



CDEC FINAL RECOMMENDATION

RIVAROXABAN

(Xarelto – Bayer Inc.)

New Indication: Atrial Fibrillation, Stroke Prevention

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that rivaroxaban be listed for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, in whom warfarin is indicated, and who meet all of the following criteria:

- Are unable to achieve adequate anticoagulation with warfarin, and
- Have a CHADS₂ score of ≥ 2 .

Reasons for the Recommendation:

1. In one large double-blind randomized controlled trial (RCT) of patients with a CHADS₂ score of ≥ 2 (ROCKET-AF), rivaroxaban was reported to be non-inferior, but not superior, to adjusted-dose warfarin, based on the incidence of stroke or systemic embolism.
2. At recommended doses of rivaroxaban (15 mg or 20 mg daily; \$2.84), the daily cost is greater than warfarin (\$0.07, or approximately \$0.78 to \$2.18 when monitoring costs are included, depending on setting) but lower than dabigatran (110 mg or 150 mg twice daily; \$3.20).

Of Note:

The Committee noted that the determination of an inability to achieve adequate anticoagulation with warfarin is sensitive both to individual patient characteristics and to locally available resources and, as such, should be determined on a jurisdictional basis. Jurisdictions may consider the following factors in making such a determination:

- Access to international normalized ratio (INR) monitoring
- Time to achieve a stable therapeutic INR, as well as time in the therapeutic range (TTR)
- Ability to maintain a stable therapeutic INR without frequent testing and dose adjustment
- Serious hypersensitivity reaction to warfarin
- Access to management of bleeding
- Ability to provide sufficient patient education and awareness.

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Background:

This submission for rivaroxaban is for the new Health Canada indication for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. 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 20 mg daily; in patients with moderate renal impairment (creatinine clearance 30 mL to 49 mL per minute), the recommended dose is 15 mg 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; rivaroxaban received a recommendation of “list with criteria/conditions” (see Notice of CEDAC Final Recommendation, December 17, 2008).

Summary of CDEC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of rivaroxaban, a critique of the manufacturer’s pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients. Additionally, the Committee reviewed the CADTH draft Therapeutic Review Report (*New Oral Anticoagulants for the Prevention of Thromboembolic Events in Patients with Atrial Fibrillation*) as well as stakeholder feedback received on that draft report. A pre-Notice of Compliance priority review of this submission was requested by the manufacturer and granted by CDR.

Clinical Trials

The systematic review included one large double-blind, multinational RCT of patients with non-valvular atrial fibrillation. The ROCKET-AF study (N = 14,236) was designed to test the non-inferiority of rivaroxaban compared with adjusted-dose warfarin (dose adjusted to a target INR of 2.5 [therapeutic range: 2.0 to 3.0]). Study participation was to be for a minimum of 14 months and a maximum of four years.

Patients in the ROCKET-AF study were aged 71 years on average and most (60%) were male. Patients’ risk of stroke was assessed through the CHADS₂ score, named for the five risk factors assessed: congestive heart failure, hypertension, age, diabetes, and previous stroke or transient ischemic attack. A CHADS₂ score of 2 or greater was required for entry to the ROCKET-AF study. A CHADS₂ score of 3 was the most common CHADS₂ score at baseline (44% of patients), followed by a CHADS₂ score of 4 (29% of patients).

Approximately 85% of randomized patients completed the study, with no difference between treatment arms. The median follow-up time was 707 days (~24 months). Limitations of the ROCKET-AF study include the uncertain generalizability of the results, due to the inadequate INR control achieved by patients, both overall (TTR of 55%) and at a number of the participating sites.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: mortality, stroke and systemic embolism, serious adverse events, and bleeding. The primary outcome in the ROCKET-AF study was the incidence of a composite end

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point consisting of stroke or non-central nervous system (CNS) systemic embolism. ROCKET-AF was designed to accept the non-inferiority of rivaroxaban compared with warfarin for the primary outcome if the upper limit of the 95% confidence interval (CI) of the hazard ratio (HR) did not exceed 1.46.

Stroke was defined as a new, sudden, focal neurological deficit resulting from a presumed cerebrovascular cause that was not reversible within 24 hours and not due to another readily identifiable cause such as a tumour, seizure, or trauma.

A non-CNS systemic embolism was defined as an abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms (e.g., trauma, atherosclerosis, instrumentation).

Major bleeding was defined as clinically overt bleeding associated with:

- A decrease in hemoglobin of 2 g/dL or more, or
- A transfusion of two or more units of packed red blood cells or whole blood, or
- Bleeding at a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal, or
- A fatal outcome.

