CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

TICAGRELOR
(Brilinta — AstraZeneca Canada Inc.)
Indication: Secondary Prevention of Atherothrombotic Events

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that ticagrelor be reimbursed when co-administered with low-dose (75 mg to 150 mg) acetylsalicylic acid (ASA) for the secondary prevention of atherothrombotic events in patients with a history (occurred at least one year ago) of myocardial infarction (MI) and a high risk of developing an atherothrombotic event, with the following condition and criteria:

Criteria:

- Patients who are between 12 and 24 months from their most recent MI, and less than 12 months since dual antiplatelet coverage with ASA and an adenosine diphosphate (ADP) receptor inhibitor, with a high risk of subsequent cardiovascular events, defined as requiring at least one of:
  - Age 65 years or older
  - Diabetes requiring medication
  - Second prior spontaneous MI
  - Angiographic evidence of multivessel coronary artery disease
  - Chronic renal dysfunction (creatinine clearance < 60 mL/min).
- Total duration of coverage does not exceed 3 years.

Condition:

- Reduced price.

Reasons for the Recommendation:

1. In the high-risk population enrolled in the PEGASUS trial, over the time period of the trial (three years), there was a clinically important reduction in the risk of cardiovascular (CV) death, MI, or stroke in the ticagrelor 60 mg twice daily plus low-dose ASA group versus the low-dose ASA plus placebo group.
2. Reanalysis by the CADTH Common Drug Review (CDR) found substantial uncertainty in the incremental cost per quality-adjusted life-year (QALY), which ranged from approximately $50,000 to $92,621 for ticagrelor co-administered with ASA, given the need to extrapolate trial data for longer time horizons. Given this uncertainty, a reduction in price would lead to a cost per QALY near a more generally accepted threshold.

Of Note:

1. Patients who were included in the PEGASUS trial had previously tolerated dual antiplatelet therapy and therefore had a lower bleeding risk than the overall population that would be eligible for therapy.
2. The benefit of ticagrelor plus ASA must be balanced against the potential harms, which requires individualized risk stratification. The benefit of CV risk reduction versus the risk of bleeding should be discussed with the patient by a physician with experience in dual antiplatelet therapy.

Background:

Ticagrelor is an oral, direct-acting, selective and reversibly binding P2Y12 receptor antagonist that inhibits platelet activation and aggregation. Health Canada has approved ticagrelor, co-administered with low-dose (75 mg to 150 mg) acetylsalicylic acid (ASA), for the prevention of atherothrombotic events in patients with a history (occurred at least one year ago) of MI and a high risk of developing an atherothrombotic event. The recommended dose is 60 mg twice daily, for up to three years.

Summary of CDEC Considerations:

The Committee considered the following information prepared by CDR: a systematic review of randomized controlled trials of ticagrelor, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients.

The submitted price of ticagrelor (Brilinta) is $1.48 per 60 mg tablet. At the recommended dose of 60 mg twice daily, the daily cost of treatment is $2.96 per patient ($1,080 annually).

Patient Input Information

The following is a summary of information provided by one patient group, the Heart and Stroke Foundation, that responded to the CDR call for patient input:

- There is considerable variation in the degrees to which, and the ways in which, having had a heart attack affects patients and their caregivers. Some patients must take medication multiple times a day, make frequent visits to a health care provider, take time off work, and reduce or limit their activities. Other patients live much less altered lives.
- Fifty of the 84 patients who had taken ticagrelor and who responded to the Heart and Stroke Foundation's survey said they weren't sure or didn't know how well it was working. About a third of patients (29) felt the drug was helping to control their condition, while five of the 84 felt it wasn't. The most commonly reported side effect was shortness of breath and other breathing problems (24/83), with nosebleeds being the next most frequently reported side effect (13/84). Six patients reported a bleed other than from the nose, but the submission did not comment on the severity of any of the reported side effects or indicate whether any were of particular concern.

Clinical Trials

The systematic review included one double-blind, event-driven, randomized controlled trial (RCT) (PEGASUS; N = 21,162) that tested the superiority of ticagrelor 90 mg or 60 mg twice daily versus placebo (as add-on therapy to low-dose ASA) in patients older than 50 years with a history of MI (one to three years prior to randomization), and with one of the following risk

factors for atherothrombotic events: age 65 years or older; diabetes requiring medication; second prior spontaneous MI (more than one year ago); angiographic evidence of multivessel coronary artery disease; or chronic renal dysfunction (creatinine clearance < 60 mL/min).

