CDEC FINAL RECOMMENDATION

RIVAROXABAN
(Xarelto – Bayer Inc.)
New Indication: Deep Vein Thrombosis (Treatment) without Symptomatic Pulmonary Embolism

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that rivaroxaban be listed for the treatment of deep vein thrombosis (DVT) in patients without symptomatic pulmonary embolism (PE), for a duration not to exceed six months.

Reasons for the Recommendation:
1. In one large randomized controlled trial (RCT) of patients with acute symptomatic DVT without symptomatic PE (the EINSTEIN DVT trial), rivaroxaban was reported to be non-inferior to a regimen of enoxaparin plus a vitamin K antagonist (VKA) based on the incidence of recurrent DVT or PE. The majority of patients received treatment for six months or less; thus, there is limited comparative clinical data for treatment durations exceeding six months.

2. Based on CDR re-analyses of the manufacturer's cost-utility analysis, rivaroxaban, at the submitted price, appeared to be cost saving compared with enoxaparin plus warfarin when treating patients for three months, and likely cost neutral when treating patients for six months.

Of Note:
The Committee noted that the generalizability of the EINSTEIN DVT trial is limited with respect to special patient populations; for example, patients with cancer.

Background:
This submission for rivaroxaban is for the new Health Canada indication for the treatment of DVT in patients without symptomatic PE. Rivaroxaban is an anticoagulant that directly inhibits Factor Xa. It is available as 15 mg and 20 mg oral tablets for this indication. The dose approved by Health Canada for this indication is 15 mg twice daily for three weeks, followed by 20 mg once daily.

Submission History:
Rivaroxaban was previously reviewed by the Canadian Expert Drug Advisory Committee (CEDAC) for prophylaxis of venous thromboembolism in patients who have undergone total hip or total knee replacement surgery; it received a recommendation of "list with criteria/condition" (see Notice of CEDAC Final Recommendation, December 17, 2008). Rivaroxaban was also previously reviewed by CDEC for the prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate; it received a recommendation of "list with criteria/condition" (see Notice of CDEC Final Recommendation, April 19, 2012).

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 rivaroxaban 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 one open-label, non-inferiority RCT of patients with acute symptomatic proximal DVT without symptomatic PE. The EINSTEIN DVT study (N = 3,449), randomized patients to either rivaroxaban (15 mg twice daily for three weeks, followed by 20 mg once daily) or a standard therapy that consisted of enoxaparin (1 mg/kg subcutaneously twice a day) plus a VKA, adjusted to maintain an international normalized ratio (INR) of 2.0 to 3.0. Enoxaparin was discontinued after at least five days of concomitant treatment when target INR was attained on two consecutive days. For patients randomized to enoxaparin plus VKA, the median duration of enoxaparin treatment was eight days (interquartile range: six to 11 days), and warfarin was the VKA used in the majority of patients.

Treatment duration was three, six, or 12 months, based on the patient's risk profile and local treatment guidelines, and was decided by the investigator at the time of randomization.

A total of 82% of patients in the rivaroxaban group completed treatment, compared with 80% of patients in the enoxaparin plus VKA group. Although 25% (n = 872) of patients in the trial had a planned treatment duration of 12 months, only 2.6% (n = 90) of patients completed 12 months of treatment with the study drug.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: mortality, recurrent DVT, PE, bleeding, and health care resource utilization.

The primary outcome in EINSTEIN DVT was the incidence of symptomatic recurrent venous thromboembolism, defined as the composite of recurrent DVT, non-fatal PE, or fatal PE. Events were centrally adjudicated by a committee blinded to treatment allocation. All confirmed events were considered up to the end of the intended duration of treatment, irrespective of the actual treatment duration. Rivaroxaban would be considered non-inferior to enoxaparin plus VKA if the upper limit of the 95% confidence interval (CI) of the hazard ratio (HR) did not exceed 2.0.

