



ZOLGENSMA Treatment Guide

For US Healthcare Providers

ZOLGENSMA is the first one-time-only gene therapy for pediatric patients less than 2 years of age with spinal muscular atrophy (SMA)¹

Indication

ZOLGENSMA 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 or the use in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated with ZOLGENSMA.

BOXED WARNING: Acute Serious Liver Injury and Acute Liver Failure

Acute serious liver injury, acute liver failure, and elevated aminotransferases can occur with ZOLGENSMA. Patients with preexisting liver impairment may be at higher risk. 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 a systemic corticosteroid to all patients before and after ZOLGENSMA infusion. Continue to monitor liver function for at least 3 months after infusion.

Please see Indication and Important Safety Information, including Boxed Warning for Acute Serious Liver Injury and Acute Liver Failure, on back cover and the accompanying Full Prescribing Information.

Introduction to ZOLGENSMA

ZOLGENSMA® (onasemnogene abeparvovec-xioi) is an adeno-associated virus (AAV) vector-based gene therapy for the one-time-only treatment of pediatric patients less than 2 years of age with SMA. ZOLGENSMA is delivered as an intravenous infusion over 1 hour, but there are essential steps to treatment before and after infusion day.

5 steps to a one-time-only ZOLGENSMA infusion

Step
1

Confirm diagnosis and run laboratory tests

Step
2

Store and handle ZOLGENSMA properly

Step
3

Premedicate and plan for infusion day

Step
4

Prepare and infuse ZOLGENSMA

Step
5

Monitor and postmedicate after ZOLGENSMA infusion



If you have questions throughout the ZOLGENSMA treatment journey, contact the OneGene Program® at:

1-855-441-GENE (4363), Monday-Friday (8 AM to 8 PM ET)

Important Safety Information

ADVERSE REACTIONS

The most commonly observed adverse reactions (incidence $\geq 5\%$) in clinical studies were elevated aminotransferases and vomiting.

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Step

1

Confirm diagnosis and run laboratory tests¹

Diagnosis and baseline testing can be performed at a ZOLGENSMA-ready institution or by a referring physician



- Confirm a genetic diagnosis of SMA
- Patients treated with ZOLGENSMA® (onasemnogene abeparvovec-xioi) should have bi-allelic mutations in the *survival motor neuron 1 (SMN1)* gene



- Determine patient weight in kilograms, as ZOLGENSMA dosing is weight based



- Perform testing for the presence of baseline anti-AAV9 antibodies
- In clinical trials, patients were required to have baseline anti-AAV9 antibody titers of $\leq 1:50$
- The safety and efficacy of ZOLGENSMA in patients with anti-AAV9 antibody titers above 1:50 have not been evaluated
- Retesting may be performed if anti-AAV9 antibody titers are reported as $>1:50$



- Postpone infusion in patients with concurrent infections until the infection has resolved. Clinical signs or symptoms of infection should not be evident at the time of ZOLGENSMA administration
- Perform baseline tests for liver function, creatinine, complete blood count (including hemoglobin and platelet count), and troponin-I
- Evaluate liver function with a clinical exam and laboratory testing of hepatic aminotransferases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), total bilirubin, and prothrombin time



To begin a ZOLGENSMA prescription, fax a signed and completed ZOLGENSMA Prescription Form and Patient Consent Form to the OneGene Program® at 1-855-951-GENE (4363)

Important Safety Information

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 for at least 3 months afterwards.

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Step 2

Store and handle ZOLGENSMA properly¹

ZOLGENSMA® (onasemnogene abeparvovec-xioi) is shipped and delivered frozen, and must be thawed prior to infusion



- ZOLGENSMA is shipped and delivered frozen at $\leq -60^{\circ}\text{C}$ (-76°F) in clear vials
- Refrigerate ZOLGENSMA immediately upon receipt at 2°C - 8°C (36°F - 46°F)
- **DO NOT REFREEZE**
- ZOLGENSMA is stable at 2°C - 8°C (36°F - 46°F) and must be used within 14 days of receipt

Do not use ZOLGENSMA unless thawed. Once thawed, ZOLGENSMA should not be refrozen

Refrigerator Thaw



- ZOLGENSMA will thaw in the refrigerator and be ready for use in approximately 12 hours
 - If thawed in the refrigerator, remove ZOLGENSMA from the refrigerator on day of dosing
- OR—**

Room Temperature Thaw

- ZOLGENSMA will thaw at room temperature and be ready for use in approximately 4 hours



- When thawed, ZOLGENSMA is a clear to slightly opaque, colorless to faint white liquid, free of particles
- Inspect ZOLGENSMA visually for particulate matter and discoloration prior to infusion
- Do not use vials if particulates or discoloration are present



- **DO NOT SHAKE ZOLGENSMA**

Important Safety Information

Thrombotic Microangiopathy

Cases of thrombotic microangiopathy (TMA) were reported approximately 1 week after ZOLGENSMA infusion. Obtain baseline creatinine and complete blood count before ZOLGENSMA infusion. Following infusion, monitor for thrombocytopenia as well as other signs and symptoms of TMA. Consult a pediatric hematologist and/or pediatric nephrologist immediately to manage if clinically indicated.

