPARVOVEC) FOR SINGLE-DOSE INTRAVENOUS INFUSION ONLY

WARNING: ACUTE SERIOUS LIVER INJURY

- Acute serious liver injury and elevated aminotransferases can occur with ZOLGENSMA (see 4.4 Special warnings and precautions for use).
- Patients with pre-existing liver impairment may be at higher risk. (see 4.4 Special warnings and precautions for use)
- Prior to infusion, assess liver function of all patients by clinical examination and laboratory testing (e.g., hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time). Administer systemic corticosteroid to all patients before and after ZOLGENSMA infusion. Continue to monitor liver function for at least 3 months after infusion (see 4.2 Dosage and method of administration, subheading Laboratory testing and monitoring to assess safety).

1 NAME OF THE MEDICINE

Onasemnogene abeparvovec

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Onasemnogene abeparvovec is a gene therapy medicinal product that expresses the human survival motor neuron (SMN) protein. It is a non-replicating recombinant adeno-associated vector serotype 9 (AAV9) containing the cDNA of the human SMN gene under the control of the cytomegalovirus enhancer/chicken- β -actin-hybrid promoter.

Onasemnogene abeparvovec is produced in human embryonic kidney cells by recombinant DNA technology.

Each mL contains onasemnogene abeparvovec with a nominal concentration of 2×10^{13} vector genomes (vg). Vials will contain an extractable volume of not less than either 5.5 mL or 8.3 mL. The total number of vials and combination of fill volumes in each finished pack will be customised to meet dosing requirements for individual patients depending on their weight (see 4.2 Dosage and Method of Administration and 6.5 Nature and contents of

container).

Excipient with known effect

This medicinal product contains 0.2 mmol sodium per mL.

For the full list of the excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Injection for intravenous infusion.

When thawed, it is a clear to slightly opaque, colourless to faint white solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ZOLGENSMA (onasemnogene abeparvovec) is indicated for the treatment of paediatric patients less than 9 months of age with symptomatic or pre-symptomatic spinal muscular atrophy with bi-allelic mutations in the *survival motor neuron 1 (SMN1)* gene and 1 to 3 copies of the SMN2 gene.

4.2 DOSAGE AND METHOD OF ADMINISTRATION

Dosage

For single-dose intravenous infusion only.

Treatment with ZOLGENSMA should be supervised by a physician experienced in the management of patients with SMA.

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

An immune response to the adeno-associated viral vector serotype 9 (AAV9) capsid will occur after infusion of ZOLGENSMA, thus patients should not be re-dosed with ZOLGENSMA.

ZOLGENSMA is for a single treatment only.

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

Table 1 Dosing

Patient Weight Range (kg)	Total Dose Volume^a (mL)
2.6 – 3.0	16.5
3.1 – 3.5	19.3
3.6 – 4.0	22.0
4.1 – 4.5	24.8

Patient Weight Range (kg)	Total Dose Volume ^a (mL)
4.6 – 5.0	27.5
5.1 – 5.5	30.3
5.6 – 6.0	33.0
6.1 – 6.5	35.8
6.6 – 7.0	38.5
7.1 – 7.5	41.3
7.6 – 8.0	44.0
8.1 – 8.5	46.8
8.6 – 9.0	49.5
9.1 – 9.5	52.3
9.6 – 10.0	55.0
10.1 – 10.5	57.8
10.6 – 11.0	60.5
11.1 – 11.5	63.3
11.6 – 12.0	66.0
12.1 – 12.5	68.8
12.6 – 13.0	71.5
13.1 – 13.5	74.3

^a Dose volume is calculated using the upper limit of the patient weight range.

Laboratory Testing and Monitoring to Assess Safety

Perform baseline anti-AAV9 antibody testing prior to ZOLGENSMA infusion. Retesting may be performed if anti-AAV9 antibody titres are reported as >1:50.

Conduct the following tests at baseline and as directed below (see 4.4. Special warnings and precautions for use, subheadings Acute serious liver injury and elevated amino transferases, Thrombocytopenia and Elevated Troponin-1):

- Liver function (clinical exam, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, prothrombin time) weekly for the first month; every other week for the second and third months, until results are unremarkable (normal clinical exam, total bilirubin, and prothrombin results, and ALT and AST levels below 2 × the upper limit of normal (ULN)).
- Platelet counts weekly for the first month, and then every other week for the second and third months, until platelet counts return to baseline.
- Troponin-I weekly for the first month, and then monthly for the second and third months, until troponin-I level returns to baseline.

Patients with ALT, AST or total bilirubin greater than 2 times ULN should not be dosed with ZOLGENSMA. The exception is when the elevated total bilirubin is due to neonatal jaundice.

Prednisolone Treatment Pre- and Post-ZOLGENSMA Infusion

To manage possible liver function abnormalities, all patients should receive prednisolone given orally before and after dosing ZOLGENSMA (see 4.4 Special warnings and precautions for use subheading Acute Serious Liver Injury and Elevated Aminotransferases).

Treatment with Prednisolone Prior to ZOLGENSMA Infusion

One day prior to ZOLGENSMA infusion, pre-treat with oral prednisolone at a dose of 1 mg/kg/day (or equivalent).

Continued Treatment with Prednisolone Following ZOLGENSMA Infusion

- Prednisolone should be administered daily at 1 mg/kg/day (or equivalent) for 30 days following infusion with ZOLGENSMA.
- At the end of the 30-day period of systemic corticosteroid treatment, check liver status clinically and by assessing ALT, AST, total bilirubin, and prothrombin time.
- For patients with unremarkable findings (normal clinical exam, total bilirubin, and prothrombin time, and ALT and AST levels below 2 × ULN), taper the corticosteroid dose over the next 28 days (see 4.4. Special warnings and precautions for use, subheading Acute serious liver injury and elevated aminotransferases).
- If liver function abnormalities persist, continue systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg/day) until AST and ALT values are both below 2 ×ULN and all other assessments return to normal range, and then taper the corticosteroid dose over the next 28 days.
- Continue to monitor liver function for at least 3 months after infusion.
- Consider consulting expert(s) if patients do not respond adequately to the equivalent of 1 mg/kg/day oral prednisolone.

