



## Canadian Drug Expert Committee Final Recommendation – Plain Language Version

### TICAGRELOR

(Brilinta – AstraZeneca)

**Indication: Prevention of Thrombotic Events in Acute Coronary Syndromes**

#### **Recommendation:**

The Canadian Drug Expert Committee (CDEC) recommends that Brilinta, which is also called ticagrelor, not be listed by Canada's publicly funded drug plans, at the submitted price, for the secondary prevention of atherothrombotic events in patients with acute coronary syndromes (ACS) – i.e., prevention of blood clots in blood vessels in patients who have had a heart attack or angina (chest pain).

#### **Reasons for the Recommendation:**

1. When looking only at the North American patients with ACS who participated in one large medical study, Brilinta was not better than clopidogrel (also called Plavix) and therefore a higher price for Brilinta cannot be justified.
2. The Committee noted that the cost-effectiveness of Brilinta could not be properly assessed because of a number of problems with the manufacturer's economic analysis.
3. The daily cost of Brilinta (\$2.96) is greater than that of clopidogrel (\$2.58).

#### **Of Note:**

Based on a review of the evidence, the Committee felt that a lower price would increase the chance of a recommendation to "list" or "list with criteria".

#### **Background:**

Brilinta belongs to a class of drugs called antiplatelet agents. Platelets are small fragments circulating in the blood. Platelets help to stop bleeding. When a blood vessel is damaged, they clump together to help form a blood clot, which stops the bleeding. However, clots which form inside a damaged blood vessel can be very dangerous because:

- the clot can cut off the blood supply completely, and this can cause a heart attack or stroke.
- the clot can partly block the blood vessels to the heart, and this can cause chest pain that comes and goes (angina).

---

#### Plain Language Recommendation

Brilinta helps to stop the clumping of platelets. This reduces the chance of the formation of a blood clot that can block a blood vessel.

When used together with acetylsalicylic acid (ASA), Brilinta has a Health Canada indication for the secondary prevention of atherothrombotic events in patients with ACS, both for patients who are to be treated with medication, and for patients who are to receive percutaneous coronary intervention (PCI) during which a balloon is inserted to widen the clogged artery, or coronary artery bypass graft (CABG) – i.e., bypass surgery.

Brilinta is available as 90 mg oral tablets. Health Canada recommends that Brilinta be started with a single 180 mg dose and then followed with 90 mg twice daily. Brilinta should be used with a daily ongoing dose of ASA of 75 mg to 150 mg.

### **Submission History:**

Brilinta was initially submitted to the Common Drug Review (CDR) as a Pre-Notice of Compliance (NOC) Priority Review submission in June 2010. The Pre-NOC submission was stopped and Brilinta was later submitted to CDR in June 2011.

### **Summary of CDEC Considerations:**

To make its decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of Brilinta and a review of economic information prepared by the manufacturer of Brilinta. Also CDEC considered information that patient groups submitted about outcomes and issues important to patients who have the condition for which the drug is indicated or who might use the drug.

### **Clinical Trials**

The systematic review included one medical study of patients with ACS. The PLATO study with 18,624 ACS patients included those with or without ST-segment elevation (a type of change on the electrocardiogram [heart tracing]) within 24 hours of the onset of symptoms. Patients were given either Brilinta (a first dose of 180 mg, followed by 90 mg twice daily) or clopidogrel (a first dose of 300 to 600 mg, followed by 75 mg daily). Both groups received ASA. According to the study plan, the ASA dose was 75 mg to 100 mg daily; however, different doses were allowed depending on what the doctor in charge of the patient felt was appropriate (this depended on the guidelines in that particular country or location). Depending on the date that patients entered the study, the duration of treatment ranged from six to twelve months, and results were collected up to 30 days following the last dose of study medication.

Patients in PLATO were mostly male (71.6%), with an average age of 62.2 years; 15.5% of patients were older than 75 years. The PLATO study included a similar percentage of patients with a final diagnosis of STEMI (heart attack with certain changes on the electrocardiogram) and NSTEMI (heart attack without these changes on the electrocardiogram) — approximately 40% each. Approximately 17% of patients had a final diagnosis of unstable angina (chest pain without heart attack). During the study, approximately 64% of patients received PCI and approximately 10% received CABG.

