CEDAC FINAL RECOMMENDATION

PRASUGREL HYDROCHLORIDE
(Effient – Eli Lilly Canada Inc.)
Indication: Acute Coronary Syndrome

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that prasugrel not be listed.

Reason for the Recommendation:
The Committee considered the comparative efficacy of prasugrel and clopidogrel to be uncertain due to the design of the TRITON-TIMI 38 study, but noted that the proportion of patients having a major bleeding event in the TRITON-TIMI 38 study was statistically significantly greater for prasugrel compared with clopidogrel.

Of Note:

1. The Committee considered that prasugrel may be of some benefit for patients in whom stent thrombosis has occurred while receiving clopidogrel and acetylsalicylic acid (ASA); however, there were no direct data to support such a recommendation.
2. The Committee expressed concern regarding the potential for an increased frequency of malignancy with prasugrel compared with clopidogrel and discussed the need for analyses of prospectively collected malignancy data. At the request of regulatory authorities, cancer data will be prospectively collected and analyzed as part of the ongoing TRILOGY-ACS study.

Background:
Prasugrel is indicated by Health Canada for co-administration with ASA, for the early and long-term secondary prevention of atherothrombotic events in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI) as follows:

- Unstable angina, or non-ST-elevation myocardial infarction (UA/NSTEMI), managed with PCI
- ST-elevation myocardial infarction (STEMI) managed with primary or delayed PCI.

Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the $P2Y_{12}$ class of adenosine diphosphate receptors on platelets. It is available as a 10 mg, unscored, film-coated tablet. Health Canada recommends that prasugrel be initiated with a single 60 mg loading dose and then continued at a 10 mg once-daily dose for long-term treatment. Patients taking prasugrel should also take ASA (75 mg to 325 mg) daily.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of published and unpublished, double-blind, randomized controlled trials of prasugrel and a critique of the manufacturer's pharmacoeconomic evaluation.

Clinical Trials
The systematic review included one multicentre, multinational, manufacturer-sponsored, double-blind randomized controlled trial (TRITON-TIMI 38) of adult patients with moderate-to-high risk ACS who were scheduled to undergo PCI. The total patient population (an all-ACS population, N = 13,608), included two pre-specified subgroups: patients with UA/NSTEMI (N = 10,074) and patients with STEMI (N = 3,534). Of the patients with UA/NSTEMI, approximately 40% underwent PCI within 24 hours of symptom onset. Of the patients with STEMI, 69% underwent PCI within 12 hours of symptom onset.

Patients were excluded if cardiovascular disease (i.e., cardiogenic shock, refractory ventricular arrhythmias, heart failure) or bleeding risk factors were present, or patients had received prior concomitant therapy with a thienopyridine (e.g., clopidogrel) within five days of study enrolment, or had received oral anticoagulation, antiplatelet, or systemic antiinflammatory agents. TRITON-TIMI 38 was designed to exclude patients undergoing coronary artery bypass grafting (CABG) as initial therapy.

The TRITON-TIMI 38 study compared prasugrel at a 60 mg loading dose followed by 10 mg daily with clopidogrel at a 300 mg loading dose followed by 75 mg daily; both were combined with ASA. Randomization was stratified by ACS type (UA/NSTEMI versus STEMI). The coronary anatomy had to be known to be suitable for PCI before randomization in all patients with UA/NSTEMI or those enrolled after medical treatment of STEMI. If the coronary anatomy was previously known, or primary PCI for STEMI was planned, pre-treatment with the study drug was permitted for up to 24 hours before PCI. The majority of patients (74%) received the loading dose of the study drug during PCI, and 26% before PCI. The median time from administration of study drug to PCI was two hours. Only 2% of patients received the loading dose more than six hours before PCI.

The sample size of the study was determined with the intention of demonstrating superiority of prasugrel over clopidogrel for the primary composite end point of cardiovascular mortality, non-fatal myocardial infarction (MI), or non-fatal stroke in patients with UA/NSTEMI. If superiority was found for the composite outcome in this subgroup, the all-ACS population would be tested. Patients, investigators, and assessors of the primary outcome were blinded to treatment assignment. The median follow-up time of patients in the study was 14.5 months (range: six to 15 months). Of the all-ACS population, 17% of patients discontinued the study drug early and thus, had a shortened follow-up period; 6% of patients did not complete the study protocol.

Outcomes

Outcomes were defined a priori in the CADTH systematic review protocol. Of the outcomes defined, the Committee discussed the following: overall mortality, cardiovascular related death, non-fatal MI, non-fatal stroke, urgent target-vessel revascularization, stent thrombosis, bleeding events, withdrawals due to adverse events, and adverse events including malignancy. The primary outcome in the TRITON-TIMI 38 study was a composite end point comprised of cardiovascular death, non-fatal MI, or non-fatal stroke.

Results

Efficacy or Effectiveness

In the all-ACS population, the primary composite end point occurred in 9.4% of prasugrel-treated patients and 11.5% of clopidogrel-treated patients (hazard ratio [HR], 95% confidence interval [CI]; 0.81 [0.73 to 0.90]). The STEMI subgroup (including both those patients undergoing PCI within 12 hours and after 12 hours of symptom onset) demonstrated a statistically significant reduction in the primary composite end point with prasugrel compared with clopidogrel, 9.8% versus 12.2% respectively, P = 0.02. Results were consistent in the UA/NSTEMI subgroup with 9.3% of prasugrel-treated patients and 11.2% of clopidogrel-treated patients experiencing a primary end point, P = 0.002. These results were primarily influenced by a statistically significantly lower frequency of non-fatal MI in patients taking prasugrel compared with clopidogrel (all ACS: 7.0% versus 9.1%; P < 0.001). The direction of this finding (for the frequency of non-fatal MI) in the UA/NSTEMI and STEMI subgroups was consistent with the all-ACS population. Although a statistically significantly lower incidence of both procedure-related and non–procedure-related MI was demonstrated in the prasugrel group, the majority of MIs were procedurally related. The majority of the primary outcome events occurred within the first 30 days following randomization.

No statistically significant differences between prasugrel and clopidogrel were observed for deaths from any cause (2.8% versus 2.9%, P = 0.64), cardiovascular deaths (2.0% versus 2.2%, P = 0.31), or non-fatal stroke (0.9% versus 0.9%, P = 0.93) in the overall population. Statistical significance was not found for these outcomes in either UA/NSTEMI or STEMI subgroups.

Patients taking prasugrel had statistically significantly lower incidences of stent thrombosis compared with clopidogrel in each of the following populations: all-ACS, UA/NSTEMI, and STEMI. In the all-ACS population, the rates of definite or probable stent thrombosis for prasugrel versus clopidogrel were 0.9% versus 1.9% respectively; (HR [95% CI] 0.48 [0.36 to 0.64], P < 0.001). There were no data from the TRITON-TIMI 38 study that permitted an assessment of the effects of prasugrel in patients who experienced stent thrombosis while receiving clopidogrel.

In a predefined subgroup analysis (based on diabetes status), prasugrel reduced the rate of the primary composite end point compared with clopidogrel in both those with diabetes (11.4% versus 15.8%; P < 0.001) and those without diabetes (8.8% versus 10.2%; P = 0.02). However, the lack of a statistically significant interaction test suggests that the relative effect of prasugrel compared with clopidogrel does not differ between these two groups. There was no difference in the primary end point in patients ≥ 75 years (N = 1,809) for prasugrel compared with clopidogrel

(HR [95% CI]; 0.94 [0.75 to 1.18], P = 0.60). The results of the subgroup analysis in patients with prior stroke or transient ischemic attack (TIA) (N = 518) indicate that there was a trend toward an increased risk of a primary end point event with prasugrel relative to clopidogrel in this subgroup (HR [95% CI]; 1.37 [0.89 to 2.13], P = 0.15).

Quality of life was measured in a substudy; however, the manufacturer did not include these data in their submission to CDR, but noted that the data were insufficient to assess due to insufficient enrolment.

Harms (Safety and Tolerability)

In the all-ACS population, there were more non–CABG-related thrombolysis in myocardial infarction (TIMI) major bleeding events in prasugrel patients compared with clopidogrel (2.2% versus 1.7%); HR [95%CI]; 1.32 [1.03 to 1.68], P = 0.03. Subsets of major bleeding included life threatening bleeding (1.3% versus 0.8%, P = 0.02) and fatal bleeding (0.31% versus 0.07%; P = 0.002), which were also higher in the prasugrel group compared with the clopidogrel group.

The UA/NSTEMI subgroup experienced a statistically significant increase in TIMI major bleeds with prasugrel compared with clopidogrel, 2.2% versus 1.6% respectively, P = 0.02. There were no statistically significant differences in TIMI major bleeding with prasugrel compared with clopidogrel in the STEMI subgroup (2.2% versus 2.0%, P = 0.65). Rates of major bleeding were similar in the prasugrel- and clopidogrel-treated patients with diabetes (2.3% versus 2.2%).