Variance from these recommendations is at the discretion of the treating physician. If another corticosteroid is used by the physician in place of prednisolone, similar considerations and approach to taper the corticosteroid dose after 30 days following infusion with ZOLGENSMA should be taken as appropriate.

Where feasible, the patient's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following ZOLGENSMA infusion (see sections 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicines and other forms of interactions).

Requirements for a genetically-modified organism

ZOLGENSMA contains a genetically-modified organism. Follow local institutional guidelines for storage, handling, administration and disposal of medicinal products containing genetically-modified organisms.

- The onasemnogene abeparvovec syringe should be prepared aseptically under sterile conditions.
- Personal protective equipment (to include gloves, safety goggles, laboratory coat and sleeves) should be worn while preparing or administering onasemnogene abeparvovec. Personnel should not work with onasemnogene abeparvovec if skin is cut or scratched.
- All spills of onasemnogene abeparvovec must be wiped with absorbent gauze pad and the spill area must be disinfected using a bleach solution followed by alcohol wipes. All clean up materials must be double bagged and disposed of per institutional guidelines for biohazard waste.
- All materials that may have come in contact with onasemnogene abeparvovec (e.g. vial, all materials used for injection, including sterile drapes and needles) must be disposed of in accordance with local institutional biosafety guidelines.
- Take precautions to avoid accidental exposure to onasemnogene abeparvovec. In the event of exposure to skin, the affected area must be thoroughly cleaned with soap and water for at least 15 minutes. In the event of exposure to eyes, the affected area must be thoroughly flushed with water for at least 15 minutes.

Method of administration

Administer ZOLGENSMA as a single-dose intravenous infusion through a venous catheter. ZOLGENSMA is for single use in one patient only. Discard any residue.

Preparation

- ZOLGENSMA should be prepared aseptically under sterile conditions.
- Thaw ZOLGENSMA before use. The contents of the ZOLGENSMA pack will thaw in approximately 12 hours when placed in a refrigerator (2°C – 8°C), or in approximately 4 hours if placed at room temperature (20°C - 25°C).
- If thawed in a refrigerator, remove from refrigerator on day of dosing.
- 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.
- Prior to dosing draw the appropriate dose volume from all vials into a syringe, remove air from the syringe, cap the syringe, and deliver the syringe at room temperature to the patient infusion location. Dispose of vials in accordance with local institutional biosafety guidelines.
- Use ZOLGENSMA within 6 hours of drawing into syringe. Discard the vector-containing syringe if the drug is not infused within the 6-hour timeframe. Dispose of the syringe in accordance with local institutional biosafety guidelines.
- DO NOT REFREEZE.

Follow the steps below for infusion:

1. Place a primary catheter into a vein (generally a peripheral vein in the arm or leg). Insertion of a back-up catheter is recommended.
2. Program syringe pump for saline priming, or prime tubing manually with saline.
3. Administer ZOLGENSMA as a slow infusion over 60 minutes. DO NOT INFUSE AS AN INTRAVENOUS PUSH OR BOLUS.
4. Flush line with saline following completion of infusion.

Special populations

Paediatric patients

Administration of ZOLGENSMA to premature neonates before reaching full-term gestational age should be carefully considered. The safety and efficacy of ZOLGENSMA in these patients have not been established.

The efficacy and safety of ZOLGENSMA was studied in paediatric patients who received ZOLGENSMA infusion at age 0.3 to 7.9 months (weight up to 8.4 kg) (see 4.8 Adverse effects (Undesirable effects) and 5.1 Clinical Studies).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in 6.1 List of excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 higher benefit.

Progressive motor neuron loss is irreversible. The treating physician should consider that the benefit is seriously reduced in patients with profound muscle weakness and respiratory failure, patients on permanent ventilation, and patients not able to swallow.

Patients requiring permanent ventilatory support have not been evaluated and treatment with ZOLGENSMA is not recommended. Permanent ventilation is defined as requiring invasive ventilation (tracheostomy), or respiratory assistance for 16 or more hours per day (including noninvasive ventilatory support) continuously for 14 or more days in the absence of an acute reversible illness, excluding perioperative ventilation.

Acute Serious Liver Injury and Elevated Aminotransferases

Acute serious liver injury has occurred with ZOLGENSMA. Prior to ZOLGENSMA infusion, a patient with infantile-onset SMA had elevated AST and ALT of unknown etiology (gamma-glutamyl transferase (GGT), total bilirubin and prothrombin time were normal). The patient

was treated under an expanded access program in the United States. The patient received corticosteroids equivalent to oral prednisolone at 1 mg/kg/day for approximately 30 days, followed by a 14-day taper. Approximately 7 weeks after receiving ZOLGENSMA, the patient became jaundiced. Laboratory testing was consistent with acute serious liver injury, with AST level approximately $80 \times$ ULN and ALT level approximately $45 \times$ ULN, total bilirubin approximately $4 \times$ ULN, and plasma prothrombin time approximately $4 \times$ ULN. Liver biopsy showed acute massive degeneration of hepatocytes, and massive mixed inflammatory infiltrate (primarily CD8-positive T lymphocytes). The patient recovered to baseline status after treatment with corticosteroids.