On average, patients took the study drug for 277 days in both groups. More patients in the Brilinta group (23.4%) stopped taking the study drug early than patients in the clopidogrel group

---

### **Plain Language Recommendation**

(21.5%). About the same percentage of Brilinta patients as clopidogrel patients stopped taking part in the study (3.3% versus 2.7% of patients, respectively).

### **Outcomes**

Outcomes were defined in advance in the CDR systematic review protocol. Of these, the Committee discussed the following: death due to any cause and death due to a cardiovascular (heart and blood vessel) cause, non-fatal myocardial infarction (heart attack without death), stroke, quality of life, bleeding events, side effects, and stopping the drug due to side effects.

The main purpose of the study was to measure the percentage of patients who had one or more of the following: non-fatal myocardial infarction, non-fatal stroke, and death from a cardiovascular cause.

Quality of life was measured using the European Quality of Life-5 Dimension questionnaire (EQ-5D), but for only one-third of patients in the PLATO study.

### **Results**

#### **Efficacy or Effectiveness**

- The rate at which patients had any one or more of the three events of interest (non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular cause) was lower for Brilinta than for clopidogrel; the percentage of patients having one or more of the aforementioned was 9.3% for Brilinta and 10.9% for clopidogrel.
- Individually, the rates of non-fatal myocardial infarction and death from cardiovascular cause were lower for Brilinta compared with clopidogrel. However, the rate of non-fatal stroke was about the same for Brilinta and clopidogrel; 1.3% of Brilinta patients and 1.1% of clopidogrel patients had a non-fatal stroke.
- Death due to any cause was lower for Brilinta-treated patients (4.5%) compared with clopidogrel (5.9%).
- When looking only at the North American patients in the study, the rate of having any one or more of the three events of interest was higher for Brilinta compared with clopidogrel, but this difference was small and from a statistical point of view was about the same.
- There was no difference between Brilinta and clopidogrel regarding quality of life as measured by the EQ-5D.

#### **Harms (Safety and Tolerability)**

- Patients on Brilinta had a higher chance of having a stroke (of unknown type) compared with those on clopidogrel. The chances of having other types of strokes (stroke with bleeding, stroke without bleeding, all strokes) were higher for Brilinta compared with clopidogrel, but from a statistical point of view were about the same.
- The percentage of patients having a major bleed was similar for Brilinta (10.4%) and clopidogrel (10.1%). However, compared with clopidogrel, Brilinta-treated patients had higher chances of having a major bleed not due to CABG (3.9% versus 3.3%), a minor bleed (4.8% versus 3.8%), and a minor bleed not due to CABG (4.2% versus 3.1%).
- The percentage of patients with breathing difficulty and severe breathing difficulty was higher for Brilinta compared with clopidogrel (12.0% versus 6.5% and 0.7% versus 0.4%, respectively).

---

### Plain Language Recommendation

- A greater percentage of patients on Brilinta compared with clopidogrel stopped taking their study drug because of a side effect (7.4% versus 5.4%). The two most common side effects which caused patients to stop taking Brilinta were breathing difficulty and nosebleed. These side effects happened more often in patients on Brilinta compared with patients on clopidogrel.

### **Cost and Cost-Effectiveness**

The manufacturer submitted economic information comparing Brilinta with clopidogrel to evaluate the health benefit in patients with ACS over both a one-year and a 30-year time period. In the economic analysis, the manufacturer used results from the PLATO study (including the chance of patients having a heart attack, having a stroke, or dying). The manufacturer also used results from an analysis done by the Canadian Institute for Health Information (CIHI) that estimated the chance of dying in hospital following a heart attack. The manufacturer reported that, over a 30-year time period, Brilinta costs less than clopidogrel (savings of \$500) and provides more of a health benefit.

