Important information regarding ZOLGENSMA® (onasemnogene abeparvovec-xioi) and the provided link to the scientific reprint.

Chand D, Mohr F, McMillan H, et al. Hepatotoxicity following administration of onasemnogene abeparvovec (AVXS-101) for the treatment of spinal muscular atrophy. *J Hepatol.* 2021;74(3):560-566.

This reprint includes information about ZOLGENSMA that is not contained in the Prescribing Information approved by the Food and Drug Administration (FDA). The information provided should in no way be construed as a recommendation for the use of this product in any manner other than as approved by the FDA and as described in the Prescribing Information for ZOLGENSMA.

ZOLGENSMA has a Boxed Warning for Acute Serious Liver Injury and Acute Liver Failure. Please see the accompanying Full Prescribing Information for details, including information regarding assessment of liver function and administration of a systemic corticosteroid.

Please note:

- This study is a retrospective review of data from 325 patients with SMA treated with ZOLGENSMA in clinical trials, open-access programs, or commercial use. Liver-related adverse events, laboratory data, concomitant medications, and prednisolone use were analyzed
- In this retrospective review hepatotoxicity related to ZOLGENSMA typically presented as elevation of serum aminotransferases, occurring most often at week 1 and month 1 post dosing
- This study and the associated clinical trials were sponsored by Novartis Gene Therapies, Inc. (formerly AveXis, Inc.). Novartis Gene Therapies was involved in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication

Indication and Important Safety Information for ZOLGENSMA® (onasemnogene abeparvovec-xioi)

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.

Important Safety Information

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.

WARNINGS AND PRECAUTIONS

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.

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.

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.

ADVERSE REACTIONS

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

Please see accompanying Full Prescribing Information.

zolgensma®
(onasemnogene abeparvovec-xioi)
suspension for intravenous infusion

Hepatotoxicity Following Administration of Onasemnogene Abeparvovec (AVXS-101) for the Treatment of Spinal Muscular Atrophy

Chand D, Mohr F, McMillan H, et al. *J Hepatol.* 2021;74(3):560-566.

A retrospective review of hepatotoxicity in patients treated with ZOLGENSMA® (onasemnogene abeparvovec-xioi) through clinical trials, open-access programs, and commercial use.[1]

ZOLGENSMA is the first and only gene therapy indicated for the one-time-only treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA).[2]

Indication and Important Safety Information

Indication

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Study methods

Study design[1]

The data in this **retrospective review** of liver abnormalities came from 3 sources: 5 sponsored open-label clinical studies (2 completed and 3 ongoing at the time of analysis), open-access programs, and postmarketing data monitored by the sponsor.

Liver data were analyzed from

325 patients

101 from the clinical studies[a]
43 from open-access programs[b]
181 from commercial use

- Liver-related adverse events (AEs), laboratory data, concomitant medications, and prednisolone use were analyzed
- All data analyzed were from patients who received ZOLGENSMA

[a]One patient was excluded from this analysis because study data for the patient was not available with the data cut.
[b]Patients were from open-access programs in the United States.

Clinical trial data[1]

- 100 patients were included in the analysis
- Patients enrolled prior to March 2019 received prednisolone 1 mg/kg/day (or equivalent) 24 hours before dosing through at least 30 days after dosing and then tapered
- Patients enrolled after March 2019 received prednisolone 2 mg/kg/day (or equivalent) for 3 days starting 24 hours before dosing, then reduced to 1 mg/kg/day for at least 30 days and then tapered
- Hepatotoxicity was evaluated based on AE reports. Laboratory data not reported as AEs were also evaluated to assess abnormal values

Open-access programs[1]

- Programs initially occurred as individual investigational new drug (IND) applications held by individual physicians, then subsequently through a managed access program (MAP) protocol, which ended with the approval of ZOLGENSMA by the FDA on May 24, 2019
- The Prospective, Long-Term Registry of Patients with a Diagnosis of Spinal Muscular Atrophy (RESTORE), initiated on May 24, 2018, is an ongoing, global, observational registry evaluating the long-term outcomes of patients with SMA. Patients who received SMA treatment other than ZOLGENSMA were excluded from this analysis

Postmarketing data[1]

- Upon approval, the safety of ZOLGENSMA is monitored in respective regions, including through spontaneous AE reports, solicited venues, and the literature
- Safety was assessed through reported AEs

Important Safety Information

WARNINGS AND PRECAUTIONS

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Clinical trial results

Overview[1]

101 patients were enrolled in intravenous studies and 100 are included in this analysis.

- Mean age at dosing was 2.9 months
- 53 patients had at least 1 comorbid condition, the most common of which were gastroesophageal reflux disease and hypotonia (each 12%), atrial septal defect (9%), and eczema (5%)
- 96 patients reported concomitant medication use (started on or after the date of ZOLGENSMA administration); acetaminophen (>40%), ibuprofen (>20%), and ranitidine (>20%) were most common

Prednisolone[1]

Due to the variability of prednisolone dosage and duration at treating physician's discretion, no correlation with magnitude and duration of increases/decreases in serum aminotransferases could be assessed.