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Step 3

Premedicate and plan for infusion day¹



- Ensure required baseline testing has been completed, including anti-AAV9 titers, liver function assessment, creatinine, complete blood count (including hemoglobin and platelet count), and troponin-I
- Monitoring should continue after ZOLGENSMA infusion. See Step 5 for monitoring instructions



- If patient weight changes prior to infusion, report those changes to the OneGene Program®



- **24 hours prior to infusion, administer systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg/day**
- Treatment with corticosteroids should continue after ZOLGENSMA infusion. See Step 5 for postmedication instructions



- Clinical signs or symptoms of infection should not be evident at the time of ZOLGENSMA administration

Important Safety Information

Elevated Troponin-I

Increases in cardiac troponin-I levels were observed following ZOLGENSMA infusion. Monitor troponin-I before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards.

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Step 4

Prepare and infuse ZOLGENSMA¹

Follow the steps to prepare ZOLGENSMA[®] (onasemnogene abeparvovec-xioi)



- ZOLGENSMA is provided as a kit customized to meet the weight-based dosing requirements of each patient (see Table 1). The recommended dose of ZOLGENSMA is 1.1×10^{14} vector genomes per kilogram (vg/kg) of body weight
- Draw the appropriate dose volume from all vials into a syringe



- Remove air from syringe
- Cap syringe and deliver at room temperature to patient infusion location
- Once dose is drawn into the syringe, it must be used within 8 hours



- Discard the vector-containing syringe if not infused within 8 hours of preparation
- **DO NOT REFREEZE**

Administer ZOLGENSMA as a single-dose, intravenous infusion through a venous catheter^a



- Place a primary catheter into a vein (generally a peripheral vein in the arm or leg)
- Insertion of a backup 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 AN INTRAVENOUS PUSH OR BOLUS**



- Flush line with saline following completion of infusion

^aDue to the increased risk of serious systemic immune response, postpone ZOLGENSMA in patients with concurrent infections until the infection has resolved. Clinical signs or symptoms of infection should not be evident at the time of ZOLGENSMA administration.

Important Safety Information

ADVERSE REACTIONS

The most commonly observed adverse reactions (incidence $\geq 5\%$) in clinical studies were elevated aminotransferases and vomiting.

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Table 1.

ZOLGENSMA DOSING AND KIT SIZES			
PATIENT WEIGHT RANGE (kg)	DOSE VOLUME ^a (mL)	TOTAL VIALS PER KIT ^b	NDC NUMBER
2.6 – 3.0	16.5	2	71894-120-02
3.1 – 3.5	19.3	3	71894-121-03
3.6 – 4.0	22.0	3	71894-122-03
4.1 – 4.5	24.8	3	71894-123-03
4.6 – 5.0	27.5	4	71894-124-04
5.1 – 5.5	30.3	4	71894-125-04
5.6 – 6.0	33.0	4	71894-126-04
6.1 – 6.5	35.8	5	71894-127-05
6.6 – 7.0	38.5	5	71894-128-05
7.1 – 7.5	41.3	5	71894-129-05
7.6 – 8.0	44.0	6	71894-130-06
8.1 – 8.5	46.8	6	71894-131-06
8.6 – 9.0	49.5	6	71894-132-06
9.1 – 9.5	52.3	7	71894-133-07
9.6 – 10.0	55.0	7	71894-134-07
10.1 – 10.5	57.8	7	71894-135-07
10.6 – 11.0	60.5	8	71894-136-08
11.1 – 11.5	63.3	8	71894-137-08
11.6 – 12.0	66.0	8	71894-138-08
12.1 – 12.5	68.8	9	71894-139-09
12.6 – 13.0	71.5	9	71894-140-09
13.1 – 13.5 ^c	74.3	9	71894-141-09

NDC = National Drug Code.

^aDose 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.

^bAll vials have a nominal concentration of 2.0×10^{13} vector genomes (vg) per mL. Each vial of ZOLGENSMA contains an extractable volume of not less than either 5.5 mL or 8.3 mL.

