COMMON DRUG REVIEW

CDEC FINAL RECOMMENDATION

TICAGRELOR
(Brilinta – AstraZeneca)
Indication: Prevention of Thrombotic Events in Acute Coronary Syndromes

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that ticagrelor not be listed at the submitted price.

Reasons for the Recommendation:
1. The pre-specified subgroup analysis (by region), in the one large randomized controlled trial (RCT) of patients with acute coronary syndromes (ACS), did not provide evidence of the superiority of ticagrelor compared with clopidogrel in a North American patient population to support a higher price for ticagrelor.
2. Given the limitations identified with the manufacturer's pharmacoeconomic submission, the Committee noted that the cost-effectiveness of ticagrelor could not be properly assessed.
3. The daily cost of ticagrelor ($2.96) is greater than clopidogrel ($2.58).

Of Note:
Based on a review of the clinical evidence, the Committee felt that a reduced price would increase the likelihood of a recommendation to "list" or "list with criteria".

Background:
Ticagrelor, co-administered with acetylsalicylic acid (ASA), has a Health Canada indication for secondary prevention of atherothrombotic events in patients with ACS (unstable angina [UA], non-ST elevation myocardial infarction [NSTEMI], or ST elevation myocardial infarction [STEMI]) who are to be managed medically and those who are to be managed with percutaneous coronary intervention (PCI) (with or without stent) and/or coronary artery bypass graft (CABG).

Ticagrelor is a selective and reversibly bound antagonist of the adenosine diphosphate $P2Y_{12}$ receptor. It is available as 90 mg oral tablets. Health Canada recommends that ticagrelor be initiated with a single 180 mg loading dose and then continued at 90 mg twice daily. Ticagrelor should be used with a daily maintenance dose of ASA of 75 mg to 150 mg.

Submission History:
Ticagrelor 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 ticagrelor was subsequently submitted to CDR in June 2011.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the CDR: a systematic review of double-blind RCTs of ticagrelor, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials
The systematic review included one double-blind RCT of patients with ACS. The PLATO trial (N = 18,624) recruited patients with ACS with or without ST segment elevation, within 24 hours of symptom onset. Patients were randomized to receive either ticagrelor (loading dose of 180 mg, followed by 90 mg twice daily) or clopidogrel (loading dose of 300 mg to 600 mg, followed by 75 mg daily). Both groups received concomitant ASA; according to study protocol, the ASA dose was 75 mg to 100 mg daily. However, dose variation at the investigators' discretion was tolerated, as per local recommendations and practice. Depending on the date that patients entered the trial, duration of treatment ranged from six to 12 months and outcomes were collected up to 30 days following the last dose of study drug.

Patients in PLATO were predominantly male (71.6%), with a mean age of 62.2 years; 15.5% of patients were older than 75 years. The PLATO trial included a similar percentage of patients with a final diagnosis of STEMI and NSTEMI (approximately 40% each), and approximately 17% of patients had a final diagnosis of UA. During the trial, approximately 64% of patients underwent PCI and approximately 10% underwent CABG.

The median exposure to study drug was 277 days in both groups. More patients in the ticagrelor group (23.4%) discontinued the study drug prematurely than in the clopidogrel group (21.5%), and the difference in discontinuation rates was statistically significant. There were slightly more premature withdrawals from the trial (any time before trial closure) in the ticagrelor group (3.3% versus 2.7% of patients), but the difference was not statistically significant.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: mortality (all-cause and cardiovascular), non-fatal myocardial infarction, stroke, quality of life, bleeding events, adverse events, and drug discontinuation due to adverse events.

The primary outcome in PLATO was a composite end point consisting of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. The primary analysis examined the between-treatment difference in the time to first occurrence of any one of the components of the primary composite end point.

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

Results

Efficacy or Effectiveness

- The primary composite end point occurred in 9.3% of ticagrelor patients, compared with 10.9% of clopidogrel patients; absolute risk reduction (ARR): 1.6%, hazard ratio (HR) (95% confidence interval [CI]): 0.84 (0.77 to 0.92). Compared with clopidogrel, ticagrelor was associated with a statistically significant reduction in the incidence of two of three components of the composite end point, based on the pre-specified analysis; cardiovascular death (ARR: 1.1%, HR [95% CI]: 0.79 [0.69 to 0.91]), and non-fatal myocardial infarction (ARR 1.1%, HR [95% CI]: 0.84 [0.75 to 0.95]).
- The incidence of non-fatal stroke (the third component of the composite end point) was not statistically significantly different between ticagrelor (1.3%) and clopidogrel (1.1%), based on the pre-specified analysis; ARR: 0.22%, HR (95% CI): 1.17 (0.91 to 1.52).
- Mortality due to any cause was statistically significantly lower for ticagrelor-treated patients (4.5%) compared with clopidogrel (5.9%).
- In a pre-specified analysis by region, compared with clopidogrel, ticagrelor-treated patients had a higher incidence of the primary composite end point in the North American patient population; however, the difference was not statistically significant; HR (95% CI): 1.25 (0.93 to 1.67).
- There was no statistically significant difference between ticagrelor and clopidogrel in terms of quality of life as measured by the EQ-5D.

