ZOLGENSMA

(**Onasemnogene abeparvovec 2.0 × 10^{13} vg/mL**) suspension for infusion, I.V

WARNING: ACUTE SERIOUS LIVER INJURY AND ACUTE LIVER FAILURE

- Acute serious liver injury**, acute liver failure,** and elevated aminotransferases can occur with ZOLGENSMA.(*see Warning and Precautions* (5.1))
- *Patients with preexisting liver impairment may be at higher risk.(see Warnings and Precautions (5.1)*)
- 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* Dosage *and Administration* (2.1) (2.3).)

Patient safety information card

The marketing of Zolgensma is subject to a risk management plan (RMP) including a `Patient safety information card`. The `Patient safety information card`, emphasizes important safety information that the patient should be aware of before and during treatment.

Please explain to the patient the need to review the card before starting treatment.

1 INDICATIONS AND USAGE

ZOLGENSMA (onasemnogene abeparvovec-xioi) is an adeno-associated virus vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the *survival motor neuron 1 (SMN1)* gene.

Limitations of Use

- The safety and effectiveness of repeat administration of ZOLGENSMA have not been evaluated [*see Adverse Reactions (6.2)*].
- The use of ZOLGENSMA in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator-dependence) has not been evaluated [*see Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

For single-dose intravenous infusion only.

2.1 Dose and Administration

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

Table 1: Dosing

Patient Weight Range (kg)	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
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[b]	74.3

[a] Dose volume is calculated using the upper limit of the patient weight range for pediatric patients less than 2 years of age between 2.6 kg and 13.5 kg

[b] Dose volume for pediatric patients less than 2 years of age weighing equal to or greater than 13.6 kg will require a combination of ZOLGENSMA kits.

- Prior to ZOLGENSMA infusion
  - Assess liver function [see Boxed Warning, Dosage and Administration (2.3), Warnings and Precautions (5.1) Use in Specific Populations (8.6)].
  - Obtain creatinine complete blood count (including hemoglobin and platelet count) and troponin-I [see Dosage and Administration (2.3), Warnings and Precautions (5.2, 5.3,5.4]

- Perform baseline testing for the presence of anti-AAV9 antibodies [see Dosage and Administration (2.3), Adverse Reactions (6.2)].

- One day prior to ZOLGENSMA infusion, begin administration of systemic corticosteroids equivalent to oral prednisolone at 1 milligram per kilogram of body weight per day (mg/kg/day) for a total of 30 days.
- Administer ZOLGENSMA as a single-dose intravenous infusion through a venous catheter.

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.

- Monitor liver function by clinical examination and by laboratory testing on a regular basis [*see Dosage and Administration (2.3)*].
  - 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 × upper limit of normal (ULN)), taper the corticosteroid dose over the next 28 days [*see Warnings and Precautions (5.1)*].
  - 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.
  - Consult expert(s) if patients do not respond adequately to the equivalent of 1 mg/kg/day oral prednisolone.

2.2 Preparation

- Thaw ZOLGENSMA before use. The contents of the ZOLGENSMA kit will thaw in approximately 12 hours if placed in a refrigerator, or in approximately 4 hours if placed at room temperature. If thawed in a refrigerator, remove from refrigerator on day of dosing.
- When thawed, ZOLGENSMA is a clear to slightly opaque, colorless to faint white liquid, free of particles. Visually inspect vials for particulate matter and discoloration prior to infusion. Do not use vials if particulates or discoloration are present.
- DO NOT SHAKE.

- 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.
- Use ZOLGENSMA within 8 hours of drawing into syringe (polypropylene syringe and plunger rod with a latex free elastomer). Discard the vector-containing syringe if the drug is not infused within the 8-hour timeframe.
- DO NOT REFREEZE.

2.3 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 titers are reported as >1:50 [*see Dosage and Administration (2.1)*].

Conduct the following tests at baseline and as directed below *[see Warnings and Precautions (5.1, 5.2, 5.4)]*:

- Liver function (clinical exam, AST, 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 × 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.

3 DOSAGE FORMS AND STRENGTHS

ZOLGENSMA is a suspension for intravenous infusion.

ZOLGENSMA is provided in a kit containing 2 to 9 vials. Vials are provided in 2 fill volumes: 5.5 mL or 8.3 mL.