Administration of AAV vector may result in transaminase elevations, which may be serious. Elevated transaminases greater than 2 times ULN were reported (see Table 2) in up to 12% of patients treated at the recommended dose and were considered study-drug related. Two patients had AST and ALT elevations of $> 20 \times$ ULN (one of these patients was experiencing a viral infection). These patients were clinically asymptomatic, did not exhibit jaundice or a clinically significant elevation of bilirubin and did not meet Hy's Law criteria.

Systemic immune response, including immune-mediated hepatotoxicity, has been reported in the ZOLGENSMA clinical program and may require adjustment of corticosteroid treatment regimen including longer prednisolone support or increased dose (see 4.2 Dosage and method of administration).

Patients with pre-existing liver impairment or acute hepatic viral infection may be at higher risk of liver injury.

The risks and benefits of infusion with ZOLGENSMA should be weighed carefully against the risks of not treating the patient.

Prior to ZOLGENSMA infusion, assess liver function by clinical examination and laboratory testing (hepatic aminotransferases [AST and ALT], total bilirubin level, and prothrombin time). Continue to monitor liver function for at least 3 months after ZOLGENSMA infusion (weekly for the first month, and then every other week for the second and third months, until results are unremarkable). In order to mitigate potential liver function abnormalities, administer systemic corticosteroid before and after ZOLGENSMA infusion. Tapering of prednisolone should not be considered until AST/ALT are less than 2 times ULN and all other assessments return to normal range (See 4.2 Dosage and method of administration).

Systemic immune response

Concurrent respiratory infection could increase the risk of serious systemic immune response. Increased vigilance in the diagnosis and active management of viral respiratory infection is recommended. In instances where clinical signs or symptoms of respiratory viral infection are not evident at the time of ZOLGENSMA administration, the treating physician should be aware of the possibility of adrenal insufficiency in the presence of systemic immune response which may require longer prednisolone support at increasing doses to effectively manage the patient and prevent serious complications. Seasonal prophylaxis against respiratory syncytial virus (RSV) is recommended and should be up-to-date. Added caution is advised regarding the timing of ZOLGENSMA dosing in the presence of prodrome or resolving viral illness.

Immunogenicity

In ZOLGENSMA clinical trials, confirmation of AAV9 antibody titres at or below 1:50 was required prior to infusion. It has not been established whether infusion of ZOLGENSMA may represent a risk for an immune response for patients with pre-existing AAV9 antibodies at higher titres. The safety and efficacy of ZOLGENSMA has not been established in patients with baseline AAV9-antibody titres above 1:50. Patients should be tested for the presence of AAV9 antibodies prior to infusion with ZOLGENSMA. Retesting may be performed if AAV9 antibody titres are reported as above 1:50. An immune response to the adeno-associated viral vector serotype 9 (AAV9) capsid will occur after infusion of ZOLGENSMA.

Thrombocytopenia

Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were observed on ZOLGENSMA clinical trials at different time points after ZOLGENSMA infusion (see 4.8 Adverse effects (Undesirable effects)). In most cases, the lowest platelet value occurred the first week following ZOLGENSMA infusion. Monitor platelet counts before ZOLGENSMA infusion and on a regular basis afterwards (weekly for the first month; every other week for the second and third months until platelet counts return to baseline. See 4.2 Dosage and method of administration, subheading Laboratory testing and monitoring to assess safety.

Thrombotic microangiopathy

Thrombotic microangiopathy (TMA) has been reported with ZOLGENSMA in the post-marketing setting (see 4.8 Adverse effects (Undesirable effects)). Thrombotic microangiopathy is characterized by thrombocytopenia, microangiopathic haemolytic anaemia, and acute kidney injury. Cases have been reported to occur approximately one week after ZOLGENSMA infusion. Concurrent immune system activation (e.g., infections, vaccinations) was identified as a contributing factor in some cases.

Thrombocytopenia is a key feature of TMA, therefore platelet counts should be monitored (see 4.4 subheading Thrombocytopenia above), as well as signs and symptoms of TMA, such as hypertension, increased bruising, seizures, and decreased urine output. If clinical signs, symptoms or laboratory findings consistent with TMA occur, manage as clinically indicated.

Elevated Troponin-I

Increases in cardiac troponin-I levels (up to 0.176 micrograms/L) were observed following ZOLGENSMA infusion in clinical trials (see 4.8 Adverse effects (Undesirable effects)). Elevated troponin-I levels found in some patients may indicate potential myocardial tissue injury. Clinical cardiac findings of concern have not been observed following administration of ZOLGENSMA. Cardiac toxicity was observed in animal studies (see 5.4 Preclinical safety data). Monitor troponin-I before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards (weekly for the first month, and then monthly for the second and third months until troponin-I level returns to baseline), see 4.2 Dosage and method of administration, subheading Laboratory testing and monitoring, to assess safety. Consider consultation with a cardiac expert as needed.

Systemic corticosteroid administration and live vaccines

Live vaccines should not be administered to patients receiving high doses of corticosteroids (i.e., ≥ 2 weeks of daily receipt of 20 mg or 2 mg/kg body weight of prednisone or equivalent) prior to and following ZOLGENSMA infusion (see 4.5 Interactions with other medicines and other forms of interactions below).

Use in hepatic impairment

ZOLGENSMA has not been studied in patients with hepatic impairment. ZOLGENSMA therapy should be carefully considered in patients with hepatic impairment. One patient who received ZOLGENSMA developed acute serious liver injury; that patient had elevated aminotransferase levels prior to ZOLGENSMA infusion. In clinical trials, elevation of aminotransferases was observed in patients following ZOLGENSMA infusion (see 4.4 subheading Acute serious liver injury and elevated aminotransferases above).

Use in renal impairment

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

Use in the elderly

Not applicable to this medicine.

