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Dear Healthcare Professionals,

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)

Your attention is drawn to the Health Canada's announcement that it 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.

Health Canada reviewed the available information from searches of the Canada Vigilance 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.

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.

Please refer to the following website in Health Canada for details:
https://hpr-rps.hres.ca/reg-content/summary-safety-review-detail.php?lang=en&linkID=SSR00241

In Hong Kong, there are 2 registered pharmaceutical products containing ticagrelor, namely Brilinta Tab 90mg (HK-61187) and Brilinta Tablets 60mg (HK-64706). Both products are registered by AstraZeneca Hong Kong Ltd, and are prescription-only medicines. So far, the Department of Health (DH) has received 6 cases of adverse drug reaction related to ticagrelor, but these cases are not related to

bradyarrhythmia or atrioventricular block. In light of the above Health Canada's announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Undesirable Medical Advertisements and Adverse Drug Reaction Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

(Joseph LEE)
for Assistant Director (Drug)