ZOLGENSMA has a nominal concentration of 2.0×10^{13} vg/mL, and each vial contains an extractable volume of not less than either 5.5 mL or 8.3 mL.

The intravenous dosage is determined by patient body weight, with a recommended dose of 1.1×10^{14} vg/kg for pediatric patients.

4 CONTRAINDICATIONS

HYPERSENSITIVITY TO THE ACTIVE SUBSTANCE OR TO ANY OF THE EXCIPIENTS LISTED IN SECTION 11.5WARNINGS AND PRECAUTIONS

5.1 Acute Serious Liver Injury , Acute Liver Failure or Elevated Aminotransferases

Acute serious liver injury, acute liver failure and elevated aminotransferases can occur with ZOLGENSMA. Hepatotoxicity (which may be immune-mediated), generally manifested as elevated ALT and/or AST levels and at times as acute serious liver injury or acute liver failure, has been reported with ZOLGENSMA use *[see Adverse Reactions (6)]*. In order to mitigate potential aminotransferase elevations, administer systemic corticosteroid to all patients before and after ZOLGENSMA infusion. Immune-mediated hepatotoxicity may require adjustment of the corticosteroid treatment regimen, including longer duration, increased dose, or prolongation of the corticosteroid taper *[see Dosage and Administration (2.1)]*.

Patients with preexisting liver impairment or acute hepatic viral infection may be at higher risk of acute serious liver injury/acute liver failure. Patients with ALT, AST, or total bilirubin levels (except due to neonatal jaundice) > 2 × ULN have not been studied in clinical trials with ZOLGENSMA. The risks and benefits of infusion with ZOLGENSMA in patients with preexisting liver impairment should be weighed carefully against the risks of not treating the patient.

Although in the clinical trials and in postmarketing experience, asymptomatic aminotransferase elevations were very commonly reported *[see Adverse Reactions (6.1)]*, in the managed access program and in the postmarketing setting, cases of acute serious liver injury and acute liver failure have been reported. Some patients have experienced elevations in ALT and AST > 20 × ULN, prolonged prothrombin time and have been symptomatic (e.g., vomiting, jaundice), which resolved with the use of prednisolone, sometimes requiring prolonged duration and/or a higher dose. If acute serious liver injury or acute liver failure is suspected, consult a pediatric gastroenterologist or hepatologist.

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). [*see Dosage and Administration (2.3)*] Administer systemic corticosteroid before and after ZOLGENSMA infusion [*see Dosage and Administration (2.1)*].

5.2 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.

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 Dosage and Administration (2.3)*].

5.3 Thrombotic Microangiopathy

Cases of thrombotic microangiopathy (TMA) were reported approximately one week after ZOLGENSMA infusion in the post-marketing setting *[see Adverse Reactions (6.3)]*. TMA is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury. Concurrent immune system activation (e.g., infections, vaccinations) was identified in some cases.

Monitor platelet counts *[see Warnings and Precautions (5.2)]*, as well as signs and symptoms of TMA, such as hypertension, increased bruising, seizures, or decreased urine output. In case these signs and symptoms occur in the presence of thrombocytopenia, further diagnostic evaluation for hemolytic anemia and renal dysfunction should be undertaken. If clinical signs, symptoms and/or laboratory findings consistent with TMA occur, consult a pediatric hematologist and/or pediatric nephrologist immediately to manage TMA as clinically indicated.

5.4 Elevated Troponin-I

Increases in cardiac troponin-I levels (up to 0.176 mcg /L) were observed following ZOLGENSMA infusion in clinical trials. The clinical importance of these findings is not known. However, cardiac toxicity was observed in animal studies *[see Nonclinical Toxicology (13.2)]*. 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). Consider consultation with a cardiologist, if troponin elevations are accompanied by clinical signs or symptoms (e.g., heart rate changes, cyanosis, tachypnea and respiratory distress) [*see Dosage and Administration (2.3)*].

6 ADVERSE REACTIONS

The most common adverse reactions (incidence ≥ 5%) were elevated aminotransferases and vomiting.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another product and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to ZOLGENSMA in four open-label studies conducted in the United States, including one completed clinical trial, two ongoing clinical trials, and one ongoing observational long-term follow-up study of the completed trial. A total of 44 patients with SMA received intravenous infusion of ZOLGENSMA, 41 patients at or

above the recommended dose, and 3 patients at a lower dose. The patient population ranged in age from 0.3 months to 7.9 months at the time of infusion (weight range 3.0 kg to 8.4 kg).