CDR noted a number of problems with the manufacturer's economic evaluation:

- Some patients may have more than one cardiovascular event, and the manufacturer's analysis did not take this into account, even though there are study results that could have been used for this purpose.
- When looking at a 30-year time period, the manufacturer did not consider the possibility of new cardiovascular events occurring, or how having a cardiovascular event could affect a patient's risk of dying beyond the first year. This could bias results in favour of Brilinta, as this medication is associated with more strokes.
- Health benefit information in the PLATO study and the PLATO HECON study (the health economics sub-study) should have been used in the manufacturer's analysis. No differences in the health benefit were seen between the treatments in the PLATO study at 12 months.

The problems with the economic analysis could not be corrected to provide better estimates of the cost-effectiveness. While the manufacturer provided information in their submission for an update to the economic analysis that was submitted to the National Institute for Health and Clinical Excellence (NICE) in the UK, the supplementary analysis had the same problems associated with the manufacturer's main analysis.

The daily cost of Brilinta (\$2.96 for 90 mg twice daily) is greater than that of clopidogrel (\$2.58 for 75 mg daily).

### **Patient Input Information:**

The following information is a summary of information provided by one patient group that responded to the CDR Call for Patient Input:

- Identified as major concerns for patients with ACS were avoiding death, preventing re-occurrence, lowering the risk of heavy bleeding if major surgery is required, reduced ability to work, and future financial security.
- Patients expect Brilinta to decrease the risk of death or subsequent heart attacks, decrease the risk of bleeding from surgery, decrease the number of days lost from work, and to have less drug interactions, particularly for patients with diabetes.

---

### **Plain Language Recommendation**

### Other Discussion Points:

- The Committee was concerned about the trend toward an increased risk of stroke in Brilinta-treated patients compared with those treated with clopidogrel.
- The Committee discussed that, when only the North American patient group was looked at, Brilinta was not better than clopidogrel based on the main outcome of interest. Further analysis by the manufacturer, which looked at the ASA dose to explain these results, was taken into consideration. However, CDEC considered that, while the ASA dose was a possible explanation for the results, more research is required, as no other medical studies provide evidence of this.
- The Committee did not have confidence in the manufacturer's cost-effectiveness estimates for Brilinta compared with clopidogrel, based on current prices, because of the many problems with the manufacturer's economic analysis. Furthermore, the Committee noted that a generic clopidogrel is likely to be available in the near future.
- The Committee considered the possibility that Brilinta may provide a benefit for patients who get blood clots, or have a stroke while taking clopidogrel. However, the reviewed study did not provide data for this type of patient.
- The Committee expressed concern that Brilinta might be used for conditions other than what Health Canada has approved it for, especially given the trend toward a higher risk of stroke in the Brilinta-treated patients compared with clopidogrel.
- Brilinta requires twice-daily dosing, compared with once daily for clopidogrel.

### CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

### November 16, 2011 Meeting

#### Regrets:

One CDEC member did not attend.

#### Conflicts of Interest:

None.

#### About this Document:

The information contained within this plain language version of the Canadian Drug Expert Committee (CDEC) Recommendation about this drug is based on the information found within the corresponding technical version of the CDEC Recommendation.

In making its recommendation, CDEC considered the best clinical and pharmacoeconomic evidence available, up to that time. Health care professionals and those requiring more detailed information are advised to refer to the technical version available in the [CDR Drug Database](http://www.cadth.ca) on the CADTH website ([www.cadth.ca](http://www.cadth.ca)).

---

### Plain Language Recommendation

### **Background on CDEC:**

CDEC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). The committee is made up of drug evaluation experts and public members. CDEC provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans; however, the individual drug plans make their own decision about whether or not to cover a drug.

In making its recommendations, CDEC decides if the drug under review ought to be covered by the participating public drug plans based on an evidence-informed review of the medication's effectiveness and safety, and based on an assessment of its cost-effectiveness in comparison with other available treatments. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient, nor is it intended to replace professional advice. CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada, the federal government, any provincial or territorial government, or any pharmaceutical manufacturer.

The manufacturer has reviewed this document and has not requested the deletion of any confidential information.

---

### **Plain Language Recommendation**