Paediatric use

Administration of ZOLGENSMA to premature neonates before reaching full-term gestational age is not recommended, because concomitant treatment with corticosteroids may adversely affect neurological development. Delay ZOLGENSMA infusion until the corresponding full-term gestational age is reached.

There is no information on whether breastfeeding should be restricted in mothers who may be seropositive for anti-AAV9 antibodies.

The efficacy and safety of ZOLGENSMA was studied in paediatric patients who received ZOLGENSMA infusion at age 0.3 to 7.9 months (weight up to 8.4 kg) (see 4.8 Adverse effects (Undesirable effects) and 5.1 Pharmacodynamic properties, Clinical trials).

Effects on laboratory tests

No data are available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed. Interactions with antiviral medicinal products are not expected. Live vaccines, such as MMR and varicella, are contraindicated for patients on a substantially immunosuppressive steroid dose (i.e., ≥ 2 weeks of daily receipt of 20 mg or 2 mg/kg body weight of prednisone or equivalent) because high doses of corticosteroids may reduce the immune response to these vaccines. Where feasible, adjust a patient's vaccination schedule to accommodate concomitant corticosteroid administration prior to

and following ZOLGENSMA infusion (see 4.2 Dosage and method of administration). Seasonal RSV prophylaxis is not precluded.

ZOLGENSMA has not been studied in conjunction with other therapies for SMA. No information is available whether use of multiple therapies might carry additional risks.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There are no fertility data available.

Use in pregnancy - B2

There are no available data regarding ZOLGENSMA use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with ZOLGENSMA.

Use in lactation

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety of ZOLGENSMA was evaluated in 97 patients who received the recommended dose (1.1×10^{14} vg/kg) from 4 open-label clinical studies (CL-101, CL-303, CL-302, CL-304) and a long-term observational follow-up study (LT-001). The patients ranged in age from 0.3 months to 7.9 months at the time of administration (weight up to 8.5 kg). The follow-up time ranged from 1.8 months to 61.9 months as of the 31 December 2019 cut-off.

Of the 97 patients who received the therapeutic dose, 45 patients (46%) had at least 1 SAE, and 39 patients (40%) had at least one Treatment-Emergent Adverse Event (TEAE) that was Grade 3 severity or higher.

At the proposed therapeutic IV dose, the most frequently reported TEAEs ($\geq 10.0\%$) were pyrexia (47 patients, 48.5%), upper respiratory tract infection (36 patients, 37.1%), vomiting (24 patients, 24.7%), constipation (22 patients, 22.7%), cough (20 patients, 20.6%), gastroesophageal reflux disease (17 patients, 17.5%), diarrhoea, (15 patients, 15.5%), pneumonia (15 patients, 15.5%), rash (14 patients, 14.4%), transaminases increased (12 patients, 12.4%), nasal congestion (11 patients, 11.3%), scoliosis (11 patients, 11.3%), gastroenteritis (10 patients, 10.3%) and teething (10 patients, 10.3%).

The adverse drug reactions identified with ZOLGENSMA in all patients treated with intravenous infusion are presented in Table 2. The most frequently reported ($\geq 10\%$) adverse reaction following administration was transaminases increased.

Adverse drug reactions from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequency categories are derived according to the following conventions (CIOMS III): very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

Table 2 Summary of adverse drug reactions from ZOLGENSMA clinical trials

Adverse Drug Reactions	Frequency %	Frequency Category
System organ class	(N=97)	
Preferred term		
Blood and lymphatic system disorders		
Thrombocytopenia	4.1	Common
Gastrointestinal disorders		
Vomiting	8.2	Common
General disorders and administration site conditions		
Pyrexia	4.1	Common
Investigations		
Transaminases increased	12.4	Very common
Aspartate aminotransferase (AST) increased	9.3	Common
Alanine aminotransferase (ALT) increased	8.2	Common
Elevated troponin-I	3.1	Common
Hepatobiliary disorders		
Hypertransaminasaemia	8.2	Common

Table 3 Summary of adverse events occurring in >5% of patients from ZOLGENSMA clinical trials

Preferred Term	Proposed Therapeutic IV Dose (N=97) n (%)
Pyrexia	48 (49.5)
Upper respiratory tract infection	36 (37.1)
Constipation	25 (25.8)
Vomiting	24 (24.7)
Cough	21 (21.6)
Gastrooesophageal reflux disease	17 (17.5)
Diarrhoea	15 (15.5)
Pneumonia	15 (15.5)
Rash	14 (14.4)
Nasal congestion	12 (12.4)
Transaminases increased	12 (12.4)
Scoliosis	11 (11.3)
Gastroenteritis	10 (10.3)
Teething	10 (10.3)
Aspartate aminotransferase (AST) increased	9 (9.3)
Bronchiolitis	9 (9.3)
Hypertransaminaemia	9 (9.3)
Respiratory distress	9 (9.3)
Respiratory tract infection	9 (9.3)
Alanine aminotransferase (ALT) increased	8 (8.2)
Conjunctivitis	8 (8.2)
Gastroenteritis viral	8 (8.2)
Nasopharyngitis	8 (8.2)
Otitis media	8 (8.2)

Rhinovirus infection	8 (8.2)
Viral upper respiratory tract infection	8 (8.2)
Ear infection	7 (7.2)
Contusion	6 (6.2)
Muscle contractions involuntary	6 (6.2)
Respiratory failure	6 (6.2)
Urinary tract infection	6 (6.2)
Use of accessory respiratory muscles	6 (6.2)
Atelectasis	5 (5.2)
Dermatitis diaper	5 (5.2)
Hypertension	5 (5.2)
Irritability	5 (5.2)
Respiration abnormal	5 (5.2)
Respiratory syncytial virus bronchiolitis	5 (5.2)
Rhinorrhoea	5 (5.2)
Tachycardia	5 (5.2)
Tachypnoea	5 (5.2)

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reaction has been derived from post-marketing experience with ZOLGENSMA via spontaneous case reports. Because this reaction is reported voluntarily, it is not possible to reliably estimate its frequency which is therefore categorised as not known. The adverse drug reaction is listed according to system organ class in MedDRA.

