CDEC FINAL RECOMMENDATION

APIXABAN
(Eliquis – Bristol-Myers Squibb Canada)
Indication: Thromboembolic Events, (Venous) Prevention

This document was originally issued on June 14, 2012. It was corrected on August 29, 2012. The apixaban dosing frequency used in the trials on which the CDEC recommendation is based was clarified in the first Reason for Recommendation on page 1

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that apixaban be listed for prevention of venous thromboembolic events (VTE) in patients who have undergone elective knee or hip replacement surgery, for treatment durations of 10 to 14 days, and 32 to 38 days, respectively.

Reasons for the Recommendation:
1. In two double-blind, randomized controlled trials (RCTs) in patients undergoing elective knee replacement (ADVANCE-2) or hip replacement (ADVANCE-3), compared with enoxaparin (40 mg daily), apixaban (2.5 mg twice daily) was associated with a statistically significantly lower incidence of the primary composite end point (deep vein thrombosis, pulmonary embolism, and death from any cause).
2. Results from the manufacturer's cost utility analysis suggest that apixaban is cost-effective compared with enoxaparin, resulting in lower costs and similar quality-adjusted life-years (QALYs) in both knee and hip replacement surgery, for treatment durations of 14 days and 35 days respectively.

Background:
Apixaban has a Health Canada indication for the prevention of VTE in adult patients who have undergone elective knee or hip replacement surgery. Apixaban is a direct factor Xa inhibitor. It is available as 2.5 mg oral tablets. The dose approved by Health Canada is 2.5 mg twice daily; the recommended duration of treatment is 10 to 14 days in patients undergoing knee replacement surgery, and 32 to 38 days in patients undergoing hip replacement surgery.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind, RCTs of apixaban and a critique of the

manufacturer's pharmacoeconomic evaluation. No patient groups responded to the CDR Call for Patient Input.

Clinical Trials

The systematic review included three double-blind, non-inferiority RCTs comparing apixaban with enoxaparin for the prevention of VTE in adults:

- ADVANCE-1 (N = 3,195) included patients undergoing elective knee replacement and randomized patients to apixaban 2.5 mg twice a day or enoxaparin 30 mg subcutaneously twice a day; treatment duration was 10 to 14 days.
- ADVANCE-2 (N = 3,057) included patients undergoing elective knee replacement and randomized patients to apixaban 2.5 mg twice a day, or enoxaparin 40 mg subcutaneously once a day; treatment duration was 10 to 14 days.
- ADVANCE-3 (N = 5,407) included patients undergoing elective hip replacement and randomized patients to apixaban 2.5 mg twice a day, or enoxaparin 40 mg subcutaneously once a day; treatment duration was 32 to 38 days.

In all trials, more than 90% of patients in each treatment group completed treatment. However, a large proportion of patients did not have an evaluable venogram. While this is a common shortcoming of VTE prevention studies, it nevertheless reduces confidence in the results.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: mortality, VTE, serious adverse events, and major bleeding.

The primary efficacy outcome in all trials was a composite of the end-of-treatment incidence of all VTE (including non-fatal pulmonary embolism, and both symptomatic and asymptomatic deep vein thrombosis) and death from any cause. Asymptomatic deep vein thrombosis was identified by venography. In all trials, based on the primary outcome, apixaban would be considered non-inferior to enoxaparin if the upper bound of the 95% confidence interval (CI) for the relative risk (RR) was < 1.25, and in ADVANCE-1 and ADVANCE-2, if the upper bound of the 95% CI for the risk difference was < 5.6%.

In all trials, major bleeding was defined as either a fatal bleeding event or acute clinically overt bleeding accompanied by at least one of the following:

- a decrease in hemoglobin of 2g/dL or more over a 24-hour period
- a transfusion of ≥ 2 units of packed red blood cells
- bleeding that occurred in a critical site, including bleeding into the operated joint needing reoperation or intervention.

Results

Efficacy or Effectiveness

- Apixaban failed to demonstrate non-inferiority compared with enoxaparin (30 mg twice daily) in patients undergoing knee replacement surgery based on the primary outcome in ADVANCE-1; RR (95% CI): 1.01 (0.77 to 1.32). However, based on the primary outcome, apixaban was superior to enoxaparin (40 mg once daily) for patients undergoing knee replacement surgery in ADVANCE-2 (RR [95% CI]: 0.62 [0.51 to 0.74]) and hip replacement surgery in ADVANCE-3 (RR [95% CI]: 0.36 [0.22 to 0.54]).

- In all trials, the incidence of asymptomatic deep vein thrombosis was the major contributor to the composite primary outcome. No trials were powered to detect a difference in symptomatic deep vein thrombosis, pulmonary embolism, or all-cause or VTE-related deaths; all of which occurred infrequently and failed to yield statistically significant between-treatment differences.

Harms (Safety and Tolerability)

- More deaths were observed with enoxaparin in ADVANCE-1 compared with apixaban (n = 5 versus n = 3, respectively). However, there were more deaths with apixaban compared with enoxaparin in ADVANCE-2 (n = 2 versus n = 0) and ADVANCE-3 (n = 3 versus n = 2).
- The proportions of patients experiencing serious adverse events were low and similar between apixaban and enoxaparin (7.7% in both groups in ADVANCE-1; 4.8% versus 5.8% respectively in ADVANCE-2; and 6.9% versus 6.5% respectively in ADVANCE-3).
- The incidence of major bleeding was not statistically significantly different between apixaban and enoxaparin in any of the reviewed trials.

Cost and Cost-Effectiveness

The manufacturer conducted a cost-utility analysis in adults undergoing elective total knee or hip replacement surgery for the prevention of VTE, comparing apixaban with enoxaparin (blend of the 30 mg twice daily and 40 mg daily dose). The manufacturer assumed a treatment duration of 14 days for total knee replacement and 35 days for total hip replacement. The economic model is divided into two time periods: the short-term (90 days post-surgery) based on data from ADVANCE-1, -2, -3 for apixaban, with relative efficacy and harms obtained from a systematic review of comparators and indirect comparison; and, a longer-term model, where transition probabilities for long-term complications were obtained from the literature. The manufacturer reported that apixaban compared with enoxaparin is associated with a saving of $181 and 0.007 additional QALYs for total knee replacement, and a cost saving of $275 and 0.004 additional QALYs compared with enoxaparin for total hip replacement; apixaban is dominant in both populations.

CDR identified the following limitation: confidence intervals cross unity for efficacy and harm estimates in the mixed treatment comparison resulting in small differences in QALYs between comparators and unstable cost-effectiveness estimates.

The daily cost of apixaban ($4.16) is lower than enoxaparin ($12.38 for 30 mg twice daily and $8.20 for 40 mg daily) and rivaroxaban ($8.86).

Patient Input Information:

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

Other Discussion Points:

- The Committee noted that no RCTs have studied apixaban in patients undergoing hip fracture surgery, and that the product monograph recommends against the use of apixaban in this patient population.

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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