NOVARTIS

Dear Healthcare Professional Communication

11 August 2022

Onasemnogene abeparvovec, ZOLGENSMA®, Fatal Cases of Acute Liver Failure Reported

Dear Healthcare professional,

Novartis in agreement with Saudi food and drug authority would like to inform you of the following:

Summary

- **The purpose of this letter is to inform you of important safety information for ZOLGENSMA® (onasemnogene abeparvovec) for intravenous infusion.**
- **The Marketing Authorisation application for Zolgengensma is currently under review by Saudi food and drug authority**
- **Recently, two fatal cases of acute liver failure associated with ZOLGENSMA®were reported.**

To date ZOLGENSMA® has been used to treat more than 2,000 patients worldwide across clinical trials, managed access programs, and in the commercial setting.

Background on the safety concern

- Hepatotoxicity is an identified risk associated with ZOLGENSMA® and the ZOLGENSMA® SPC highlights this risk in local "Warnings and Precautions" section to advise the prescribers.

- Acute serious liver injury or acute liver failure have been reported with ZOLGENSMA® use, although hepatotoxicity reported with ZOLGENSMA® is often manifested as abnormal liver function such as elevated aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)].

- The SPC instructs prescribers to (1) prior to infusion, liver function of all patients should be assessed by clinical examination and laboratory testing (e.g., AST, ALT, and total bilirubin), (2) a systemic corticosteroid should be administered to all patients before and

after Zolgensma infusion, and (3) liver function should be monitored for at least 3 months after infusion.

Fatal acute liver failure

- Recently, two fatal cases of acute liver failure have been reported in patients with SMA treated with ZOLGENSMA®, at 4 and 28 months of age respectively. The deaths occurred 6-7 weeks post- ZOLGENSMA® infusion, coinciding with tapering of the corticosteroid dose.

Common clinical characteristics of the two fatal cases associated with ZOLGENSMA® treatment, are summarized below:

  - The first manifestation was asymptomatic elevation of liver aminotransferases within the first 1-2 weeks post ZOLGENSMA® infusion, which was treated with an increased prednisolone dose.

  - The clinical presentation of hepatotoxicity included vomiting, weakness and a second elevation of liver aminotransferases, starting between 5 to 6 weeks post ZOLGENSMA® infusion, approximately 1-10 days following the initiation of prednisolone taper.

  - Rapid deterioration in liver function, and progression to hepatic encephalopathy and multi-organ failure followed. Death occurred 6-7 weeks after ZOLGENSMA® infusion.

- Novartis is in the process of updating the ZOLGENSMA® SPC, to add information that fatal cases of acute liver failure have been reported.

Guidance for the Healthcare Professional

1. It is critical that prescribers regularly monitor liver function for at least 3 months after ZOLGENSMA® infusion, and longer times as clinically indicated.
   The recommended liver function monitoring includes aminotransferases [e.g., AST and ALT], and total bilirubin.

   In case hepatic injury is suspected, further testing is recommended (e.g., albumin, prothrombin time, partial thromboplastin time [PTT], and international normalized ratio [INR]).

   The recommended frequency for laboratory monitoring is:
   - Weekly for the month after ZOLGENSMA® infusion.

   - Weekly during corticosteroid dose tapering period, or more frequently as clinically indicated (see below).

- If the patient is clinically stable with unremarkable findings at the end of the corticosteroid taper period, continue to monitor liver function every other week for another month.

Promptly clinically assess and closely monitor patients with worsening liver function test results and/or signs or symptoms of acute illness.

2. For patients with **unremarkable liver findings** (normal clinical examination, total bilirubin, and ALT and AST levels below 2 × ULN) after the first 30 days, **taper the corticosteroid dose gradually** over the next 28 days with careful monitoring. Do not stop systemic corticosteroids abruptly.

3. **Promptly** consult a pediatric gastroenterologist or hepatologist if patients do not respond adequately to the equivalent of 1 mg/kg/day oral prednisolone and/or if acute serious liver injury and acute liver failure is suspected.

4. Prescribers should note that patients may require **adjustment of the corticosteroid** treatment regimen, including the use of corticosteroid for a longer duration, and/or increased dose, or more gradual taper to manage hepatotoxicity.

5. **Inform** your patients about the known risk of hepatic injury, including death, and the need for periodic monitoring. Patients presenting with signs or symptoms suggestive of hepatic dysfunction should be evaluated for liver injury.

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:

Novartis Pharma AG Patient Safety Department - Saudi Arabia -.
Toll Free Number: 8001240078
Phone: +966112658100
Fax: +966112658107
Email: adverse.events@novartis.com
Or by online: https://report.novartis.com/

Saudi Food and Drug Authority National Pharmacovigilance Center
Unified Contact Center: 19999
Email: npc.drug@sfda.gov.sa
Or by online: https://ade.sfda.gov.sa

Company contact point

Should you need any further information, please do not hesitate to contact us:

Hajer M. AlSaleh, Patient Safety Manager and Risk Management Plan Manager
Novartis Patient Safety - GDD,
Riyadh, Saudi Arabia
Phone (+966) 11 265 8100

Email :Hager.alsaleh@novartis.com or adverse.events@novartis.com
Or by online: www.novartis.com

This letter is not intended as a complete description of the benefits and risks related to the use of ZOLGENSMA®. Please refer the full SPC (prescribing information).

Sincerely,

Hajer Alsaleh

Country Patient Safety Manager / Novartis QPPV

Alsaleh Hager

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