PLEASE READ

IMPORTANT MEDICINE SAFETY INFORMATION

APPROVED BY THE HPRA

An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Novartis Pharmaceuticals UK Ltd

Direct Healthcare Professional Communication

16th February 2023

Onasemnogene abeparvovec, ZOLGENSMA - Fatal Cases of Acute Liver Failure

Dear Healthcare professional,

Novartis in agreement with the European Medicines Agency and the Health Products Regulatory 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.

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. Reporting suspected adverse reactions of the

medicinal product is important to Novartis and the HPRA. It allows continued monitoring of the benefit/risk profile of the medicinal product. All suspected adverse reactions should be reported via HPRA Pharmacovigilance, website: www.hpra.ie. Adverse events could also be reported to Novartis preferably via www.report.novartis.com or by email: drugsafety.dublin@novartis.com or by calling 01 2080 612.

Company contact point

If you have any questions regarding Zolgensma, please contact:

Novartis Pharmaceuticals UK Ltd (UK branch)

Medical Information at Tel: +44 20 7949 4555 or MedinfoEMEA.gtx@novartis.com

General enquiries at Tel: +44 20 3580 4484

Yours Sincerely,

Dr Anil Abeyewickreme MA MRCP PhD MFPM,
Medical Director
Novartis UK Limited