The most frequent adverse reactions (incidence ≥ 5%) observed in the 4 studies are summarized in Table 2.

Table 2: Adverse Reactions Following Treatment With ZOLGENSMA (N = 44)

Adverse Reactions	**Patients n (%)**
Elevated aminotransferases[ab](> ULN)	12 (27.3%)
Vomiting	3 (6.8%)

Abbreviation: ULN = upper limit of normal.

[a] Elevated aminotransferases include elevation of alanine aminotransferase and/or aspartate aminotransferase .

[b] In the completed clinical trial, one patient (the first patient infused in that study) was enrolled prior to the protocol amendment instituting administration of prednisolone before and after ZOLGENSMA infusion.

One patient in an ongoing non-United States clinical trial initially presented with respiratory insufficiency 12 days after ZOLGENSMA infusion and was found to have respiratory syncytial virus (RSV) and parainfluenza in respiratory secretions. The patient had episodes of serious hypotension, followed by seizures, and was found to have leukoencephalopathy (brain white matter defects) approximately 30 days after ZOLGENSMA infusion. The patient died after withdrawal of life support 52 days after ZOLGENSMA infusion.

6.2 Immunogenicity

In ZOLGENSMA clinical trials, patients were required to have baseline anti-AAV9 antibody titers of ≤ 1:50, measured using an enzyme-linked immunosorbent assay (ELISA). Evidence of prior exposure to AAV9 was uncommon. The safety and efficacy of ZOLGENSMA in patients with anti-AAV9 antibody titers above 1:50 have not been evaluated. Perform baseline testing for the presence of anti-AAV9 antibodies prior to ZOLGENSMA infusion. Retesting may be performed if anti-AAV9 antibody titers are reported as > 1:50 [*see Dosage and Administration (2.1, 2.3),)*].

Following ZOLGENSMA infusion, increases from baseline in anti-AAV9 antibody titers occurred in all patients. In the completed clinical trial, anti-AAV9 antibody titers reached at least 1:102,400 in every patient, and titers exceeded 1:819,200 in most patients. Re-administration of ZOLGENSMA in the presence of high anti-AAV9 antibody titer has not been evaluated.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ZOLGENSMA. Because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: thrombotic microangiopathy *[see Warnings and Precautions (5.3)]*, thrombocytopenia *[see Warnings and Precautions (5.2)]*.

Hepatobiliary Disorders: acute liver failure, acute liver injury *[see Warnings and Precautions (5.1)]*.

General Disorders and Administration Site Conditions: pyrexia

Investigations: troponin increased *[see Warnings and Precautions (5.4)]*

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

7 DRUG INTERACTIONS

Where feasible, adjust a patient's vaccination schedule to accommodate concomitant corticosteroid administration prior to and following ZOLGENSMA infusion [*see Dosage and Administration (2.1)*]. Certain vaccines, such as measles, mumps and rubella, 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). Seasonal RSV prophylaxis is not precluded. (General Best Practice Guidelines for Immunization [www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf], eds2017)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

8.2 Lactation

Risk Summary

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. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZOLGENSMA and any potential adverse effects on the breastfed child from ZOLGENSMA or from the underlying maternal condition.

8.4 Pediatric 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 safety of ZOLGENSMA was studied in pediatric patients who received ZOLGENSMA infusion at age 0.3 to 7.9 months (weight range 3.0 kg to 8.4 kg) [*see Adverse Reactions (6)*].

The efficacy of ZOLGENSMA was studied in pediatric patients who received ZOLGENSMA infusion at age 0.5 to 7.9 months (weight range 3.6 kg to 8.4 kg) [*see Clinical Studies (14)*].

8.6 Hepatic Impairment

ZOLGENSMA therapy should be carefully considered in patients with liver impairment. Cases of acute serious liver injury and acute liver failure have been reported with ZOLGENSMA in patients with preexisting liver abnormalities. In clinical trials, elevation of aminotransferases was observed in patients following ZOLGENSMA infusion [*see Warnings and Precautions (5.1)*].