- **Blood and lymphatic system disorders:** *Thrombotic microangiopathy*

Description of selected adverse drug reactions

Hepatobiliary disorders

Elevated transaminases greater than 2 times ULN were reported in up to 12% of patients treated at the recommended dose and were considered study-drug related. Two patients had AST and ALT elevations of greater than 20 times ULN (one of these patients was experiencing

a viral infection). These patients were clinically asymptomatic, did not exhibit jaundice or a clinically significant elevation of bilirubin and did not meet Hy's Law criteria. Serum transaminase elevations resolved with prednisolone treatment, and patients recovered without clinical sequelae. One patient in the US Managed Access Program (MAP) who had abnormal AST/ALT levels (>3 times ULN) before administration of ZOLGENSMA experienced worsening of acute liver injury after administration of ZOLGENSMA. The patient had resolution of liver injury within 4 months with prednisolone administration.

Transient thrombocytopenia

Transient decreases from baseline in mean platelet counts reaching levels of potential clinical significance were seen in 6.2% of patients at multiple time points post-dose and normally resolved within two weeks; the decreases were reported as adverse events in 4.1% of patients. Decreases in platelet counts were more prominent during the first week of treatment. No patients had clinical symptoms associated with decreased platelets (see 4.4 Special warnings and precautions for use).

Increases of troponin-I levels

Increases in cardiac troponin-I levels were reported as adverse events in 3.1% of patients (up to 0.2 microgram/L) following ZOLGENSMA infusion. The clinical relevance of these findings is not known (see 4.4 Special warnings and precautions for use).

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 neutralising 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. Pre- and post-gene therapy titres of AAV9 antibody were measured in the clinical studies (see 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties subheading Clinical trials).

In ZOLGENSMA clinical trials, patients were required to have baseline anti-AAV9 antibody titres of $\leq 1:50$, measured using an enzyme-linked immunosorbent assay (ELISA). Evidence of prior exposure to AAV9 was uncommon. Mean increases from baseline in anti-AAV9 antibody titres were observed in all patients at all but one time point for antibody titre levels to AAV9 peptide, reflecting normal response to non-self viral antigen. Some patients experienced anti-AAV9 titres exceeding the level of quantification, however most of these patients did not have potentially clinically significant adverse drug reactions. Thus, no relationship has been established between high AAV9 antibody titres and the potential for adverse drug reactions or efficacy parameters.

In the CL-101 clinical study, 16 patients were screened for AAV9 antibody titre: 13 had titres less than 1:50 and were enrolled in the study; three patients had titres greater than 1:50, two of whom were retested following cessation of breast-feeding and their titres were measured at less than 1:50 and both were enrolled in the study. There is no information on whether breastfeeding should be restricted in mothers who may be seropositive for AAV9 antibodies. Patients all had less than or equal to 1:50 AAV9 antibody titre prior to treatment

with ZOLGENSMA and subsequently demonstrated an expected increase in AAV9 antibody titres to at least 1:102,400 and up to greater than 1:819,200. No ZOLGENSMA-treated patient demonstrated an immune response to the transgene. Re-administration of ZOLGENSMA in the presence of high anti-AAV9 antibody titre has not been evaluated.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reportingproblems.

4.9 OVERDOSE

No data from clinical studies are available regarding overdose of ZOLGENSMA. The dose of the medicinal product is specific to each individual patient's weight and is administered once only (see 4.2 Dosage and method of administration), therefore overdose is considered unlikely. Adjustment of the dose of prednisolone, close clinical observation and monitoring of laboratory parameters (including clinical chemistry and haematology) for systemic immune response are recommended (see section 4.4 Special warnings and precautions for use).

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other drugs for disorders of the musculo-skeletal system, ATC code: M09AX09.

Mechanism of action

SMA is caused by a bi-allelic mutation in the *SMN1* gene, which results in insufficient SMN protein expression. ZOLGENSMA (onasemnogene abeparvovec) is a non-replicating recombinant AAV vector that utilises the AAV9 capsid to deliver a stable fully functional copy of the transgene encoding the human survival motor gene (SMN1) protein. 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 AAV9 virus is not known to cause disease in humans. Intravenous administration of ZOLGENSMA that results in cell transduction and expression of the SMN protein has been observed in two human case studies (see 5.2 Pharmacokinetic properties).

Pharmacodynamics (PD)

There are no clinically relevant pharmacodynamics data for ZOLGENSMA.