Harms (Safety and Tolerability)

- The incidence of stroke of unknown classification was statistically significantly higher for ticagrelor patients compared with clopidogrel; risk ratio (RR) (95% CI): 4.98 (1.09 to 22.71). Compared with clopidogrel, there was a non-statistically significant higher incidence of other stroke outcomes for ticagrelor patients, including all stroke (RR [95% CI]: 1.17 [0.91 to 1.52]); non-hemorrhagic stroke (RR [95% CI]: 1.05 [0.79 to 1.39]); and hemorrhagic stroke (RR [95% CI]: 1.76 [0.89 to 3.47]).
- The percentage of patients having a major bleed was similar between ticagrelor (10.4%) and clopidogrel (10.1%); however, compared with clopidogrel, ticagrelor-treated patients had a statistically significantly higher frequency of major bleeds not related to CABG (3.9% versus 3.3%), minor bleeds (4.8% versus 3.8%), and minor bleeds not related to CABG (4.2% versus 3.1%).
- The percentage of patients with both dyspnea and severe dyspnea was statistically significantly higher for ticagrelor compared with clopidogrel; 12.0% versus 6.5%, and 0.7% versus 0.4%, respectively.
- The percentage of patients who discontinued study drug due to an adverse event was statistically significantly higher for ticagrelor compared with clopidogrel (7.4% versus 5.4%). The two most common adverse events resulting in discontinuation of ticagrelor were dyspnea and epistaxis. These events occurred more frequently in the ticagrelor arm compared with clopidogrel.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-effectiveness analysis comparing the costs and clinical effects of ticagrelor with those of clopidogrel in patients with ACS over both a one-year and a 30-year time horizon. The short-term analysis was conducted using a simple decision tree, while the long-term analysis was conducted using a basic Markov model structure. At baseline,

patients were in one of four health states: myocardial infarction event, stroke event, death, and no event, which is assumed to be a recovered state. After the first cycle, there were only two health states – death and the recovered state. During the first year, patients with myocardial infarction and stroke could transition to the recovered state or death, and, from the recovered state, patients could either stay in this state or die. Thus, no further clinical events were considered. Transition probabilities at baseline (probabilities of myocardial infarction, stroke, and death) were derived from the PLATO trial. After the first year, the only transition probability required, given the simplicity of the model, is the probability of death, which was obtained from an analysis of Canadian Institute of Health Information (CIHI) data estimating 30-day in-hospital mortality post an acute myocardial infarction. In the base case analysis, the manufacturer reported that ticagrelor is less expensive than clopidogrel over a lifetime (savings of $500) and more effective (a gain of 0.067 quality-adjusted life-years [QALYs]).

CDR noted a number of limitations with the manufacturer's economic evaluation:
- Clinical event rates do not account for the possibility of multiple events, despite the availability of data to appropriately capture the clinical pathways.
- The longer-term model structure oversimplifies the clinical pathways and natural history of ACS – survival beyond the first year is not influenced by previous events, and subsequent events were not considered. This may bias results in favour of ticagrelor, as it is associated with a higher incidence of stroke.
- Given the availability of utility data in the PLATO trial and the PLATO HECON study, these data should have been considered in the manufacturer's analysis. No differences in utility values were observed in PLATO at 12 months between treatment groups.

In summary, given the limitations, the model could not be corrected effectively to provide more accurate cost-effectiveness estimates.

While the manufacturer provided a Canadian adaptation of a model submitted to the National Institute for Health and Clinical Excellence (NICE) in the UK to support the results of this economic evaluation, the analysis did not offer any additional information, given common limitations.

The daily cost of ticagrelor (90 mg twice daily, $2.96) is greater than clopidogrel (75 mg daily, $2.58).

Patient Input Information:
The following is a summary of information provided by one patient group that responded to the CDR Call for Patient Input:
- Major concerns for patients with ACS included averting death, preventing reoccurrence of coronary events, lowering the risk of excessive bleeding if invasive surgery is required, and minimizing reduced productivity and risks to future financial security.
- Patients expect ticagrelor to reduce the risk of death or subsequent heart attacks, reduce the risk of bleeding managed by invasive treatments, decrease absenteeism and increase productivity, and to have fewer drug interactions, particularly for patients with diabetes.

Other Discussion Points:
- The Committee expressed concern over the trend toward an increased incidence of stroke in ticagrelor-treated patients compared with clopidogrel.

- The Committee discussed the fact that the superiority of ticagrelor over clopidogrel for the primary composite end point was not demonstrated in the pre-specified North American subgroup. The post hoc analysis based on ASA dose, supplied by the manufacturer as an explanation for ticagrelor's failure to meet its primary end point in the United States, was considered by the Committee to be hypothesis generating. The Committee noted the lack of additional RCT evidence to support this hypothesis.
- The Committee was not confident in the manufacturer's cost-effectiveness estimates for ticagrelor compared with clopidogrel, based on current prices, because of the many limitations in the models. Further, the Committee noted the likely availability of generic clopidogrel in the near future.
- The Committee considered the possibility that ticagrelor may provide a benefit for patients who experience thrombotic events while taking clopidogrel; however, the reviewed trial did not provide evidence relevant to this patient population.
- The Committee expressed concern about the potential for off-label use of ticagrelor, especially given the trend toward a higher incidence of stroke in the ticagrelor-treated patients compared with clopidogrel.
- Ticagrelor 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:
CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. 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 not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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