11 DESCRIPTION

ZOLGENSMA is a suspension of an adeno-associated viral vector-based gene therapy for intravenous infusion. It is a recombinant self-complementary AAV9 containing a transgene encoding the human survival motor neuron (SMN) protein, under the control of a cytomegalovirus enhancer/chicken-β-actin hybrid promoter.

ZOLGENSMA has a nominal concentration of 2.0×10^{13} vg/mL. Each vial contains an extractable volume of not less than either 5.5 mL or 8.3 mL and the excipients tromethamine, magnesium chloride, sodium chloride , poloxamer 188, hydrochloric acid, and water for injection. ZOLGENSMA is packaged as a sterile suspension and contains no preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Onasemnogene abeparvovec is a recombinant AAV9-based gene therapy designed to deliver a copy of the gene encoding the human SMN protein. SMA is caused by a bi-allelic mutation in the *SMN1* gene, which results in insufficient SMN protein expression. Intravenous administration of ZOLGENSMA that results in cell transduction and expression of the SMN protein has been observed in two human case studies *[see Clinical Pharmacology (12.3)*].

12.2 Pharmacodynamics

There are no clinically relevant pharmacodynamics data for Onasemnogene abeparvovec.

12.3 Pharmacokinetics

Vector shedding after infusion with Onasemnogene abeparvovec was investigated at multiple time points during the completed clinical trial. 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 Onasemnogene abeparvovec vector DNA shedding analysis through the Month 18 visit.

Vector DNA was shed in saliva, urine and stool after infusion of Onasemnogene abeparvovec, with much higher concentrations of vector DNA found in stool than in saliva or urine. 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 was evaluated in two patients who died 5.7 months and 1.7 months, respectively, after infusion of Onasemnogene abeparvovec at the dose of 1.1×10^{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 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been performed to evaluate the effects of Onasemnogene abeparvovec on carcinogenesis, mutagenesis or impairment of fertility.

13.2 Animal Toxicology and/or Pharmacology

In toxicology studies conducted in neonatal mice, dose-dependent cardiac and hepatic toxicities were observed following intravenous administration of Onasemnogene abeparvovec. Onasemnogene abeparvovec-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 edema, 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.

14 CLINICAL STUDIES

The efficacy of ZOLGENSMA in pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the *SMN1* gene was evaluated in an open-label, single-arm clinical trial (ongoing) and an open-label, single-arm, ascending-dose clinical trial (completed). Patients experienced onset of clinical symptoms consistent with SMA before 6 months of age. All patients had genetically confirmed bi-allelic *SMN1* gene deletions, 2 copies of the *SMN2* gene, and absence of the c.859G>C modification in exon 7 of *SMN2* gene (which predicts a milder phenotype). All patients had baseline anti-AAV9 antibody titers of ≤ 1:50, measured by ELISA. In both trials, ZOLGENSMA was delivered as a single-dose intravenous infusion.

Efficacy was established on the basis of survival, and achievement of developmental motor milestones such as sitting without support. Survival was defined as time from birth to either death or permanent ventilation. Permanent ventilation was 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. Efficacy was also supported by assessments of ventilator use, nutritional support and scores on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND). CHOP-INTEND is an assessment of motor skills in patients with infantile-onset SMA.

The ongoing clinical trial enrolled 21 patients (10 male and 11 female) with infantile-onset SMA. Before treatment with ZOLGENSMA, none of the 21 patients required non invasive ventilator (NIV) support, and all patients could exclusively feed orally (i.e., no need for non-oral nutrition). The mean CHOP-INTEND score at baseline was 31.0 (range 18 to 47). All the patients received 1.1×10^{14} vg/kg of ZOLGENSMA. The mean age of the 21 patients at the time of treatment was 3.9 months (range 0.5 to 5.9 months).

As of the March 2019 data cutoff, 19 patients were alive without permanent ventilation (i.e., event-free survival) and were continuing in the trial, while one patient died at age 7.8 months due to disease progression, and one patient withdrew from the study at age 11.9 months. The 19 surviving patients who were continuing in the trial ranged in age from 9.4 to 18.5 months. By the data cutoff, 13 of the 19 patients continuing in the trial reached 14 months of age without permanent ventilation, one of the study's co-primary efficacy endpoints. In addition to survival, assessment of the other co-primary efficacy endpoint found that 10 of the 21 patients (47.6%) achieved the ability to sit without support for ≥ 30 seconds between 9.2 and 16.9 months of age (mean age was 12.1 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. In addition, 16 of the 19 patients had not required daily NIV use.