Results

Efficacy or Effectiveness

- The proportion of patients in the per-protocol population who experienced a primary outcome event was numerically lower for rivaroxaban (2.7%) than for warfarin (3.4%), and rivaroxaban was determined to be non-inferior to warfarin; HR (95% CI): 0.79 (0.66 to 0.96). Rivaroxaban also met the criteria for non-inferiority in the intention to treat (ITT) population. The superiority of rivaroxaban compared with warfarin was not demonstrated in the ITT population.
- A subgroup analysis of primary outcome events by baseline age suggested that rivaroxaban patients older than 75 years were less likely than warfarin patients to have a primary outcome event; 2.6% versus 3.9%, HR (95% CI): 0.68 (0.50 to 0.92).
- In a subgroup analysis, based on centre TTR, the incidence of primary outcome events was numerically lower for rivaroxaban compared with warfarin in all four quartiles; however, none of the differences were statistically significant.
- Fewer rivaroxaban than warfarin patients died during the study (2.9% versus 3.5%); however, the difference was not statistically significant. Vascular deaths were the most common cause of death in both rivaroxaban and warfarin groups (2.4% versus 2.7%), but the difference between treatments was not statistically significant.
- There was a numerically lower incidence of stroke with rivaroxaban than with warfarin, but this difference was not statistically significant (2.6% versus 3.1% of patients). Most strokes were ischemic, and although there was a numerically lower incidence of ischemic stroke with rivaroxaban than with warfarin, this difference was not statistically significant. There was, however, a statistically significantly lower incidence of hemorrhagic stroke with rivaroxaban than with warfarin (0.4% versus 0.7% of patients).

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Harms (Safety and Tolerability)

- The proportion of patients experiencing a serious adverse event was not statistically significantly different between rivaroxaban and warfarin; 35.0% versus 36.5%, respectively. The most common serious adverse event in both groups was cardiac failure, which was reported in numerically fewer rivaroxaban than warfarin patients (3.7% versus 4.1%).
- The proportion of patients experiencing a major bleed was not statistically significantly different between rivaroxaban (4.0%) and warfarin (3.9%); however, the proportion of patients experiencing an intracranial hemorrhage was statistically significantly lower for rivaroxaban than for warfarin (0.8% versus 1.2%).
- The proportion of patients experiencing a non-major clinically relevant bleed was statistically significantly higher for rivaroxaban (11.2%) than for warfarin (9.4%), based on CDR analysis. However, when the incidence of non-major clinically relevant bleeding was adjudicated by the study's clinical end point committee, the difference was not statistically significantly higher for rivaroxaban than for warfarin (16.7% versus 16.2%, respectively).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis based on a 30-year time horizon, to compare rivaroxaban with adjusted-dose warfarin in patients with atrial fibrillation at moderate to high risk of stroke (CHADS₂ ≥ 2). The model utilized information regarding baseline risk of events and relative risk of events between the rivaroxaban and warfarin groups from the ROCKET-AF study. The long-term impact on health-related quality of life and medical costs associated with the disability from events were estimated from the literature. The manufacturer reported that when compared with adjusted-dose warfarin, rivaroxaban is associated with a cost per quality-adjusted life-year (QALY) of \$37,555.

The manufacturer's economic evaluation is limited by the absence of dabigatran as a comparator, and the approach of evaluating the impact of warfarin monitoring costs on the incremental cost per QALY of rivaroxaban, which could drive the cost per QALY up to \$56,366.

At recommended doses of rivaroxaban (15 mg or 20 mg daily; \$2.84), the daily cost is greater than warfarin (\$0.07, or approximately \$0.78 to \$2.18 when monitoring costs are included, depending on setting) but is lower than dabigatran (110 mg or 150 mg twice daily; \$3.20).

Patient Input Information:

The following is a summary of information provided by two patient groups who responded to the CDR Call for Patient Input.

Patient groups described issues related to chronic warfarin therapy that adversely affect quality of life; they also mentioned the expectation that rivaroxaban would represent an improvement over warfarin on these issues. The following specific issues with warfarin treatment were noted:

- Fear of bleeding resulting from falls, especially in the elderly
- The inconvenience of INR monitoring with warfarin treatment
- The additional vigilance often required of patients because of concerns related to potential drug, food, and alcohol interactions with warfarin
- The challenges of restabilizing warfarin dosing in cases of temporary interruptions in therapy
- The burden to the caregiver related to supporting the patient's monitoring appointments.

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The potential risk to patients opting to take a less effective therapy or no therapy at all as a possible consequence of these perceived quality of life issues was also highlighted.

Other Discussion Points:

- The Committee noted that, according to the Health Canada product monograph, the use of rivaroxaban is not recommended in patients with severe renal impairment (creatinine clearance < 30 mL per minute). The Committee took into consideration that the older target patient population may have declining and/or unpredictable renal function. The product monograph recommends a reduced dose of rivaroxaban (15 mg daily) in patients with moderate renal impairment (creatinine clearance 30 mL to 49 mL per minute).
- The Committee noted that the ROCKET-AF study did not include quality of life outcomes, but recognized that the design of the study did not allow for an assessment of between-treatment differences in quality of life.
- The Committee discussed the issue that the higher incidence of stroke among rivaroxaban-treated patients compared with warfarin, in the period immediately after the double-blind treatment phase, may have been related to the short elimination half-life of rivaroxaban coupled with the typical delay in achieving INR control with subsequent warfarin. The Committee considered that occasional non-adherence with rivaroxaban may pose a greater stroke risk to patients than occasional non-adherence with warfarin. The Committee further noted that INR monitoring of warfarin-treated patients facilitates identification of non-adherence.
- The Committee noted that there is no reversal agent for rivaroxaban. The Committee considered access to management of bleeding and a jurisdiction's ability to provide sufficient patient education and awareness to be as important for patients treated with rivaroxaban as it is for warfarin.
- The Committee considered that the 30-year time horizon used in the manufacturer's cost utility analysis to possibly be too long, given the length of the available clinical trials.

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.

March 21, 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.

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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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