Direct Healthcare Professional Communication

October 2022

Onasemnogene abeparvovec - Fatal Cases of Acute Liver Failure Reported

Dear Healthcare Professional,

The General Administration for Pharmaceutical Vigilance of the Central Administration for Pharmaceutical Care at The Egyptian 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 Onasemnogene abeparvovec for intravenous infusion.
- Recently, two fatal cases of acute liver failure associated with Onasemnogene abeparvovec were reported.

To date Onasemnogene abeparvovec 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 Onasemnogene abeparvovec highlights this risk in insert local "Warnings and Precautions" section title from NPI> to advise the prescribers.

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

The <NPI> 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 Onasemnogene abeparvovec 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 Onasemnogene abeparvovec, at 4 and 28 months of age respectively. The deaths occurred 6-7 weeks post- Onasemnogene abeparvovec infusion, coinciding with tapering of the corticosteroid dose.
  Common clinical characteristics of the two fatal cases associated with Onasemnogene abeparvovec treatment, are summarized below:

21st Abdel-Aziz Al-Saud, Manial Al-Roda,Cairo
pv.head@edaegypt.gov.eg; pv.safety@edaegypt.gov.eg;
Tel.: 237484988 Ext.:1470

- The first manifestation 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, starting between 5 to 6 weeks post Onasemnogene abeparvovec 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 Onasemnogene abeparvovec infusion.

- Novartis is in the process of updating the Onasemnogene abeparvovec, 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 Onasemnogene abeparvovec 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 Onasemnogene abeparvovec 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.

21st Abdel-Aziz Al-Saud, Manial Al-Roda,Cairo
pv.head@edaegypt.gov.eg; pv.safety@edaegypt.gov.eg;
Tel.: 237484988 Ext.:1470

References

FDA https://www.novartis.com/us-en/sites/novartis_us/files/zolgensma.pdf

Health Canada https://recalls-rappels.canada.ca/en/alert-recall/zolgensma-onasemnogene-abeparvovec-and-fatal-cases-acute-liver-failure

Call for reporting

Healthcare professionals are asked to report any suspected adverse reactions via the Egyptian reporting system:

Name: General Administration for Pharmaceutical Vigilance

Email: pv.followup@edaegypt.gov.eg

Online reporting: https://primaryreporting.who-umc.org/EG
QR Code:

Hotline: 15301

21st Abdel-Aziz Al-Saud, Manial Al-Roda,Cairo
pv.head@edaegypt.gov.eg; pv.safety@edaegypt.gov.eg;
Tel.: 237484988 Ext.:1470