CDEC FINAL RECOMMENDATION

RIVAROXABAN
(Xarelto — Bayer Inc.)
New Indication: Pulmonary Embolism

Note: The Canadian Drug Expert Committee (CDEC) previously reviewed rivaroxaban for the treatment of deep vein thrombosis (DVT) in patients without symptomatic pulmonary embolism (PE) (see CDEC Final Recommendation, August 12, 2012). The current CDEC recommendation is for the new indication of treatment of venous thromboembolic events (VTE) (DVT and PE) and prevention of recurrent DVT and PE.

Recommendation:
CDEC recommends that rivaroxaban be listed for the treatment of VTE (DVT and PE) and prevention of recurrent DVT and PE, for a duration of up to six months. If treatment is to be extended beyond six months, the following condition must be met:

Condition:
- A reduction in price is required if rivaroxaban is funded for a treatment duration of more than six months.

Reason for the Recommendation:
1. In one randomized controlled trial (RCT) involving patients with acute PE (EINSTEIN-PE), 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, non-fatal PE, or fatal PE. Given that the majority of patients in EINSTEIN-PE received treatment for six months or less, there is limited comparative clinical data for treatment durations exceeding six months.
2. Based on a cost-minimization analysis, rivaroxaban is less costly than enoxaparin plus warfarin when treating patients for up to six months.

Background:
Rivaroxaban has multiple approved indications, including the prevention of VTE in patients who have undergone elective total hip replacement or total knee replacement surgery; the treatment of VTE (DVT and PE) and prevention of recurrent DVT and PE; and the prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate.

Rivaroxaban is available as 10 mg, 15 mg, and 20 mg oral tablets. The dose recommended in the product monograph for the treatment of PE is 15 mg twice daily for three weeks, followed by 20 mg once daily. The duration of therapy should be for a minimum of three months; however, it could be extended over a longer period of time if the benefits exceed the risk of bleeding.

Submission History:
Rivaroxaban was previously reviewed by the Canadian Expert Drug Advisory Committee (CEDAC) for prophylaxis of VTE 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). CDEC also reviewed rivaroxaban for the treatment of DVT in patients without symptomatic PE; it received a recommendation of "list with criteria/condition" (see Notice of CDEC Final Recommendation, August 12, 2012). The current CDR review of rivaroxaban was for the new indication of treatment of VTE (DVT and PE) and prevention of recurrent DVT and PE.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CDR: a systematic review of RCTs of rivaroxaban for the treatment of DVT and PE, and a critique of the manufacturer's pharmacoeconomic evaluation. No patient groups responded to the CDR call for patient input.

Clinical Trials
The CDR systematic review included two open-label, non-inferiority RCTs. The EINSTEIN-DVT study (N = 3,449) included patients with acute symptomatic proximal DVT without symptomatic PE, and the EINSTEIN-PE study (N = 4,832) included patients with acute symptomatic PE with or without symptomatic DVT. In both trials, patients were randomized to either rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily), or a standard therapy that consisted of enoxaparin (1 mg/kg subcutaneously twice daily) 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. In both trials, 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.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- All-cause mortality.
- Symptomatic recurrent VTE — defined as the composite of recurrent DVT, non-fatal PE, or fatal PE.
- Clinically relevant bleeding — defined as the composite of major bleeding 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 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.
- Length of hospitalization — reported for the duration of the hospitalization for the initial episode and for recurrent DVT and PE episodes.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The primary outcome in the EINSTEIN-DVT and EINSTEIN-PE trials was the incidence of symptomatic recurrent VTE, 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. In the manufacturer's analysis, 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.

Efficacy

PE with or without DVT (EINSTEIN-PE)

- All-cause mortality was reported for 2.4% of patients in the rivaroxaban group and 2.1% in the enoxaparin plus VKA group (HR, 1.13 [95% CI, 0.77 to 1.65]).
- The proportion of patients who experienced the primary end point (symptomatic recurrent VTE) with rivaroxaban and enoxaparin plus VKA was [redacted] and [redacted] respectively in the per-protocol (PP) analysis, and 2.1% and 1.8% respectively in the intention-to-treat (ITT) analysis. The associated HRs were [redacted] in the PP analysis and 1.12 (95% CI, 0.75 to 1.68) in the ITT analysis. The upper limit of the CI was below the manufacturer's pre-specified non-inferiority margin for both the PP and ITT analyses.
- The average duration of hospital stay for the initial VTE episode was [redacted] days with rivaroxaban and [redacted] days with enoxaparin plus VKA.

DVT with or without asymptomatic PE (EINSTEIN-DVT)

- There were numerically fewer events of all-cause mortality in the rivaroxaban group (2.2%) compared with the enoxaparin plus VKA (2.9%); however, the difference was not statistically significant (HR, 0.67 [95% CI, 0.44 to 1.02]).
- The proportion of patients who experienced the primary end point (symptomatic recurrent VTE) with rivaroxaban and enoxaparin plus VKA was [redacted] and [redacted] respectively in the PP analysis, and 2.1% and 3.0% respectively in the ITT analysis. The associated HRs were [redacted] in the PP analysis and 0.68 (95% CI, 0.44 to 1.04) in the ITT analysis. The upper limit of the CI was below the manufacturer's pre-specified non-inferiority margin for both the PP and ITT analyses.
- The average duration of hospital stay for the initial VTE episode was [redacted] days with rivaroxaban and [redacted] days with enoxaparin plus VKA.

