

Direct Healthcare Professional Communication

ZOLGENSMA (onasemnogene abeparvovec) - Fatal cases of acute liver failure

Dear Healthcare professional,

Novartis in agreement with the European Medicines Agency and the <National Competent Authority > would like to inform you of the following:

Summary

- **Fatal cases of acute liver failure have been reported in patients treated with onasemnogene abeparvovec.**
- **Liver function should be monitored before treatment and regularly for at least 3 months after infusion.**
- **Promptly assess patients with worsening liver function tests and/or signs or symptoms of acute illness.**
- **If patients do not respond adequately to corticosteroids, consult a pediatric gastroenterologist or hepatologist and consider adjustment of the corticosteroid regimen.**
- **Corticosteroids should not be tapered until liver function tests become unremarkable (normal clinical examination, total bilirubin, and ALT and AST levels below 2 × ULN).**
- **Inform caregivers about the serious risk of hepatic injury and the need for periodic monitoring of liver function.**

Background on the safety concern

Zolgensma (onasemnogene abeparvovec) is indicated for the treatment of spinal muscular atrophy (SMA). The overall cumulative exposure is approximately 3,000 patients to date.

Hepatotoxicity reported with onasemnogene abeparvovec often manifests as abnormal liver function such as elevated aminotransferases (AST, ALT). However, acute serious liver injury or acute liver failure, including with fatal outcome, have been reported.

The underlying mechanism is likely related to an innate and/or adaptive immune response to the vector. A prophylactic corticosteroid regimen and monitoring of liver function at baseline and regularly for at least 3 months after onasemnogene abeparvovec infusion are therefore recommended. This includes weekly monitoring for the first month, and during the entire corticosteroid tapering period, followed by every two weeks for another month, and at other times if clinically indicated.

Patients presenting with signs or symptoms suggestive of hepatic dysfunction should promptly be evaluated for liver injury. In case patients do not respond adequately to the corticosteroids, consult a pediatric gastroenterologist or hepatologist. Consider adjustment of the

corticosteroid regimen, including a longer duration, and/or increased dose, or more gradual taper to manage hepatotoxicity.

Recently, two fatal cases of acute liver failure have been reported in patients with SMA treated with onasemnogene abeparvovec, at 4 and 28 months of age respectively. Common clinical characteristics of these two cases are summarized below:

- The initial manifestation of liver injury was asymptomatic elevation of liver aminotransferases within the first 1-2 weeks post onasemnogene abeparvovec infusion, which was treated with an increased prednisolone dose.
- The clinical presentation of hepatotoxicity included vomiting, weakness and a second elevation of liver aminotransferases. This was seen between 5 to 6 weeks post onasemnogene abeparvovec infusion, and approximately 1-2 weeks after the initiation of the prednisolone taper.
- Rapid deterioration in liver function, and progression to hepatic encephalopathy and multi-organ failure followed. Death occurred 6-7 weeks after the onasemnogene abeparvovec infusion, during the period of corticosteroid dose tapering.

The product information for onasemnogene abeparvovec is being updated to reflect the information outlined above.

Call for reporting

Please report any suspected adverse reactions associated with the use of onasemnogene abeparvovec in accordance with the national requirements via the national spontaneous reporting system, to:

<Details of national reporting systems as per Appendix V to be included prior to submission to national MS Competent Authorities>

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

▼ Zolgensma is subject to additional monitoring to allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions as soon as possible

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Zolgensma (onasemnogene abeparvovec)
Marketing authorisation holder(s)	Novartis
Safety concern and purpose of the communication	Fatal Cases of Acute Liver Failure – revised risk minimisation measures
DHPC recipients	Paediatric neurologists, paediatric haematologists, paediatric nephrologists Health Care Practitioners involved in the Zolgensma Global Managed Access Program Health Care Practitioners involved in Early Access Request for Zolgensma The target group should be further defined at national level, in agreement with the respective national competent authority.
Member States where the DHPC will be distributed	All EU/EEA Member states where Zolgensma is marketed
Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	January 12, 2023
DHPC and communication plan (in English) agreed by CAT / CHMP	January 26, 2023
Submission of translated DHPCs to the national competent authorities for review	February 2, 2023
Agreement of translations by national competent authorities	February 9, 2023
Dissemination of DHPC	February 16, 2023