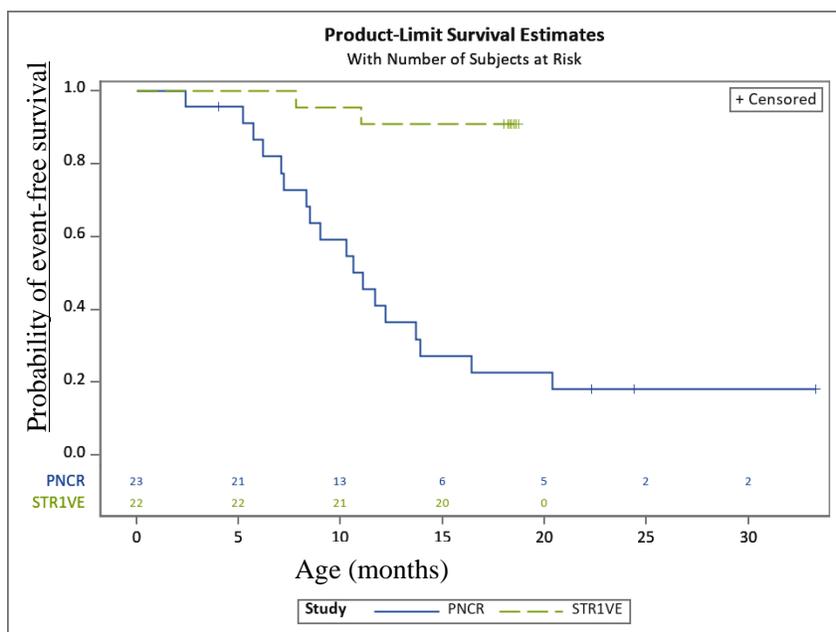
Clinical trials

ZOLGENSMA has not been studied in patients with a bi-allelic mutation of the SMN1 gene and only 1 copy of SMN2 or ≥ 4 copies SMN2 in clinical trials.

AVXS-101-CL-303 Phase 3 Study in Patients with Type 1 SMA

AVXS-101-CL-303 (Study CL-303) is a phase 3, open-label, single-arm, single-dose study of intravenous administration of ZOLGENSMA at the therapeutic dose (1.1×10^{14} vg/kg). All patients had genetically confirmed bi-allelic SMN1 gene deletions, 2 copies of the SMN2 gene, absence of the c.859G>C modification in exon 7 of the SMN2 gene and onset of clinical symptoms consistent with SMA prior to 6 months of age. Patient ages and weight at administration ranged from 0.5 to 5.9 months and 3.9 to 7.5 kg. Of the 22 enrolled patients, three patients discontinued the study and two patients had an event (death or permanent ventilation) leading to 90.9% (95% CI: 79.7%, 100.0%) event-free survival (alive without permanent ventilation) at 14 months of age (see Figure 1). This is markedly improved compared to the natural history of infantile onset SMA as reported in the Pediatric Neuromuscular Clinical Research natural history cohort (PNCr), in which only 25% of subjects were alive without permanent ventilation by the age of 14 months.

Figure 1 Time (months) to death or permanent ventilation in Study 303



The PNCr Natural History dataset was drawn from a prospective natural history study of patients with any form of SMA. An appropriate comparator cohort for Study AVXS-101-CL-303 was drawn from the larger PNCr Natural History Dataset, consisting of all patients with age of onset ≤ 6 months, bi-allelic deletion of survival motor neuron 1 gene (SMN1) and 2 copies of SMN2.
STRIVE = Study 303

For the 14 patients in Study CL-303 that achieved the milestone of independent sitting for at least 30 seconds, the median age when this milestone was first demonstrated was 12.5 months (range 9.2 to 18.6 months). Thirteen patients confirmed the milestone of independent sitting for at least 30 seconds at the 18 month visit (co-primary endpoint, $p < 0.0001$). One patient 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. The video-confirmed developmental milestones for patients in Study CL-303 are summarised in Table 4.

Table 4 Median time to video document achievement of motor milestones in Study 303

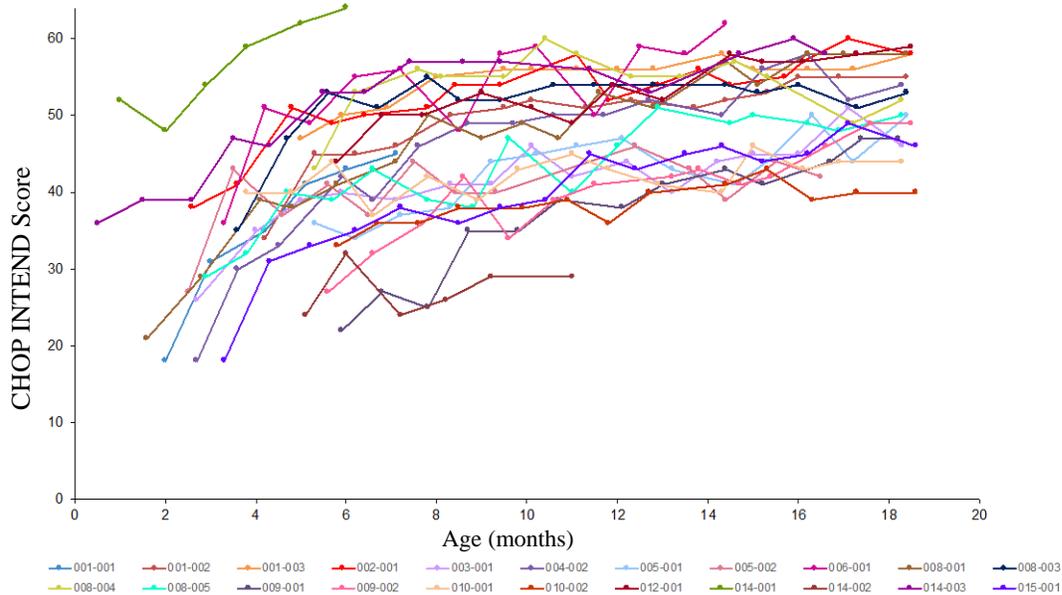
Video documented milestone	Number of patients achieving milestone n/N (%)	Median age to the milestone achievement (Months)	95% Confidence interval
Head control	17/20* (85)	6.8	(4.77, 7.17)
Rolls from back to sides	13/22 (59)	11.5	(7.77, 14.53)
Sits without support for 30 seconds (Bayley)	14/22 (64)	12.5	(10.17, 15.20)
Sitting without support for at least 10 seconds (WHO)	14/22 (64)	13.9	(11.00, 16.17)

*2 patients were reported to have Head Control by clinician assessment at baseline.

