



ZOLGENSMA Treatment Guide

For 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)

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

Acute serious liver injury and elevated aminotransferases can occur with ZOLGENSMA. Patients with pre-existing 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, 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)

Selected Important Safety Information

ADVERSE REACTIONS

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

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

Step
1

Confirm diagnosis and run laboratory tests

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 biallelic 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 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 $>1:50$



- Perform baseline tests for liver function, 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)

Selected Important Safety Information

Thrombocytopenia

Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were observed at different time points 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 properly

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**

Selected Important Safety Information

Elevated Troponin-I

Transient 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 3

Premedicate and plan for infusion day



- Ensure required baseline testing has been completed, including anti-AAV9 antibody titers, liver function assessment, platelet count, and troponin-I levels



- 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

Selected Important Safety Information

ADVERSE REACTIONS

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Step 4

Prepare and infuse ZOLGENSMA

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



- 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

Selected Important Safety Information

ADVERSE REACTIONS

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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.

Selected Important Safety Information

ADVERSE REACTIONS

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Step 5

Monitor and postmedicate after ZOLGENSMA infusion

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

Liver Function

- Acute liver injury 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

Platelet Count

- Transient decreases in platelet count were observed following infusion
- Monitor platelet counts before and after ZOLGENSMA infusion (see Table 2)

Troponin-I

- Transient increases in cardiac troponin-I were observed following ZOLGENSMA infusion
- Monitor troponin-I before and after ZOLGENSMA infusion (see Table 2)

Table 2.

TEST	BASELINE	TIME FROM INFUSION												
		MONTH 1				MONTH 2				MONTH 3				
		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	
Liver function	✓	✓	✓	✓	✓		✓		✓			✓		✓
Platelet count	✓	✓	✓	✓	✓		✓		✓			✓		✓
Troponin-I	✓	✓	✓	✓	✓				✓					✓

Selected Important Safety Information

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Step
5

Monitor and postmedicate after ZOLGENSMA infusion (cont'd)

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

Corticosteroid Dose Day:	Day 1	Day 2	Day 30 and beyond
Action:	24 hours prior to ZOLGENSMA infusion, initiate 30 day corticosteroid regimen equivalent to oral prednisolone at 1 mg/kg/day.	Infuse ZOLGENSMA. Continue the corticosteroid regimen.	<p>After 30 days, if AST and ALT are $< 2 \times$ the ULN, and liver function appears normal, taper the corticosteroid dose over 28 days.*</p> <p>If AST and ALT are $> 2 \times$ the ULN, and liver abnormalities persist, continue systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg/day) until AST and ALT values are both below $2 \times$ ULN and all other assessments return to normal range, and then taper the corticosteroid dose over the next 28 days.*</p> <p>Consult expert(s) if patients do not respond adequately to the equivalent of 1 mg/kg/day oral prednisolone.*</p>

*Continue to monitor liver function for at least 3 months following ZOLGENSMA infusion. See Table 2 for monitoring schedule.

ULN=upper limit of normal.

Selected Important Safety Information

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Indication and Important Safety Information

Indication

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WARNINGS AND PRECAUTIONS

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Elevated Troponin-I

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ADVERSE REACTIONS

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Please see accompanying Full Prescribing Information.