^cDose 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.

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.

Important Safety Information

ADVERSE REACTIONS

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Step 5

Monitor and postmedicate after ZOLGENSMA infusion¹

After infusion, assess liver function, platelet count, and troponin-I for at least 3 months following infusion (see Table 2 for schedule of assessments)

Liver Function

- Acute serious liver injury, acute liver failure, and elevated aminotransferases may occur with ZOLGENSMA[®] (onasemnogene abeparvovec-xioi)
- Liver function should be evaluated by clinical exam and an analysis of hepatic aminotransferases (AST and ALT), total bilirubin, and prothrombin time
- Elevated liver function tests, or elevated hepatic aminotransferases, may reflect acute serious liver injury
- The recommended corticosteroid regimen is detailed in Table 3 on the next page and in the Prescribing Information

Platelet Count

- Transient decreases in platelet count, some of which met the criteria for thrombocytopenia, were typically observed within the first 2 weeks following infusion
- Monitor for thrombocytopenia (including platelet counts) as well as signs and symptoms of TMA, such as hypertension, increased bruising, seizures, or decreased urine output (see Table 2)
- Consult a pediatric hematologist and/or pediatric nephrologist immediately to manage if clinically indicated

Troponin-I

- Increases in cardiac troponin-I were observed following ZOLGENSMA infusion
- Monitor troponin-I before and after ZOLGENSMA infusion (see Table 2)
- Consider consultation with a cardiologist if troponin elevations are accompanied by clinical signs or symptoms (eg, heart rate changes, cyanosis, tachypnea, and respiratory distress)

Table 2.

BASELINE ASSESSMENTS PRIOR TO INFUSION												
At baseline, assess liver function, creatinine, complete blood count (including hemoglobin and platelet count), and troponin-I												
MONITORING AFTER INFUSION ^a												
TEST	MONTH 1				MONTH 2				MONTH 3			
	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12
Liver function	✓	✓	✓	✓		✓		✓		✓		✓
Platelet count ^b	✓	✓	✓	✓		✓		✓		✓		✓
Troponin-I	✓	✓	✓	✓				✓				✓

W=week; ✓=monitoring performed.

^aMonitor liver function for 3 months or longer until results are unremarkable (normal clinical exam, total bilirubin, and prothrombin results, and ALT and AST levels below 2 × ULN). Monitor platelet counts and troponin-I levels for 3 months or longer until they return to baseline.

^bMonitor platelet counts as well as signs and symptoms of TMA, such as hypertension, increased bruising, seizures, or decreased urine output.

Important Safety Information

ADVERSE REACTIONS

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Step
5

Monitor and postmedicate after ZOLGENSMA infusion (cont'd)¹

Treat with systemic corticosteroids (equivalent to oral prednisolone) before and after infusion

If oral corticosteroid therapy is not tolerated, consider intravenous corticosteroids as clinically indicated.

Table 3.

Corticosteroid Dose Day:	Day 1	Day 2	Day 30 and beyond
Action:	24 hours prior to ZOLGENSMA infusion, initiate 30-day, systemic corticosteroid regimen equivalent to oral prednisolone at 1 mg/kg/day.	<ul style="list-style-type: none"> • Infuse ZOLGENSMA • Continue the corticosteroid regimen 	<p>Do not stop systemic corticosteroids abruptly.</p> <p>If liver function findings are unremarkable (including AST and ALT <2 x ULN):</p> <ul style="list-style-type: none"> • Taper the corticosteroid dose gradually over the next 28 days <p>If liver function abnormalities persist:</p> <ul style="list-style-type: none"> • Continue systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg/day) until AST and ALT values are both below 2 x ULN and all other assessments return to normal range, and then taper the corticosteroid dose gradually over the next 28 days or longer if needed • Consult a pediatric gastroenterologist or hepatologist

¹Monitor liver function for at least 3 months following ZOLGENSMA infusion and until results are unremarkable. Liver function assessment includes a clinical exam and laboratory testing of hepatic aminotransferases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT], total bilirubin, and prothrombin time.) See Table 2 for monitoring schedule.

ULN=upper limit of normal.

Important Safety Information

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Indication and Important Safety Information

Indication

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WARNINGS AND PRECAUTIONS

Thrombocytopenia

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Thrombotic Microangiopathy

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ADVERSE REACTIONS

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Please see accompanying Full Prescribing Information.

Reference: 1. ZOLGENSMA [prescribing information]. Bannockburn, IL: Novartis Gene Therapies, Inc; 2021.