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

Motor function improvements were also observed as measured by the Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), see Figure 2. Twenty-one patients (95.5%) achieved a CHOP-INTEND score ≥ 40 , 14 (64%) had achieved a CHOP-INTEND score ≥ 50 , and 5 patients (23%) had achieved a CHOP-INTEND score ≥ 60 . Patients with untreated SMA Type 1 almost never achieve a CHOP-INTEND score ≥ 40 .

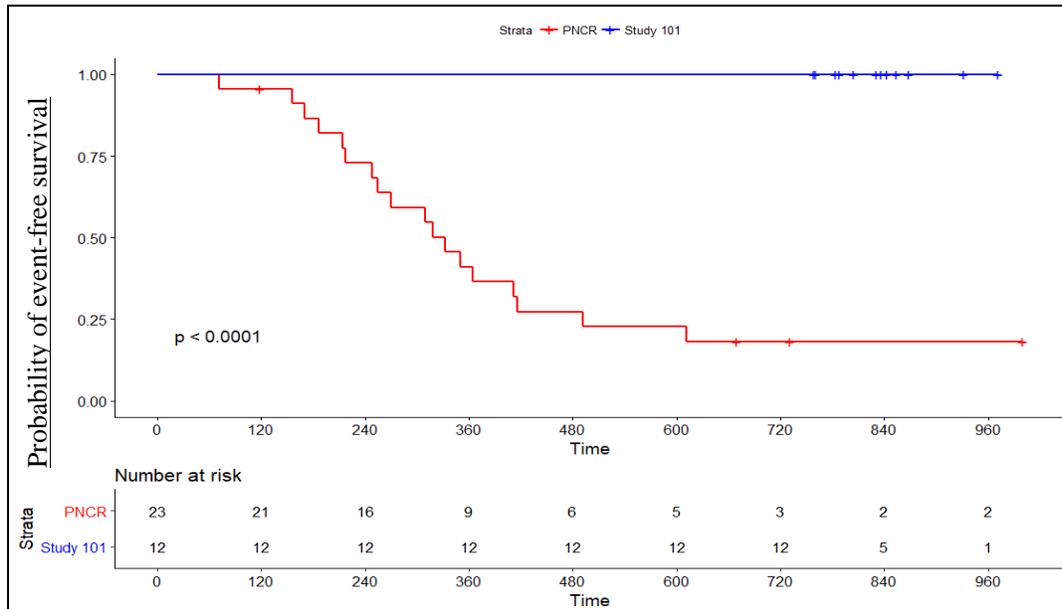
Figure 2 CHOP-INTEND Motor Function Scores in Study 303



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

The results seen in Study CL-303 are supported by study AVXS-101-CL-101. All patients had genetically confirmed bi-allelic SMN1 gene deletions, 2 copies of the SMN2 gene, absence of the c.859G>C modification in exon 7 of the SMN2 gene and onset of clinical symptoms consistent with SMA prior to 6 months of age. ZOLGENSMA was administered in study AVXS-101-CL-101 (Phase 1 study in Type 1 SMA, Study CL-101) as a single intravenous infusion in 12 patients from 2.6 kg to 8.5 kg (0.9 to 7.9 months of age). Patients were followed for 24 months. At 14 months of age, all treated patients were event free; i.e. survived without permanent ventilation, compared to 25% in the PNCR natural history cohort. At the end of the study (24 months post dose), all treated patients were event free, compared to less than 8% in the natural history cohort (see Figure 3).

Figure 3 Time (days) to death or permanent ventilation Study 101



The PNCR Natural History dataset was drawn from a prospective natural history study of patients with any form of SMA. An appropriate comparator cohort for Study AVXS-101-CL-101 was drawn from the larger PNCR Natural History Dataset, consisting of all patients with age of onset ≤ 6 months, bi-allelic deletion of survival motor neuron 1 gene (SMN1) and 2 copies of SMN2.

At 24 months of follow up post dose, 10 patients treated with the therapeutic dose were able to sit without support for ≥ 10 seconds, 9 patients were able to sit without support for ≥ 30 seconds and 2 patients were able to stand alone, walk with assistance and walk alone.

Ten of 12 patients from Study CL-101 who received the proposed therapeutic dose of ZOLGENSMA continue to be followed in a long-term study (for up to 5.7 years after dosing) and all have either maintained all previously attained milestones or even gained new milestones including sitting with support, stand with assistance and walk alone.

AVXS-101-CL-304 Phase 3 Study in Patients with pre-symptomatic SMA

Study CL-304 is an ongoing, global, Phase 3, open-label, single-arm, single-dose, multicentre study of intravenous ZOLGENSMA in pre-symptomatic newborn patients up to 6 weeks of age with genetically confirmed bi-allelic SMN1 gene deletions, 2 or 3 copies of the SMN2 gene and absence of the c.859G>C modification in exon 7 of the SMN2 gene. Study CL-304 treated 14 patients with 2 copies of SMN2 and 15 patients with 3 copies of SMN2. At the time of the last study visit prior to 31 December 2019, treated patients with 2 copies of SMN2 were between 6 months and 18.6 months of age and had been in the study for an average of 10.5 months (range: 5.1 to 18.0 months), and the 15 patients with 3 copies of SMN2 were between 3.3 and 15.1 months of age and had been in the study for an average of 8.74 months (range: 2 to 13.9 months). All patients in Study CL-304 were alive and free of permanent ventilation as of their last study visit prior to 31 December 2019. At the time of their last visit before the

data cut-off, 6 of the 14 (42.9%) patients with 2 copies of SMN2 were less than 9.2 months of age. The 8 older individuals achieved sitting prior to their last visit before 31 December 2019, at ages ranging from 6.4 to 11.8 months, with 7 of these 8 (87.5%) achieving independent sitting prior to the 9.2 months of age, the 99th percentile for development of this milestone. Twelve patients (85.7%) have achieved CHOP-INTEND scores ≥ 60 as of the 31 December 2019 data cut-off. Of the patients with 3 copies of SMN2, 10 of 15 patients were able to sit without support for at least 30 seconds, 4 patients were able to stand alone without support for at least 3 seconds, and 2 patients were able to walk at least five steps independently. Patients with 3 copies of SMN2 who have not yet achieved the Cohort 2 primary endpoint developmental milestone of standing alone without support for at least 3 seconds are 6.4 to 13.6 months of age. These patients remain within the normal age development window for obtaining these milestones.

