

# Committee to Evaluate Drugs (CED)

## Recommendations and Reasons

Document Posted: January 2016

### Rivaroxaban for pulmonary embolism

**Product:** rivaroxaban (Xarelto®)

**Class of Drugs:** anticoagulant

**Reason for Use:** pulmonary embolism (PE)

**Manufacturer:** Bayer Inc.

**Date of Review:** April 9, 2014

#### CED Recommendation

The CED did not recommend rivaroxaban (Xarelto®) for funding for the treatment of pulmonary embolism (PE) due to concerns with the cost-effectiveness of rivaroxaban compared to other treatments. It was noted that rivaroxaban is as effective as enoxaparin plus warfarin (an alternative blood thinner regimen) for the treatment of PE.

#### Executive Officer Decision\*

Based on the CED's recommendation and an agreement with the manufacturer to help address concerns raised by the CED, the Executive Officer decided to fund rivaroxaban (Xarelto®) for treatment of pulmonary embolism (PE).

#### Funding Status\*

Funded on the Ontario Drug Benefit Formulary as a Limited Use Benefit.

\* This information is current as of the posting date of the document. For the most up-to-date information on Executive Officer decision and funding status, see: [www.health.gov.on.ca/en/pro/programs/drugs/status\\_single\\_source\\_subm.aspx](http://www.health.gov.on.ca/en/pro/programs/drugs/status_single_source_subm.aspx).

## Highlights of Recommendation:

- Two clinical studies support that rivaroxaban provides similar effectiveness as enoxaparin plus warfarin (an alternative blood thinner regimen) for the treatment of venous thromboembolism (deep vein thrombosis and pulmonary embolism).
- The two studies also showed similar rates of serious adverse events between rivaroxaban and enoxaparin plus warfarin.
- The majority of patients in the two studies had intended treatment duration of six months. There is a lack of clinical trial data evaluating rivaroxaban compared to enoxaparin plus warfarin for treatment durations exceeding six months.
- At the list price, rivaroxaban costs \$5.68 daily for the first three weeks, and \$2.84 daily thereafter. Several concerns were identified with the cost-effectiveness of rivaroxaban. In particular, a significant number of patients require greater than six months of therapy, and in those cases, rivaroxaban is more expensive than existing alternative treatments.

## Background:

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two potential outcomes of venous thromboembolism (VTE). DVT occurs when a blood clot forms inside a vein deep in the leg, causing leg pain and swelling. A blood clot in a leg vein can grow, break off, and travel to the lungs, resulting in shortness of breath, chest pain, and, in some cases, death. A clot that travels to the lungs is called PE.

The standard treatment for PE has been low molecular weight heparin (LMWH), overlapped and followed by warfarin. Patients on warfarin require regular monitoring of international normalised ratio (INR), which is used to determine the effects of warfarin on blood clotting.

Rivaroxaban is an anticoagulant (blood thinner) used to prevent harmful blood clots. This drug is funded by the Ontario Drug Benefit Program for various other indications associated with abnormal blood clotting.

## Detailed Discussions:

- For this evaluation, the CED considered:
  - Findings from the Common Drug Review (CDR) and the recommendation of the Canadian Drug Expert Committee (CDEC);
  - Information in the manufacturer's submission.
  - (There were no patient group submissions for this review.)
- The CED evaluated two open-label, non-inferiority, randomized controlled trials (RCTs): EINSTEIN-DVT, which included 3,449 patients with acute symptomatic DVT without symptomatic PE, and EINSTEIN-PE, which included 4,832 patients with acute symptomatic PE with or without symptomatic DVT. Patients in the trials were randomized to receive either rivaroxaban alone or enoxaparin plus warfarin. The intended treatment duration in the studies was 3, 6, or 12 months, based on the patient's risk profile, and was decided by the investigator at the time of randomization. The primary outcome in both trials was

symptomatic recurrent VTE (recurrent DVT, or non-fatal or fatal PE). Subgroup analyses examined patients by their intended treatment duration.

- In EINSTEIN-DVT, the primary outcome occurred in 2.1% versus 2.9% of patients in the rivaroxaban and the enoxaparin plus warfarin groups, respectively (HR, 0.70; 95% CI, 0.44-1.10). In EINSTEIN-PE, the primary outcome occurred in 1.7% versus 1.6% of patients in the rivaroxaban and the enoxaparin plus warfarin groups, respectively.
- The majority of patients in the trials had intended treatment duration of six months. In this subgroup, the primary outcome occurred in 2.3% versus 2.7% of patients (rivaroxaban versus enoxaparin plus warfarin) in EINSTEIN-DVT and in 1.9% versus 1.7% of patients in EINSTEIN-PE.
- The CED noted that the percentage of time in the therapeutic INR range for the enoxaparin plus warfarin group was 58% in EINSTEIN-DVT and 63% in EINSTEIN-PE. These values represented suboptimal warfarin control. This may have biased the efficacy results in favour of rivaroxaban.
- Quality of life and other patient-reported outcomes were not evaluated in the trials.
- The two studies showed no statistically significant difference in clinically relevant bleeding between patients on rivaroxaban and those on enoxaparin plus warfarin. There was no difference in major bleeding between the two study groups in EINSTEIN-DVT. In EINSTEIN-PE, major bleeding was lower with rivaroxaban than with enoxaparin plus warfarin (1.1% versus 2.2%; HR, 0.49; 95% CI, 0.31-0.79). Serious adverse events were similar between groups in both studies.
- At the list price, rivaroxaban costs \$5.68 daily for the first three weeks, and \$2.84 daily thereafter. The manufacturer's economic analysis reported that rivaroxaban is cost-saving compared with enoxaparin plus warfarin for treatment durations of three months and six months but was more expensive with longer treatment durations. Limitations with the manufacturer's analysis include an overestimation of the costs associated with INR monitoring and LMWH administration. The availability of LMWHs that are less costly than enoxaparin was not considered. Furthermore, it was noted that there are patients who cannot take warfarin (e.g., due to allergy or other contraindications), and that these patients would generally be treated long-term with LMWH. An economic analysis comparing rivaroxaban with long-term LMWH use would have been valuable.
- Overall, two clinical studies show that rivaroxaban is non-inferior to enoxaparin plus warfarin for the treatment of VTE. There are limited comparative clinical data for treatment durations exceeding six months. Several concerns were identified with the manufacturer's economic analysis. In particular, many patients require greater than six months of therapy, and in those cases, rivaroxaban is markedly more expensive than LMWH plus warfarin.

### **Committee to Evaluate Drugs (CED)**

The Committee to Evaluate Drugs (CED) is comprised of practicing physicians, pharmacists, health economists, and patient representatives. In conducting its review, the CED considers data contained in the drug manufacturer's submission, input provided by patient groups, findings from the national Common Drug Review and the pan-Canadian Oncology Drug Review, and other scientific information as necessary.

For more information, please contact:

Ministry of Health and Long-Term Care

Ontario Public Drug Programs

Hepburn Block, 9th Floor

80 Grosvenor Street, Queen's Park

Toronto, Ontario M7A 1R3

[www.health.gov.on.ca/en/pro/programs/drugs/](http://www.health.gov.on.ca/en/pro/programs/drugs/)