

## **Summary Safety Review - Direct-acting antiviral products containing a Protease Inhibitor - Assessing the Potential Risks of Hepatic Decompensation and Hepatic Failure**

**Product:** Direct-acting antiviral products containing a protease inhibitor

**Potential Safety Issue:** Worsening liver function (hepatic decompensation) and liver failure (hepatic failure) in some patients with pre-existing significant liver disease

### **Key Messages**

- **Direct-acting antiviral products containing a protease inhibitor are authorized for sale in Canada to treat chronic (long-lasting) hepatitis C virus infection.**
- **Health Canada reviewed the risk of worsening liver function and liver failure with the use of direct-acting antiviral products containing a protease inhibitor. This review was triggered by a United States Food and Drug Administration (U.S. FDA) drug safety communication.**
- **Health Canada's review concluded that there may be a link between the use of direct-acting antiviral products containing a protease inhibitor and the risk of worsening liver function and liver failure in some patients with pre-existing significant liver disease.**
- **Health Canada will work with the manufacturers to update the Canadian product safety information for direct-acting antiviral products containing a protease inhibitor to include information about these risks.**

### **Overview**

Health Canada reviewed the potential risk of worsening liver function and liver failure with the use of direct-acting antiviral products containing a protease inhibitor. The safety review was triggered by a U.S. FDA drug safety communication warning about these risks in chronic hepatitis C virus-infected patients with advanced liver disease.

### **Use in Canada**

- Direct-acting antiviral products containing a protease inhibitor are prescription drugs authorized for sale in Canada to treat chronic (long-lasting) hepatitis C virus infection.
- Direct-acting antiviral products containing a protease inhibitor have been marketed under different brand names in Canada since 2016. At the time of this review, Maviret (glecaprevir, pibrentasvir), Vosevi (sofosbuvir, velpatasvir, voxilaprevir) and Zepatier (grazoprevir, elbasvir) are authorized for sale in Canada as fixed dose combination products.
- There were about 30,000 prescriptions in total filled for these products annually in 2018 and 2019.

### **Safety Review Findings**

- Health Canada reviewed information from searches of the Canada Vigilance database<sup>a</sup>, international databases, from manufacturers and published scientific and medical literature
- At the time of the review, Health Canada had received 53 case reports for Maviret (1 Canadian), 23 case reports for Vosevi (6 Canadian) and 18 case reports for Zepatier (1 Canadian) related to worsening liver function and liver failure.

- Health Canada’s review found that there may be a link between the use of direct-acting antiviral products containing a protease inhibitor and worsening liver function and liver failure. For Maviret, 51 cases (1 Canadian) showed a possible link and 2 cases could not be assessed due to insufficient information in the reports. For Vosevi, 15 cases (3 Canadian) were found to be possibly linked, 1 case was not likely to be linked, and 7 cases (3 Canadian) did not have enough information to be assessed. For Zepatier, 16 cases (1 Canadian) were considered possibly linked, and 2 cases could not be assessed due to insufficient information in the reports. For most of these cases, contributing factors including existing medical conditions and other medications taken by the patient could not be ruled out. Pre-existing significant liver disease was present in all of the cases.
- Health Canada also reviewed 2 studies from the published scientific literature. These studies did not provide additional information beyond what was obtained from the above case reports.

### **Conclusions and Actions**

- Health Canada’s review concluded that there may be a link between the use of direct-acting antiviral products containing a protease inhibitor and the risks of worsening liver function and liver failure in some patients with pre-existing significant liver disease.
- Health Canada has requested that the manufacturers of direct-acting antiviral products containing a protease inhibitor update the Canadian product safety information to include information about these risks.
- Health Canada will continue to monitor safety information involving direct-acting antiviral products containing a protease inhibitor, as it does for all health products on the Canadian market, to identify and assess potential harms. Health Canada will take appropriate and timely action should new health risks be identified.

### **Additional Information**

The analysis that contributed to this safety review included scientific and medical literature, Canadian and international information, and what is known about the use of direct-acting antiviral products containing a protease inhibitor both in Canada and internationally.

For additional information, [contact the Marketed Health Products Directorate](#)

- 
- a. Canadian reports can be accessed through the [Canada Vigilance Online Database](#).