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following:

- Time to first occurrence of CV death, non-fatal MI, or non-fatal stroke
- Time to CV mortality
- Time to all-cause mortality
- EuroQol 5-Dimensions Health-Related Quality of Life questionnaire (EQ-5D) — a non–disease-specific measure of health status. EQ-5D consists of five domains (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression). Utility function-based scoring algorithms are applied to the EQ-5D health states to generate an index score ranging from 1 (best possible health) to 0 (represents dead), with the possibility of health states being valued as worse than dead (< 0). The visual analogue scale (VAS) provides a self-rating of overall health, ranging from 0 (worst) to 100 (best imaginable health state).
- Time to major bleeding events using the Thrombolysis in Myocardial Infarction (TIMI) definition— which includes intracranial bleeding, or clinically overt signs of hemorrhage associated with a drop in hemoglobin ≥ 50 g/L (or hematocrit ≥ 15%), or fatal bleeding.

The primary outcome was the time to first occurrence of CV death, non-fatal MI, or non-fatal stroke.

Efficacy

- The risk of CV death, MI, or stroke was statistically significantly lower for the ticagrelor 60 mg twice daily plus low-dose ASA group versus the low-dose ASA plus placebo group (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.74 to 0.95). Fewer patients in the ticagrelor 60 mg group experienced a primary composite outcome event than in the placebo group (risk difference [RD], –1.3%; 95% CI, –2.3% to –0.3%).
- No statistically significant differences were detected between groups for time to CV mortality or all-cause mortality.
- [redacted]

Harms (Safety and Tolerability)

- Most patients reported one or more adverse events during the PEGASUS trial (placebo: 69%; ticagrelor 60 mg: 76%).
- Serious adverse events were reported in 22% of patients in each treatment group.
- More patients stopped treatment due to adverse events in the ticagrelor 60 mg group (16%) than in the placebo group (9%).
- Dyspnea (12% versus 4%) and bleeding (29% versus 12%) were reported more frequently among patients who received ticagrelor 60 mg than placebo.
- Ticagrelor 60 mg was associated with an increased risk of TIMI major bleeding versus placebo (HR, 2.32; 95% CI, 1.68 to 3.21), with a reported absolute risk difference of [redacted]. An increased risk of bleeding was also observed when the PLATO, GUSTO, and International Society on Thrombosis and Haemostasis (ISTH) standard

definitions of bleeding were utilized instead of TIMI, and across the subgroups tested in PEGASUS.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis using a patient-level simulation model comparing ticagrelor + ASA versus ASA alone, and considering a lifetime time horizon (40 years) and a Canadian public health care system perspective. The model incorporated the individual patient profiles from the PEGASUS-TIMI 54 trial. Model cycles were three months. During each cycle, the patient was at risk of various clinical events (MI, stroke, fatal CV event, fatal other event and adverse events — dyspnea and bleeds). The probabilities of clinical events were modelled through parametric survival analyses accounting for competing risks. After the initial event, further parametric survival analyses were adopted to model the long-term risk of further events. Each event was associated with costs and utility values. Utility values were derived from panel data analysis of EQ-5D data completed within the PEGASUS-TIMI 54 trial. Costs were derived from the Ontario Schedule of Fees and Benefits (2015) and published literature.

CDR identified the following key limitations with the manufacturer's economic submission:

- The manufacturer assumed that [redacted] of patients with a TIMI major bleed required hospitalization, with a cost of one bed day applied. During the PEGASUS-TIMI 54 trial, the mean length of stay for all patients with a TIMI bleed was [redacted] for ticagrelor + ASA and [redacted] days for ASA alone. CDR reanalysis applied the weighted average length of stay of [redacted] to both treatment arms.
- The analysis was based on three-year trial data from which the benefit of adding ticagrelor to ASA was extrapolated up to 40 years (lifetime). Avoidance of events beyond the trial period was estimated by the model. Only 6% of QALY and life-year gains for ticagrelor + ASA versus ASA alone occurred during the three years of treatment. Although it was recognized that avoidance of events from ticagrelor treatment would have a beneficial impact in the long term, the manufacturer's analysis was viewed to be too optimistic in the absence of any clinical evidence to support the large benefit beyond the treatment period. The model could not be modified to recalibrate the longer-term predictions in events; as such, to try to address this issue, CDR considered a number of scenarios with reductions in the time horizon (from 10 to 20 years) to examine the impact of fewer long-term benefits for ticagrelor that may be more in line with what might be observed in practice.

Addressing the issue of length of hospital stay for major bleeds led to an incremental cost-utility ratio (ICUR) of $49,870 for ticagrelor + ASA versus ASA alone. In addition, reducing the time horizon to 10 years led to an ICUR of $92,621. Given this uncertainty in long-term impact, a price reduction would be necessary to achieve an incremental cost per QALY gained of $50,000.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

July 20, 2016 Meeting

Regrets:
None

Conflicts of Interest:
None

About this Document:
CDEC provides formulary reimbursement recommendations or advice to CDR-participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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