Summary Safety Review - Brilinta (ticagrelor) - Assessing the Potential Risks of a Worsening of a Slow and Irregular Heartbeat (Bradyarrhythmia) and Partial or Complete Block in the Transmission of Heart Impulses (Second- and Third-Degree Atrioventricular Block).

Product: Brilinta (ticagrelor)

Potential Safety Issue: Worsening of a slow and irregular heartbeat (bradyarrhythmia) and partial or complete block in the transmission of heart impulses (second-and third-degree atrioventricular block).

Key Messages

- **Brilinta is a prescription drug authorized for sale in Canada that is used with low-dose acetylsalicylic acid (ASA), for example Aspirin, to decrease the risk of having a stroke, another heart attack, or dying from heart or blood vessel disease.**
- **This safety review was triggered by published international reports of partial or complete block in the transmission of heart impulses (second-and third-degree atrioventricular [AV] block) in patients treated with Brilinta.**
- **Health Canada reviewed the following 2 potential risks with the use of Brilinta:**
    - **Worsening of a slow and irregular heartbeat (bradyarrhythmia) in patients with history of bradyarrhythmias.**
    - **Second- and third-degree AV block.**
- **Health Canada's review concluded that there may be a link between the use of Brilinta and the risk of bradyarrhythmia including second-and third-degree AV block.**
- **Health Canada will work with the manufacturer to update the Canadian product safety information for Brilinta to include information about these risks.**

Overview

Health Canada reviewed the potential risk of a worsening of a slow and irregular heartbeat (bradyarrhythmia) in patients with a history of bradyarrhythmia as well as the risk of developing a partial or complete block in the transmission of heart impulses (second and third-degree atrioventricular [AV] block) in patients treated with Brilinta. The safety review was triggered by published international reports of second-and third-degree AV block in patients taking Brilinta.

Bradyarrhythmia is a slow and irregular heart rate of less than 60 beats per minute. In second and third-degree AV block, the transmission of heart impulses (electrical signals) from the upper chambers of the heart (atria) to the lower chambers (ventricles) is partly or completely interrupted, leading to bradyarrhythmia.

Use in Canada

- In Canada, Brilinta, when given with low dose acetylsalicylic acid, is used to lower the risk of having a stroke, another heart attack, or dying from a heart or blood vessel disease. Brilinta 90 mg tablets are given to patients who have recently had a heart attack or severe chest pain (unstable angina). Brilinta 60 mg tablets are given to patients who require prolonged treatment (more than one year) after having a heart attack.
- Brilinta has been marketed in Canada since 2011 and is currently available as 60 mg and 90 mg tablets.
- There were about 2 million prescriptions for Brilinta filled in Canada between 2014 and 2019.

Safety Review Findings

- Health Canada reviewed the available information from searches of the Canada Vigilance[a] database, international databases, and published literature.
- The review of the risk of worsening of bradyarrhythmia focused on 18 international cases of patients with a history of bradyarrhythmia who were taking Brilinta. At the time of the review, no Canadian cases of worsening of bradyarrhythmia related to the use of Brilinta in patients with a history of bradyarrhythmia have been reported to Health Canada. Of the 18 case reports, 15 reports were found to be possibly linked to the use of Brilinta, one report was not likely to be linked, and 2 reports did not have enough information to be assessed. Assessing whether the worsening of bradyarrhythmia was related to use of Brilinta in these reports was challenging due to several contributing factors including other existing medical conditions (present in all 18 case reports) and patients taking other medications besides Brilinta (present in more than half of the case reports). Of the 18 case reports, one resulted in death; however, a link between the death and use of Brilinta was not established due to lack of information.
- Health Canada also assessed the risk of second or third-degree AV block related to the use of Brilinta. At the time of the review, 2 Canadian cases of second- and third-degree AV block in patients who used Brilinta have been reported to Health Canada. The review focused on 44 case reports (2 Canadian and 42 international) of patients with or without a history of bradyarrhythmia, who suffered from second or third-degree AV block while taking Brilinta. Of the 44 case reports, 2 reports were found to be probably linked to the use of Brilinta, 40 cases (including 2 Canadian cases) were possibly linked, one report was not likely to be linked, and one did not have enough information to be assessed. Assessing whether AV blocks were related to use of Brilinta in these reports was challenging due to several contributing factors including other existing medical conditions (present in all 44 case reports) and patients taking other medications in addition to Brilinta (present in more than half of the case reports). Of the 44 case reports, 9 resulted in death. Of the 9 reports, 3 reports were found to be possibly linked with use of Brilinta, one report was not likely to be linked, and 5 reports did not have enough information to be assessed. In the 3 reports where the death outcome was deemed

possibly linked to the use of Brilinta, assessing whether the death was related to the use of Brilinta was challenging since other medical conditions, such as coronary artery disease, could have been the cause of death.

- Health Canada also assessed 4 population-based studies found in the scientific literature in order to determine the link between the use of Brilinta and the risk of worsening of the bradyarrhythmia and second or third-degree AV block. Health Canada's review of these studies did not give additional information beyond what was obtained from the above case reports.
- Product safety information of Brilinta in the United States has been updated to include the risk of bradyarrhythmia including AV block.

Conclusions and Actions

- Health Canada's review concluded that there may be a link between the use of Brilinta and the risk bradyarrhythmia, including second and third- degree AV block.
- Health Canada will work with the manufacturer to update the product safety information for Brilinta, and to inform healthcare professionals and patients about these risks.
- Once the product safety information of Brilinta is updated, a communication will be published in the Health Product InfoWatch, to further inform healthcare professionals and patients about these potential risks.
- Health Canada will continue to monitor safety information of Brilinta to identify and assess potential risks, as it does for all health products on the Canadian market. Health Canada will take appropriate and timely action if and when any new health risks are identified.

Additional Information

The analysis that contributed to this safety review included scientific and medical literature, Canadian and international adverse reaction reports and what is known about the use of Brilinta 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