CDEC FINAL RECOMMENDATION

RIVAROXABAN
(Xarelto – Bayer Inc.)
Indication: Stroke Prevention in Atrial Fibrillation

This recommendation supersedes the Canadian Drug Expert Committee (CDEC) recommendation for this drug and indication dated April 19, 2012.

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that rivaroxaban be listed for the prevention of stroke and systemic embolism in patients with atrial fibrillation who meet all of the following clinical criteria:

Clinical Criteria:
1. Patients with a $CHADS_2$ score ≥ 2.
2. Patients who are unable to readily achieve adequate anticoagulation with warfarin.

Reasons for the Recommendation:
1. In one large, double-blind, randomized controlled trial (RCT) of patients with a $CHADS_2$ score of greater than or equal to 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, the daily cost of rivaroxaban (15 mg or 20 mg daily; $2.84) is less than the daily cost of dabigatran (110 mg or 150 mg twice daily; $3.20) and apixaban (2.5 mg or 5 mg twice daily; $3.20), but is greater than the cost of warfarin (2 mg to 10 mg daily; $0.07) or ASA (80 mg to 325 mg daily; $0.01).

Of Note:
CDEC noted that because patients with a $CHADS_2$ score of less than 2 were excluded from the ROCKET-AF trial, there was no evidence from this trial related to the use of rivaroxaban in patients with a $CHADS_2$ score of 1 or less.

Background:
This rivaroxaban submission is for the 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 recommended in the product monograph 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:
In April 2012, CDEC recommended 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
- have a $CHADS_2$ score of ≥ 2.

As part of a Canadian Agency for Drugs and Technologies in Health (CADTH) Therapeutic Review *(Antithrombotic Therapy for Patients with Atrial Fibrillation)*, CDEC issued recommendations to address the optimal use of antithrombotic therapy for patients with atrial fibrillation. These recommendations stated that new oral anticoagulants should be considered for the prevention of stroke for patients with non-valvular atrial fibrillation and patients who have a $CHADS_2$ score ≥ 1 and are unable to readily achieve adequate anticoagulation with warfarin.

The Common Drug Review (CDR) participating drug plans submitted a request for advice to ask CDEC for additional clarity on the following: Should the CDR recommendation for rivaroxaban be updated to align with the recommendations from the Therapeutic Review of *Antithrombotic Therapy for Patients with Atrial Fibrillation*?

Summary of CDEC Considerations:
CDEC considered the following information from the 2011 CDR review of rivaroxaban:

- a systematic review of RCTs
- a critique of the manufacturer's pharmacoeconomic evaluation
- patient group-submitted information about outcomes and issues important to patients.

CDEC considered the following to address the request for advice:

- Materials included in the CDEC brief for the 2012 CDR review of rivaroxaban.
- The 2012 CDEC recommendation for rivaroxaban (April 19, 2012).
- The 2012 CDEC recommendations from the Therapeutic Review of *Antithrombotic Therapy for Patients with Atrial Fibrillation*.
- The CDR Request for Advice Brief, which included an updated literature search from the Therapeutic Review.

Patient Input Information:
The following is a summary of information provided by two patient groups who responded to the CDR call for patient input in the 2012 CDR review of rivaroxaban.

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
- inconvenience of international normalized ratio (INR) monitoring with warfarin treatment
- additional vigilance often required of patients because of concerns related to potential drug, food, and alcohol interactions with warfarin

- challenges of restabilizing warfarin dosing in cases of temporary interruptions in therapy
- burden to the caregiver related to supporting the patient's monitoring appointments.

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.

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 71 years old on average and most (60%) were male. Patients' risk of stroke was assessed through the $CHADS_2$ score, named for the five risk factors assessed: congestive heart failure, hypertension, age, diabetes, and previous stroke or transient ischemic attack. A $CHADS_2$ score of 2 or greater was required for entry to the ROCKET-AF study. A $CHADS_2$ score of 3 was the most common $CHADS_2$ score at baseline (44% of patients), followed by a $CHADS_2$ score of 4 (29% of patients).

Approximately 85% of randomized patients completed the study, with no difference between-treatment groups. The median follow-up time was 707 days (approximately 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 (time spent in therapeutic range [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, CDEC 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 point consisting of stroke or non-central nervous system 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-central nervous system 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 one of the following:

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

Results

Efficacy

- 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 population. The superiority of rivaroxaban compared with warfarin was not demonstrated in the intention to treat population.
- A subgroup analysis of primary outcome events by baseline age suggested that patients older than 75 years taking rivaroxaban were less likely than patents taking warfarin 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 patients taking rivaroxaban than those taking warfarin 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).

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 patients taking rivaroxaban than warfarin (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 who had a moderate to high risk of stroke ($CHADS_2 \geq 2$). 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, the daily cost of rivaroxaban (15 mg or 20 mg daily; $2.84) is less than the daily cost of dabigatran (110 mg or 150 mg twice daily; $3.20) and apixaban (2.5 mg or 5 mg twice daily; $3.20), but is greater than the cost of warfarin (2 mg to 10 mg daily; $0.07) and ASA (80 mg to 325 mg daily; $0.01).

Other Discussion Points:
CDEC noted the following:

- 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). CDEC 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 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.
- CDEC 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. CDEC considered that occasional non-adherence with rivaroxaban may pose a greater stroke risk to patients than occasional non-adherence with warfarin. CDEC further noted that INR monitoring of warfarin-treated patients facilitates identification of non-adherence.
- There is no reversal agent for rivaroxaban. CDEC 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.
- CDEC 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.
- As part of a CADTH Therapeutic Review *(Antithrombotic Therapy for Patients with Atrial Fibrillation)*, CDEC also recommended that consideration be given to patient-specific clinical factors in selecting a new oral anticoagulant for an individual patient. The lack of trial evidence in the ROCKET-AF study for use of rivaroxaban for individuals with a $CHADS_2$ score of less than 2 is considered to be of clinical significance in this regard.

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.

June 19, 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/has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer.