CDEC FINAL RECOMMENDATION

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

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

Reasons for the Recommendation:
1. The economic evaluation submitted by the manufacturer was limited by its uncertain generalizability to the Canadian population. Specifically, the protocol requirements in the TRITON-TIMI 38 trial, with respect to clopidogrel treatment in relation to percutaneous coronary intervention (PCI), could overstate the comparative clinical benefit of prasugrel in the Canadian population.
2. The daily cost of prasugrel (10 mg, $2.66) is approximately four-fold greater than generic clopidogrel (75 mg, $0.66).

Of Note:
Based on a review of the clinical evidence and cost, the Committee noted that a reduced price would increase the likelihood of a recommendation to “list” or “list with criteria.”

Background:
Prasugrel is indicated by Health Canada for co-administration with acetylsalicylic acid (ASA), for the early and long-term secondary prevention of atherothrombotic events in patients with acute coronary syndromes (ACS) who are to be managed with PCI as follows:
- Unstable angina (UA) or non–ST-segment elevation myocardial infarction (NSTEMI) managed with PCI
- ST-segment 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 10 mg tablets and the Health Canada-approved dose is a single 60 mg loading dose followed by 10 mg once daily. Patients taking prasugrel should also take ASA (75 mg to 325 mg) daily.

Submission History:
Prasugrel was previously reviewed for the treatment of ACS by the Canadian Expert Drug Advisory Committee (CEDAC) and received a recommendation of "do not list" (see Notice of CEDAC Final Recommendation, February 16, 2011).

The original Common Drug Review (CDR) systematic review of prasugrel included one double-blind randomized controlled trial (RCT) of adult patients with moderate to high-risk ACS scheduled to undergo PCI; randomization was stratified by ACS type (UA/NSTEMI versus STEMI). The TRITON-TIMI 38 study compared prasugrel 60 mg loading dose followed by 10 mg daily with clopidogrel 300 mg loading dose followed by 75 mg daily, both combined with ASA. The majority of patients (74%) received the antiplatelet loading dose during PCI and 26% prior to PCI. Only 2% of patients received the loading dose more than six hours prior to PCI.

In the total ACS population, and the UA/NSTEMI and STEMI subgroups, the incidence of the primary composite end point (cardiovascular death, non-fatal myocardial infarction [MI], or non-fatal stroke) was statistically significantly lower for prasugrel compared with clopidogrel. In the total ACS population, the incidence of non- coronary artery bypass graft-related major bleeds was statistically significantly higher for prasugrel compared with clopidogrel. The Committee considered that the results of TRITON-TIMI 38 may not be generalizable to Canadian practice due to the timing of the antiplatelet loading dose in relation to PCI, and the loading dose of clopidogrel employed.

This resubmission is based on a new price (reduced price compared to the original submission). In addition, the manufacturer provided information related to the main concerns raised in the original CDR review; that is, regarding that the TRITON-TIMI 38 trial may have overestimated the benefit of prasugrel compared with clopidogrel due to the lack of pre-treatment for most patients, and regarding the use of a clopidogrel 300 mg loading dose instead of 600 mg.

Summary of CDEC Considerations:
No new RCTs met the inclusion criteria for the CDR systematic review. The Committee considered the following information prepared by CDR:

- the final CDR clinical and pharmacoeconomic review reports for the original prasugrel submission for ACS
- a critique of the manufacturer's pharmacoeconomic evaluation
- a summary of information provided by the manufacturer to address the main concerns raised in the original CDR review, consisting of: sub-studies of TRITON-TIMI 38, German registry data, clopidogrel trial data related to the issues of pre-treatment and high versus low dose, and platelet inhibition data and the influence of genetic variations on clopidogrel efficacy.

No patient groups responded to the CDR Call for Patient Input.

Summary of Findings:
No new information was obtained from the three sub-studies of the TRITON-TIMI 38. Rather, the sub-studies confirmed the results of the trial across geographic regions, and in patients without a known history of stroke or transient ischemic attack (TIA), < 75 years old, and weight ≥ 60 kg. Manufacturer-provided German registry data for patients with STEMI reported a lower frequency of in-hospital death among prasugrel users compared with clopidogrel (2.5% versus 5.8%), but no between-treatment differences in reinfarction, stroke, or bleeding.

Evidence supports the efficacy of clopidogrel pre-treatment in ACS patients undergoing PCI, and a clopidogrel loading dose of 600 mg has demonstrated benefit over a dose of 300 mg. Studies provided by the manufacturer reported superior platelet inhibition with prasugrel compared with clopidogrel. However, a recent meta-analysis reported that patients predicted to have diminished bioactivation of clopidogrel due to reduced function variants of CYP2C19 did not have worse cardiovascular outcomes; thus, the relationship between the variability of clopidogrel's platelet effects and clinical outcome is uncertain.

Cost and Cost-Effectiveness
The manufacturer submitted 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 a dominant treatment compared with clopidogrel, as it is associated with similar total costs (savings of $48 over 40 years) and greater quality-adjusted life-years (QALYs) of 0.03 and life years (0.04) based on a reduction in cardiovascular death and MI.

CDR noted the following limitations with the manufacturer's submission: the economic evaluation is based on the TRITON-TIMI 38 trial and the Committee's concerns with the generalizability to the Canadian setting remain; the cost of clopidogrel was based on the branded price. A generic version of clopidogrel became available since the manufacturer's resubmission, which reduced the cost to $0.66 daily from $2.63. When considering the price of generic clopidogrel, the incremental cost per QALY for prasugrel increased to $21,546 for the ACS population and $10,212 for the STEMI non-stroke subpopulation.

The daily cost of prasugrel (10 mg, $2.66) is approximately four-fold greater than clopidogrel (75 mg, $0.66).

Patient Input Information:
No patient groups responded to the CDR Call for Patient Input.

Other Discussion Points:
- The Committee noted that direct links between platelet inhibition and clinical outcomes with clopidogrel have not been established.
- The Committee further considered that patients who develop stent thrombosis while taking clopidogrel may benefit from switching to prasugrel; however, there are no RCT data to support a recommendation in this patient population.

- The Committee noted that no new harms information was identified in the resubmission, although enhanced surveillance of neoplasm development in future trials was requested by regulatory authorities.

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.

May 16, 2012 Meeting

Regrets:
None

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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