- 99/100 patients received prophylactic prednisolone
- Mean duration of prednisolone treatment was 83 days, and a majority of the patients received prednisolone for 60–120 days

Adverse events[1]

99/100 patients experienced at least one AE after dosing, 57% of AEs were considered related to ZOLGENSMA.

- The most frequent treatment-related AEs were elevations in serum aminotransferases and vomiting

Liver evaluation[1]

34% of patients had at least one hepatotoxicity AE. 100% of events associated with increased serum aminotransferases resolved completely, some with alterations in prednisolone dosing.

- 90% of patients had some degree of ALT and/or AST elevation; the majority of elevations were <3 × ULN
- Elevation of LFTs typically began week 1 post dosing, with a second peak occurring at month 1 (at the time of prednisolone taper and discontinuation)
- 61% of patients had elevated ALT and/or AST and/or bilirubin concentrations prior to dosing

Important Safety Information

WARNINGS AND PRECAUTIONS

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Open-access programs and postmarketing safety cases

Open-access programs results

Overview[1]

54 patients were enrolled in US MAP and/or RESTORE combined as of December 31, 2019. 43 patients received ZOLGENSMA

Prednisolone[1]

Detailed prednisolone dosing and duration data were not available.

Adverse events[1]

Excluding liver-related AEs, the most commonly reported treatment-related AEs were thrombocytopenia (n=4) and vomiting (n=2).

Liver evaluation[1]

ALT and/or AST concentration increases were among the most common AEs reported. In all cases from the open-access programs, transaminase elevations were completely resolved.

- 10 patients reported ALT and/or AST increases
- 5 patients reported liver function test increases (4 of which overlap with ALT and/or AST increases)
- 2 patients developed concurrent bilirubin elevations with severe ALT and AST elevations (>40 × ULN). Both patients responded to re-initiation or dosage increase of prednisolone therapy and were ultimately removed from immunosuppressive therapy

Postmarketing safety cases

Overview[1]

181 patients had received ZOLGENSMA commercially as of December 31, 2019. 192 reports of 488 AEs were retrieved from the Novartis Global Patient Safety database.

Prednisolone[1]

Detailed prednisolone dosing and duration data were not available.

Adverse events[1]

Excluding liver-related AEs, the most commonly reported AEs included:

- 50 reports of pyrexia
- 42 reports of vomiting
- 16 reports of platelet decreased
- 7 reports of thrombocytopenia
- 7 reports of troponin increased

Liver evaluation[1]

Liver-related AEs were among the most commonly reported and included:

- 24 reports of hepatic enzyme increased
- 23 reports of AST increased
- 19 reports of ALT increased
- 17 reports of liver function test increased

Important Safety Information

ADVERSE REACTIONS

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

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Conclusions

Authors' conclusions[1]

Hepatotoxicity related to ZOLGENSMA presents typically as elevation of serum aminotransferases, occurring most often at week 1 and month 1 post dosing. These elevations should be anticipated by monitoring physicians.

The mechanism of ZOLGENSMA-related liver damage is unknown, though liver effects are likely associated with hepatocellular uptake of adeno-associated virus serotype 9 (AAV9).

As the mechanism of hepatotoxicity is suspected to be immune related, prednisolone should be used with ZOLGENSMA as standard of care. Prednisolone should be used prophylactically in accordance with the Prescribing Information. Greater dosages and/or longer duration can be considered in the setting of post-dose elevations in serum aminotransferase concentrations. Consultation with a pediatric gastroenterologist or hepatologist should be considered as clinically appropriate.

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Prevalence of liver abnormalities	• 90% of patients in clinical trials had elevations in liver function test results (ALT, AST, and/or bilirubin concentrations) based on AEs or laboratory data • 61% had mild baseline elevations prior to dosing • 76.7% of presymptomatic patients had baseline elevations • Prevalence and causality of inherent liver dysfunction in patients with SMA are unknown
Severity of liver involvement	• In the clinical studies, all cases had resolution of transaminase elevations by the end of the observation period • Magnitude of transaminase elevations may not predict severity or outcome • Serum laboratory evaluations may not reflect histopathologic findings obtained from biopsy
Causes of liver transaminase elevations	• Children with SMA may have an inherent underlying liver abnormality, possibly due to abnormal fatty acid metabolism and decreased stores of glutathione • Concomitant use of potentially hepatotoxic medications • Potential underlying liver disease unrelated to SMA
Mitigation strategies	• Consider gastroenterology or hepatology evaluation in patients with preexisting elevations in aminotransferases and/or signs of biliary disease • Potentially hepatotoxic medications should be avoided when possible • Prednisolone has been used prophylactically in patients in clinical trials, and is recommended to be used routinely with ZOLGENSMA administration

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Study summary

Hepatotoxicity is a known risk associated with ZOLGENSMA use. Healthcare professionals should identify contributing factors and mitigate risk through monitoring and intervention as appropriate.

Learn more about the one-time-only treatment for SMA at ZOLGENSMA-hcp.com

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