Direct Healthcare Professional Communication

<Date>

Onasemnogene abeparvovec, ZOLGENSMA®▼ - Fatal Cases of Acute Liver Failure

Dear Healthcare professional,

Novartis in agreement with the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency (MHRA) would like to inform you of the following:

Summary

- **2 Fatal cases of acute liver failure were reported last year in patients treated with onasemnogene abeparvovec.**
- **A baseline liver function test should be performed 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 paediatric 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) in type I patients or patients with up to 3 copies of SMN2. 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 paediatric hepatologist. Consider adjustment of the corticosteroid regimen, including a longer duration, and/or increased dose, or more gradual taper to manage hepatotoxicity.
Last year, two fatal cases of acute liver failure were reported outside the UK 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 continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme.

Please report:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason
- all suspected ADRs associated with new drugs and vaccines identified by the black triangle▼

It is easiest and quickest to report ADRs online via the Yellow Card website - https://yellowcard.mhra.gov.uk/ or via the Yellow Card app available from the Apple App Store or Google Play Store.

Alternatively, prepaid Yellow Cards for reporting are available:
• by writing to FREEPOST YELLOW CARD (no other address details necessary)

• by emailing yellowcard@mhra.gov.uk
• at the back of the British National Formulary (BNF)
• by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789
• by downloading and printing a form from the Yellow Card website (see link above)

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

▼ Zolgensma is subject to additional monitoring. This will allow quick identification of new safety information. Please report ANY suspected adverse drug reactions (ADRs) to new drugs and vaccines identified by the black triangle▼ to the MHRA through the Yellow Card Scheme.

Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.report.novartis.com.

Company contact point

If you have any questions regarding Zolgensma, please contact:

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

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Yours faithfully,

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Medical Director

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