Clinically relevant bleeding was the primary safety outcome and was defined as the composite of major or clinically relevant non-major bleeding. A bleeding event was considered major if it was clinically overt and accompanied by at least one of the following:

- A fall in the hemoglobin level of 20 g per litre (2 g/dL) or more.
- Transfusion of two or more units of packed red blood cells or whole blood.
- Bleeding that was retroperitoneal, intracranial, occurred in a critical site, or contributed to death.

Results

Efficacy or Effectiveness

- The percentage of patients in the per protocol population who experienced the primary outcome was numerically lower for rivaroxaban (2.1%) compared with enoxaparin plus VKA (2.9%) and rivaroxaban was determined to be non-inferior to enoxaparin plus VKA; HR (95% CI), 0.70 (0.44 to 1.10). Superiority of rivaroxaban relative to enoxaparin plus VKA was not demonstrated in either the intention-to-treat or per-protocol populations.
- Results for the secondary efficacy outcome (a composite of recurrent venous thromboembolism and all-cause mortality) were consistent with those of the primary outcome.
- Overall, health care resource utilization data were similar between rivaroxaban and enoxaparin plus VKA treatment groups in terms of the number of visits to health care providers, hospitalizations (and duration of stay), intensive care unit admissions, rehabilitations, and diagnostic tests.

Harms (Safety and Tolerability)

- Mortality was not statistically significantly different between treatment groups, with *[confidential mortality data removed at manufacturer's request, pursuant to the CDR Confidentiality Guidelines].*
- There was no statistically significant between-treatment difference in the incidence of clinically relevant bleeding (8.1% in both treatment groups); HR (95% CI), 0.97 (0.76 to 1.22).
- The percentage of patients experiencing a major bleed in the rivaroxaban and enoxaparin plus VKA groups was 0.8% and 1.2% respectively; HR (95% CI), 0.65 (0.33 to 1.28).
- The incidence of total adverse events and serious adverse events was similar between treatment groups.

Cost and Cost-Effectiveness

The manufacturer conducted a cost-utility analysis in adults with symptomatic DVT without PE, comparing rivaroxaban with enoxaparin (twice daily for eight days) plus warfarin (day nine onward) over a five-year time horizon. The Markov model was comprised of health states that describe the management and consequences of venous thromboembolism. Clinical inputs for the economic model were based on the EINSTEIN DVT trial. Treatment durations of three and six months were both considered in the manufacturer's analysis based on the clinical trial data. Long-term implications of treatment were estimated based on published literature. The manufacturer reported that rivaroxaban is dominant when compared with enoxaparin plus warfarin when patients are treated for three or six months; however, the gains in quality-adjusted life-years (QALYs) were small (0.001 to 0.003).

CDR noted the following limitations with the manufacturer's analysis: the manufacturer assumed a shorter length of hospital stay with rivaroxaban which may not apply in the Canadian setting; the treatment duration of rivaroxaban affects the cost or cost savings; and the small gains in ALYs lead to unstable cost-effectiveness results in sensitivity analyses. Based on CDR re-analyses for these parameters, rivaroxaban appeared to be cost saving when treating patients for three months and likely to be cost neutral when treating patients for six months.

The daily cost of rivaroxaban is $5.68 for the first 21 days (15 mg twice daily) and $2.84 thereafter (20 mg daily). The alternative treatment is a low molecular weight heparin plus warfarin: the daily cost of enoxaparin ranges from $20.50 (1.5 mg/kg daily) to $30.75 (1 mg/kg twice daily) administered for the first five to 10 days (assuming a 70 kg patient), followed by treatment with warfarin ($0.07 daily, not including monitoring costs).

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

Other Discussion Points:
- The Committee discussed that patients who require treatment of DVT for a period exceeding six months may be switched to a VKA, employing a transition period as described in the product monograph.
- The Committee discussed that, in Canada, the majority of patients with DVT without symptomatic PE are treated in the outpatient setting.

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.

July 18, 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 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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