DVT and/or PE (Pooled EINSTEIN-PE and EINSTEIN-DVT)

- The pooled results from both trials yielded numerically fewer events of symptomatic recurrent VTE in the rivaroxaban group ([redacted]) than in the enoxaparin plus VKA group ([redacted]); the associated relative risk was [redacted]. The upper limit of the CI was below the pre-specified non-inferiority margins.

Harms (Safety and Tolerability)

PE with or without DVT (EINSTEIN-PE)

- There was no statistically significant difference between rivaroxaban and enoxaparin plus VKA for the proportion of patients who experienced clinically relevant bleeding (10.3% and 11.4% respectively); however, major bleeding events were statistically significantly lower with rivaroxaban compared with enoxaparin plus VKA (1.1% versus 2.2%; HR 0.49 [95% CI, 0.31 to 0.79]).
- Serious adverse events were reported for [redacted] of patients in the rivaroxaban group and [redacted] of patients in the enoxaparin plus VKA group.
- Withdrawals due to adverse events were reported for 5.1% of patients in the rivaroxaban group and 4.1% of patients in the enoxaparin plus VKA group.
- At least one adverse event was reported by [redacted] of patients in the rivaroxaban group and [redacted] of patients in the enoxaparin plus VKA group.

DVT with or without asymptomatic PE (EINSTEIN-DVT)

- There was no statistically significant difference between rivaroxaban and enoxaparin plus VKA for the proportion of patients who experienced clinically relevant bleeding (8.1% in both groups) or the proportion of patients who experienced major bleeding (0.8% and 1.2% respectively).
- Serious adverse events were reported for 12.0% of patients in the rivaroxaban group and 13.6% of patients in the enoxaparin plus VKA group.
- Withdrawals due to adverse events were reported for 4.9% of patients in the rivaroxaban group and 4.7% of patients in the enoxaparin plus VKA group.
- At least one adverse event was reported by 62.7% of patients in the rivaroxaban group and 63.1% of patients in the enoxaparin plus VKA group.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing rivaroxaban with enoxaparin plus VKA, based on assumed equal efficacy and harms (from EINSTEIN-PE). They considered the treatment regimens used in EINSTEIN-PE and treatment durations of three, six and 12 months. The manufacturer reported that rivaroxaban is cost-saving compared with enoxaparin plus VKA for treatment durations of three months (savings of $249 per patient) and six months (savings of $113 per patient). However, for longer treatment durations (12 to 36 months), rivaroxaban would be more costly ($152 to $952 more per patient, respectively) compared with enoxaparin plus VKA. CDR calculated that the price of rivaroxaban would need to be reduced by 20% to remain cost-saving at 12 months compared with enoxaparin plus VKA.

The key limitation with the manufacturer's analysis was uncertainty with respect to the true cost of VKA monitoring. If monitoring costs are less than those estimated by the manufacturer, the cost savings of rivaroxaban would be attenuated.

Rivaroxaban is priced at $2.84 per tablet regardless of strength (15 mg or 20 mg). At the recommended daily doses, rivaroxaban costs $5.68 for days 1 to 21 (15 mg twice daily) then $2.84 from day 22 onward (20 mg daily). The alternative treatment is a low molecular weight heparin plus warfarin: the daily cost of enoxaparin is $33.92 (based on 1 mg/kg twice daily for 7 days for a 70 kg patient), followed by treatment with warfarin ($0.08 to $0.14 daily, not including monitoring costs).

Other Discussion Points:
CDEC noted the following:

- The manufacturer requested that rivaroxaban be listed for the treatment of PE for up to six months; however, the clinical experts consulted by CDR and CDEC stated that a significant proportion of patients would require treatment beyond six months. Furthermore, the additional clinical experts noted that it is difficult to provide clear clinical criteria that could be used to characterize patients who would only require treatment for up to six months.
- In the manufacturer's analysis of the EINSTEIN-PE trial, rivaroxaban would be considered non-inferior to enoxaparin plus VKA if the upper limit of the 95% CI of the HR did not exceed 2.0. The non-inferiority margin was based on a meta-analysis of 14 studies that provided HRs ranging from 1.54 to 2.00, depending on the calculation method. There was limited statistical and clinical justification provided by the manufacturer for selecting this non-inferiority margin. Clinically, this non-inferiority margin would signify that rivaroxaban would be considered non-inferior to the current standard of care even if the upper limit of the 95% CI indicated double the incidence of symptomatic recurrent VTE.
- Additional clinical experts consulted in the interpretation of the wide non-inferiority margin accepted the results based upon the small baseline changes in recurrent PE. The declared HR would not have been accepted at higher baseline recurrences.
- The meta-analysis used to estimate the non-inferiority margin used a fixed-effects model as opposed to a random-effects model.
- The generalizability of the EINSTEIN-DVT and EINSTEIN-PE trials is limited with respect to patients with cancer.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- The majority of patients in the EINSTEIN-PE trial received treatment for six months or less; therefore, there is limited comparative clinical data for treatment exceeding six months.

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. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

October 16, 2013 Meeting

Regrets:
None

Conflicts of Interest:
None

About this Document:
CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. 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*.

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