Important Safety Information on ZOLGENSMA® (onasemnogene abeparvovec) and Fatal Cases of Acute Liver Failure

NOVARTIS

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Audience
Healthcare professionals including hospital pharmacists, treating physicians, pediatric neurologists, pediatric gastroenterologists and pediatric hepatologists in specialized treatment centres.

Key messages

- **Two cases of fatal acute liver failure have recently been reported internationally in pediatric patients with spinal muscular atrophy (SMA) treated with ZOLGENSMA (onasemnogene abeparvovec). The deaths occurred 6-7 weeks post-ZOLGENSMA infusion, following the initiation of corticosteroid taper.**
- **Hepatotoxicity (acute liver failure, acute liver injury and elevated liver aminotransferases) is an identified risk in the current Canadian Product Monograph for ZOLGENSMA. Patients with pre-existing liver impairment or hepatic viral infection may be at higher risk.**
- **Healthcare professionals are advised to:**
  - **assess liver function by clinical examination and laboratory testing (AST and ALT, total bilirubin, prothrombin time, albumin, PTT, and INR) before ZOLGENSMA infusion. Continue to monitor liver function for at least 3 months after ZOLGENSMA infusion through to the end of the corticosteroid tapering period (see the "Information for healthcare professionals" section for details).**
  - **administer corticosteroid (oral prednisolone or equivalent) to all patients before and for 30 days after ZOLGENSMA infusion.**
  - **taper the corticosteroid dose gradually over 28 days, with careful monitoring, in patients with unremarkable liver function findings after the first 30 days. Do not stop systemic corticosteroids abruptly.**
  - **consider adjusting the corticosteroid treatment regimen, including longer duration, and/or increased dose, or more gradual taper to manage hepatotoxicity.**
  - **monitor any suspected hepatic injury closely, and 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.

- **Health Canada is currently working with the manufacturer to update the Canadian Product Monograph, including the *Serious Warnings and Precautions Box*, to include fatal cases of acute liver failure and revise the guidance for monitoring liver function.**

What is the issue?
Two cases of fatal acute liver failure associated with ZOLGENSMA have recently been reported internationally. The deaths occurred 6-7 weeks post-ZOLGENSMA infusion, following the initiation of corticosteroid taper. No fatal cases of acute liver failure have been reported in Canada.

Products affected
ZOLGENSMA (onasemnogene abeparvovec) solution for intravenous infusion, 2×10^{13} vector genomes/mL.

Background information
ZOLGENSMA is indicated for the treatment of pediatric patients with 5q spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene and:

- 3 or fewer copies of SMN2 gene, or
- infantile-onset SMA.

Hepatotoxicity (acute liver failure, acute liver injury and elevated liver aminotransferases) is an identified risk associated with ZOLGENSMA that is included in the *Serious Warnings and Precautions Box*, *Warnings and Precautions*, and *Adverse Reactions (Post-Market Adverse Reactions)* sections of the current Canadian Product Monograph. Recently, two fatal cases of acute liver failure have been reported internationally in patients who were at 4 and 28 months of age with SMA treated with ZOLGENSMA.

Common clinical characteristics of the two fatal cases 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.

To date, ZOLGENSMA has been used to treat more than 2,300 patients worldwide across clinical trials, managed access programs, and in the post-market setting. At this time, the benefits of ZOLGENSMA to treat SMA continues to outweigh the risks.

Information for consumers
ZOLGENSMA is a type of medicine called a 'gene therapy'. It contains the active ingredient onasemnogene abeparvovec, which contains human genetic material. ZOLGENSMA is used to treat babies and young children who have a rare, serious inherited condition called 'spinal muscular atrophy' (SMA), a genetic condition that causes muscle weakness and atrophy (loss of muscle mass). SMA can affect a child's ability to crawl, walk, sit up, and control head movements. Severe SMA can damage the muscles used for breathing and swallowing.

ZOLGENSMA can cause an immune response that could damage the child's liver, which can lead to serious outcomes, including liver failure and death. If the child has had any liver problems, inform the child's healthcare professional before starting treatment with this medicine. If the child develops symptoms such as vomiting, jaundice (yellowing of the skin or whites of the eyes) or reduced alertness, immediately inform the child's healthcare professional.

Parents/Caregivers should discuss any questions or concerns about this information with their healthcare professional.

Information for healthcare professionals
Healthcare professionals are advised of the following:

- Clinically assess liver function, including aminotransferase and synthetic function testing (AST and ALT, total bilirubin, prothrombin time, albumin, PTT, and INR), in all patients before ZOLGENSMA infusion.
- Administer corticosteroid (oral prednisolone or equivalent) to all patients before and for 30 days after ZOLGENSMA infusion.
- Regularly monitor liver function (AST and ALT, and total bilirubin) for at least 3 months, or longer as clinically indicated, after ZOLGENSMA infusion. If hepatic injury is suspected, then further testing is recommended (albumin, prothrombin time, PTT, and INR).
- The recommended frequency for laboratory monitoring is:
    - weekly for the first month after ZOLGENSMA infusion.
    - weekly during the corticosteroid tapering period, or more frequently as clinically indicated.
    - every other week for another month if the patient is clinically stable with unremarkable findings at the end of the corticosteroid taper period.
- Clinically assess and closely monitor patients with worsening liver function test results and/or signs or symptoms of acute illness.
- 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.

- Monitor suspected hepatic injury closely, and 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.
- Hepatotoxicity may require adjustment of the corticosteroid treatment regimen, including longer duration, and/or increased dose, or more gradual taper.
- Inform caregivers/parents about the known risk of hepatic injury, including death, and the need for regular monitoring. Patients presenting with signs or symptoms suggestive of hepatic dysfunction should be evaluated for liver injury.

Action taken by Health Canada
Health Canada is working with the manufacturer to update the Canadian Product Monograph for ZOLGENSMA to include this safety information.

Health Canada is communicating this important safety information to healthcare professionals and Canadians via the Recalls and Safety Alerts Database on the Healthy Canadians Web Site. This communication will be further distributed through the MedEffect™ e-Notice email notification system, as well as through social media channels, including LinkedIn and Twitter.

Report health or safety concerns
Health Canada's ability to monitor the safety of marketed health products depends on healthcare professionals and consumers reporting adverse reactions and medical device incidents. Any serious or unexpected side effects in patients receiving ZOLGENSMA should be reported to Novartis Pharmaceuticals Canada Inc. or Health Canada.

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.
Dorval, Québec, H9S 1A9
1-800-363-8883

www.novartis.ca/en/our-products/pharmaceuticals

To correct your mailing address or fax number, contact Novartis Pharmaceuticals Canada Inc.

You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

- Calling toll-free at 1-866-234-2345; or
- Visiting MedEffect Canada's Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax.

For other health product inquiries related to this communication, contact Health Canada at:

Marketed Health Product Directorate
E-mail: mhpd-dpsc@hc-sc.gc.ca

Telephone: 613-954-6522
Fax: 613-952-7738

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