There was evidence suggesting a higher risk of major bleeding in elderly patients (≥ 75 years old), patients who weighed less than 60 kg, and patients with a history of TIA or stroke. Related to these findings, prasugrel is contraindicated in patients with a history of TIA or stroke and there are black box warnings for patients ≥ 75 years old or those who weigh < 60 kg. The manufacturer indicated that, based on the above criteria, 20% of patients in the TRITON-TIMI 38 study would be ineligible to receive prasugrel.

Analysis of the TRITON-TIMI 38 data by the Food and Drug Administration (FDA) found a statistically significant increase in the incidence of new or worsened neoplasm with prasugrel compared with clopidogrel (2.2% versus 1.6%, P = 0.01; calculated by CDR). However, a number of additional analyses were undertaken by the FDA that distinguished between pre-existing and new neoplasms and between malignant and non-malignant neoplasms. The FDA concluded that, although there is a trend toward an increased frequency of new, non-benign neoplasms in the prasugrel group compared with clopidogrel, these data may be spurious. However, as a condition of licensing, the FDA required that baseline cancer history and cancer event data be gathered from an ongoing clinical trial (TRILOGY-ACS) and submitted. The Health Canada product monograph for prasugrel warns prescribers about the increased frequency of malignancy in the TRITON-TIMI 38 trial and that the causality is currently unknown.

The proportion of patients reporting a serious adverse event (SAE) were similar between patients receiving prasugrel (24.7%) and patients receiving clopidogrel (24.5%), P = 0.55. Hemorrhagic SAEs occurred significantly more often in the prasugrel treatment group compared with the clopidogrel treatment group; 5.9% versus 4.1% respectively, P < 0.001. The proportion

of patients reporting any adverse event was also similar between patients receiving prasugrel (80.3%) and patients receiving clopidogrel (80.0%), P = 0.63.

Cost and Cost-Effectiveness

The manufacturer conducted a cost-utility analysis comparing the costs and clinical effects of prasugrel with clopidogrel in patients with ACS undergoing PCI over a 40-year time horizon. The analysis was conducted using a Markov model, where the first 15 months were based on data from the TRITON-TIMI 38 trial; beyond 15 months, the model is driven by the occurrence of cardiovascular or non-cardiovascular death. The manufacturer reported that prasugrel is associated with a small improvement in survival (0.04 years) and quality-adjusted life-years (0.03), based on a reduction in cardiovascular death and MI, when compared with clopidogrel. Total costs over the 40-year time horizon for patients receiving prasugrel was higher ($129 more) than for patients receiving clopidogrel, largely owing to the higher drug cost, which was administered in the first 15 months. The manufacturer estimated a cost per quality-adjusted life-year of $4,431 and an incremental cost per life-year of $3,003 for prasugrel compared with clopidogrel.

The analysis is limited primarily by the lack of generalizability of the TRITON-TIMI 38 trial. Consequently, the Committee felt that the cost-effectiveness of prasugrel is uncertain in Canadian clinical settings.

The daily cost of prasugrel ($3.14) is greater than clopidogrel ($2.58).

Other Discussion Points:

- The Committee considered that the timing of clopidogrel administration relative to PCI in the TRITON-TIMI 38 study was not reflective of Canadian practice for patients with UA/NSTEMI, as the majority of patients participating in the TRITON-TIMI 38 study received their initial antiplatelet loading dose only during the PCI procedure.
- The timing of clopidogrel administration relative to PCI was thought to be reflective of Canadian practice in only a subset of the patients in the TRITON-TIMI 38 study, that is, STEMI patients that proceeded to PCI within 12 hours of symptom onset. However, the TRITON-TIMI 38 study was not designed to test between-treatment differences for this particular subset of patients.
- Although the Health Canada-approved dose of clopidogrel in ACS is 300 mg as a loading dose followed by 75 mg daily, some centres in Canada use a 600 mg loading dose of clopidogrel for patients requiring primary PCI.
- The reported benefit of prasugrel compared with clopidogrel for the primary composite end point in the TRITON-TIMI 38 study was not statistically significant beyond 30 days for the total patient population, or the STEMI or UA/NSTEMI subgroups.
- There is a potential application for prasugrel in patients who have reduced responsiveness to clopidogrel for various reasons, including resistance or pharmacogenetic variation in metabolism. However, the Committee considered that procedures available for testing response to clopidogrel are not widely used in Canadian clinical practice and routine genetic or platelet testing is currently not recommended. Currently, there is no randomized controlled trial evidence that supports a prasugrel versus clopidogrel strategy based on genetic testing or platelet function assays.

CEDAC Members Participating:
Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, and Dr. Yvonne Shevchuk.

Regrets:
None

Conflicts of Interest:
One CEDAC member reported a conflict of interest and did not participate in the vote.

About this Document:
CEDAC 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 CEDAC made its recommendation.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CEDAC 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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