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetics (PK)

Vector shedding after infusion with ZOLGENSMA was investigated at multiple time points during the completed clinical trial CL-101. Samples of saliva, urine and stool were collected the day after infusion, weekly through Day 30, and then monthly through Month 12 and every 3 months thereafter. Samples from 5 patients were used for ZOLGENSMA vector DNA shedding analysis through the Month 18 visit.

Vector DNA was shed in saliva, urine and stool after infusion of ZOLGENSMA. Clearance was primarily via faeces and the majority was cleared within 30 days after dose administration. The vector DNA concentration in saliva was low on Day 1 after infusion and declined to undetectable levels within 3 weeks. In urine, the vector DNA concentration was very low on Day 1 after infusion and declined to undetectable levels within 1 to 2 weeks. In stool, the vector DNA concentration was much higher than in saliva or urine for 1 to 2 weeks after infusion and declined to undetectable levels by 1 to 2 months after infusion.

Biodistribution

Biodistribution was evaluated in two patients who died 5.7 months and 1.7 months, respectively, after infusion of ZOLGENSMA at the dose of 1.1×10^{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, spinal cord, brain, and thymus. Immunostaining for SMN protein showed generalised SMN expression in spinal motor neurons, neuronal and glial cells of the brain, and in the heart, liver, skeletal muscles, and other tissues evaluated.

5.3 PRECLINICAL SAFETY DATA

In toxicology studies conducted in neonatal mice, dose-dependent cardiac and hepatic toxicities were observed following intravenous administration of ZOLGENSMA. ZOLGENSMA-related findings in the myocardium, at doses of 7.9×10^{13} vg/kg and higher, included slight to mild mononuclear cell inflammation accompanied by oedema, slight to mild fibrosis, and scattered myocardial cell degeneration/regeneration. Additional cardiac

findings at dose levels of 1.5×10^{14} vg/kg and higher included minimal to moderate atrial thrombosis and slight to marked atrial dilation. Liver findings included hepatocellular hypertrophy, Kupffer cell activation, perinuclear vacuolation, and scattered hepatocellular necrosis. Target organ toxicity in the heart and liver was associated with mortality at dose levels of 2.4×10^{14} vg/kg and above, approximately 2.2-fold higher than the recommended clinical dose level.

In a toxicology study conducted in non-human primates, administration of a single dose of onasemnogene abeparvovec intrathecally, without corticosteroid treatment, resulted in minimal to marked mononuclear cell inflammation in the dorsal root ganglia, with neuronal satellitosis, neuronal necrosis, or complete neuronal loss with rare mineralisation. The clinical relevance of this finding is unknown.

Genotoxicity and carcinogenicity

No studies have been performed to evaluate the genotoxic or carcinogenic potential of onasemnogene abeparvovec.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Trometamol, magnesium chloride hexahydrate, sodium chloride, poloxamer, hydrochloric acid (for pH adjustment) and water for injections.

Contains no preservative.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this product must not be mixed with other medicinal products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Preparation of pack contents is carried out aseptically under sterile conditions. To reduce microbiological hazard, use as soon as practicable after dispensing into the syringe. If storage is necessary, hold at room temperature (20°C – 25°C) for not more than 6 hours.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store and transport frozen ($\leq -60^{\circ}\text{C}$).

Upon receipt, immediately place the pack (in original carton to protect from light) in a refrigerator at 2°C to 8°C.

ZOLGENSMA is stable for 14 days from receipt when stored at 2°C to 8°C.

For storage conditions after thawing of the medicinal product, see section 6.3 Shelf life above.

DO NOT REFREEZE.

6.5 NATURE AND CONTENTS OF CONTAINER

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

The dose of ZOLGENSMA and exact number of vials required for each patient is calculated according to the patient's weight (see 4.2 Dosage and method of administration and Table 5 below).

Table 5 ZOLGENSMA pack configurations

Patient weight (kg)	5.5 mL vial ^a	8.3 mL vial ^b	Total vials per carton
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
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

^a Vial nominal concentration is 2×10^{13} vg/mL and contains an extractable volume of not less than 5.5 mL.

^b Vial contains nominal concentration is 2×10^{13} vg/mL and an extractable volume of not less than 8.3 mL.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

This medicine contains genetically modified organisms. Unused medicine and waste products must be disposed of in compliance with the local institutional guidelines for genetically modified organisms or biohazardous waste, as appropriate.

Temporary onasemnogene abeparvovec shedding may occur, primarily through bodily waste. Caregivers and patient families should be advised on the proper handling of patient stools. Instructions should be provided regarding good hand-hygiene when coming into direct contact with patient bodily waste for a minimum of 1 month after onasemnogene abeparvovec treatment. Disposable nappies should be sealed in plastics bags and can be disposed of in household waste.

6.7 PHYSICOCHEMICAL PROPERTIES

CAS Number: 1922968-73-7.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine.

8 SPONSOR

Novartis Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
Macquarie Park NSW 2113.
Telephone No. 1800 671 203.

9 DATE OF FIRST APPROVAL

04 March 2021

10 DATE OF REVISION

Not applicable.

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