Comparison of the results of the ongoing clinical trial to available natural history data of patients with infantile-onset SMA provides primary evidence of the effectiveness of ZOLGENSMA.

The completed clinical trial enrolled 15 patients (6 male and 9 female) with infantile-onset SMA, 3 in a low-dose cohort and 12 in a high-dose cohort. At the time of treatment, the mean age of patients in the low-dose cohort was 6.3 months (range 5.9 to 7.2 months), and 3.4 months (range 0.9 to 7.9 months) in the high-dose cohort. The dosage received by patients in the

low-dose cohort was approximately one-third of the dosage received by patients in the high-dose cohort. However, the precise dosages of ZOLGENSMA received by patients in this completed clinical trial are unclear due to a change in the method of measuring ZOLGENSMA concentration, and to decreases in the concentration of stored ZOLGENSMA over time. The retrospectively-estimated dosage range in the high-dose cohort is approximately 1.1×10^{14} to 1.4×10^{14} vg/kg.

By 24 months following ZOLGENSMA infusion, one patient in the low-dose cohort met the endpoint of permanent ventilation; all 12 patients in the high-dose cohort were alive without permanent ventilation. None of the patients in the low-dose cohort were able to sit without support, or to stand or walk; in the high-dose cohort, 9 of the 12 patients (75.0%) were able to sit without support for ≥ 30 seconds, and 2 patients (16.7%) were able to stand and walk without assistance. Comparison of the results of the low-dose cohort to the results of the high-dose cohort shows a dose-response relationship that supports the effectiveness of ZOLGENSMA.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ZOLGENSMA is shipped frozen (≤ -60°C in 10 mL vials with 2 fill volumes (either 5.5 mL or 8.3 mL).

ZOLGENSMA is provided as a customized kit to meet dosing requirements for each patient [*see Dosage and Administration (2.1)*], with each kit containing:

- Two (2) to nine (9) vials of ZOLGENSMA (see below)

Kit sizes and Israel specific product number are provided in Table 3.

Table 3: ZOLGENSMA Kit Sizes

Patient Weight (kg)	5.5 mL vial[a]	8.3 mL vial[b]	Total Vials per Kit	Israel Specific Product Number
2.6 – 3.0	0	2	2	07290103848552
3.1 – 3.5	2	1	3	07290103848569
3.6 – 4.0	1	2	3	07290103848576
4.1 – 4.5	0	3	3	07290103848583
4.6 – 5.0	2	2	4	07290103848590
5.1 – 5.5	1	3	4	07290103848606
5.6 – 6.0	0	4	4	07290103848613
6.1 – 6.5	2	3	5	07290103848620
6.6 – 7.0	1	4	5	07290103848637
7.1 – 7.5	0	5	5	07290103848644
7.6 – 8.0	2	4	6	07290103848651
8.1 – 8.5	1	5	6	07290103848668
8.6 – 9.0	0	6	6	07290103848675
9.1 – 9.5	2	5	7	07290103848682
9.6 – 10.0	1	6	7	07290103848699
10.1 – 10.5	0	7	7	07290103848705
10.6 – 11.0	2	6	8	07290103848712
11.1 – 11.5	1	7	8	07290103848729
11.6 – 12.0	0	8	8	07290103848736
12.1 – 12.5	2	7	9	07290103848743
12.6 – 13.0	1	8	9	07290103848750
13.1 – 13.5	0	9	9	07290103848767

[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.

16.2 Storage and Handling

- The expiry date of the product is indicated on the package materials.
- Product is shipped and delivered frozen (≤ -60 °C in clear vials.
- Upon receipt, immediately place the kit 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 .
- **DO NOT REFREEZE**.
- Must use within 14 days of receipt.
- Use ZOLGENSMA within 8 hours of drawing into syringe (see "Preparation" section)
- Store in the original carton until time of use

Manufacturer: Novartis Gene Therapies, Inc., 1940 USG Dr., Libertyville, IL 60048, USA

License Holder: TrueMed Ltd., 10 Beni Gaon St., Poleg Industrial Park, P.O.B 8105, South Netanya 4250499

Registration Number: 134-99-31483

Revised in November 2021 according to MoH guidelines.

PI-1047 04-11.21