FINAL CDEC RECOMMENDATION

APIXABAN
(Eliquis — Bristol-Myers Squibb Canada and Pfizer Canada Inc.)
New Indication: Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation

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

Clinical Criteria:
1. Patients with a CHADS$_2$ score ≥ 1.
2. Patients who are unable to readily achieve adequate anticoagulation with warfarin.

Reasons for the Recommendation:
1. The results of two double-blind randomized controlled trials (RCTs) suggest that apixaban is superior to warfarin and acetylsalicylic acid (ASA) for preventing SSE in patients with AF who have a moderate or high risk of stroke (CHADS$_2$ score ≥ 1).
2. At recommended doses, the daily cost of apixaban (2.5 mg or 5 mg twice daily; $3.20) is equal to the cost of dabigatran (110 mg or 150 mg twice daily; $3.20), but is greater than the cost of warfarin (2 mg to 10 mg daily; $0.07), ASA (80 mg to 325 mg daily; $0.01), and rivaroxaban (15 mg or 20 mg daily; $2.84).

Background:
This submission for apixaban is for the new Health Canada indication of prevention of SSE in patients with AF. Apixaban is available as 2.5 mg and 5 mg tablets and the recommended dose is 5 mg taken orally twice daily. In patients fulfilling at least two of the following characteristics, a reduced dose of 2.5 mg twice daily is recommended: age 80 years or older, body weight of 60 kg or less, or serum creatinine level of 133 micromole/L or greater. These patients are considered to be at a higher risk of bleeding.
Submission History:
Apixaban was previously reviewed by CDEC for the prevention of venous thromboembolic events in patients who have undergone elective knee or hip replacement surgery, for treatment durations of 10 to 14 days, and 32 to 38 days, respectively, and it received a recommendation to “list” (see Notice of CDEC Final Recommendation, June 14, 2012).

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of apixaban, a critique of the manufacturer’s pharmacoeconomic evaluation, and a patient group submission regarding important outcomes and issues for patients. Additionally, the Committee reviewed the Canadian Agency for Drugs and Technologies in Health (CADTH) Therapeutic Review Report (Antithrombotic Agents for the Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation).

Patient Input Information
The following is a summary of key information provided by one patient group that responded to the CDR Call for Patient Input:
- Hospitalization is a very common consequence of AF and accounts for a high proportion of morbidity and costs related to this rhythm disorder.
- The ongoing monitoring of patients on anticoagulant therapy and hospitalization places a significant cost on the Canadian health care system.

Clinical Trials
The systematic review included the following two double-blind, manufacturer-sponsored, active-controlled RCTs:
- ARISTOTLE (N = 18,201) was a non-inferiority and superiority trial comparing apixaban 5 mg twice daily or warfarin titrated to an international normalized ratio (INR) of 2 to 3 in patients with AF. Apixaban was provided at a dose of 2.5 mg twice daily for a subset of patients considered to be at a higher risk of bleeding (i.e., those with two or more of the following criteria: aged 80 years or older, body weight 60 kg or less, or a serum creatinine level of 133 micromole/L per liter or greater). Patients were treated for a median of 89 weeks with apixaban and 88 weeks with warfarin.
- AVERROES (N = 5,598) was a superiority trial comparing apixaban 5 mg twice daily with ASA in patients with AF who are ineligible for vitamin K antagonist (VKA) therapy. Patients were treated for a median of 60 weeks with apixaban and 59 weeks with ASA. The data and safety monitoring board recommended early termination of the trial because of a clear benefit in favour of apixaban.

The mean CHADS2 scores were similar between studies (2.1 in ARISTOTLE and 2.0 in AVERROES). Both trials excluded patients with a CHADS2 score of 0; therefore, results may not be generalizable to a population with a low risk of stroke.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: all-cause mortality, cardiovascular mortality, stroke, systemic embolism, major bleeding, serious adverse events, withdrawals due to adverse events, and total adverse events.
The primary efficacy outcome of each study was the incidence of SSE, while the primary safety outcome was the incidence of major bleeding. ARISTOTLE employed a non-inferiority design for the primary efficacy end point (SSE), with a pre-specified non-inferiority margin of a hazard ratio (HR) < 1.38 based on the upper bound of the two-sided 95% confidence interval (CI).

Results

Efficacy

- In ARISTOTLE, there was a statistically significantly lower incidence of SSE in patients treated with apixaban compared to patients treated with warfarin (2.3% versus 2.9%). The HR for apixaban versus warfarin was 0.79 (95% CI, 0.66 to 0.95) achieving the pre-specified criteria for non-inferiority and superiority.
- In AVERROES, there was a statistically significantly lower incidence of SSE in patients treated with apixaban compared to patients treated with ASA (1.8% versus 4.1%). The HR for apixaban versus ASA was 0.45 (95% CI, 0.32 to 0.62) achieving the pre-specified superiority criteria.
- The risk of death from any cause was statistically significantly lower with apixaban compared with warfarin in ARISTOTLE (HR [95% CI], 0.89 [0.80 to 0.998]). The risk of death from any cause was also lower with apixaban compared with ASA in AVERROES (HR [95% CI], 0.79 [0.62 to 1.01]); however, the difference did not reach statistical significance.
- There was no significant difference in the incidence of cardiovascular deaths between treatment groups in either ARISTOTLE or AVERROES.
- Subgroup analyses of the ARISTOTLE data suggested that apixaban may be superior to warfarin in preventing SSE in patients with poor INR control, in patients who are > 65 years of age, and in patients with a high risk of stroke (CHADS² score ≥ 3).
- Subgroup analyses of the AVERROES data suggested that apixaban may be superior to ASA irrespective of prior VKA therapy and history of stroke or transient ischemic attack (TIA). Superiority was also demonstrated in the following subgroups: patients younger than 65 years old; patients at least 75 years or older, and patients with a CHADS² score of 2 or greater.

Harms (Safety and Tolerability)

- The risk of major bleeding was statistically significantly lower with apixaban compared to warfarin in ARISTOTLE (3.6% versus 5.1%). The HR for apixaban versus warfarin was 0.69 (95% CI, 0.60 to 0.80).
- The risk of major bleeding was numerically higher for apixaban compared with ASA in AVERROES (1.6% versus 1.0%). The HR for apixaban versus ASA was 1.54 (95% CI, 0.97 to 2.45); however, statistical significance was not reached.
- Fewer apixaban-treated patients experienced a serious adverse event compared with warfarin-treated patients in ARISTOTLE (35.0% versus 36.5%) and compared with ASA-treated patients in AVERROES (23.5% versus 28.9%). Aside from bleeding, there were no other notable safety issues noted in the trials.
- The proportion of patients with at least one adverse event was slightly lower with apixaban compared with warfarin in ARISTOTLE (81.5% versus 83.1%) and compared with ASA in AVERROES (65.5% versus 69.2%).
Withdrawals due to adverse events were less common with apixaban than warfarin (7.6% versus 8.4%) and ASA (9.5% versus 13.0%).

**Cost and Cost-Effectiveness**

The manufacturer conducted a cost-utility analysis to assess apixaban during a 20-year time horizon, in two population cohorts: individuals who are suitable for VKA (VKA suitable) — warfarin as a comparator and individuals who have demonstrated and/or are expected to be unsuitable for VKA (VKA unsuitable) — rivaroxaban and dabigatran (new oral anticoagulants [NOACs]) as a comparator. In the Markov model, patients could experience the following events: non-valvular AF alone; systemic embolism; ischemic stroke; bleeding events comprised of intracranial hemorrhage, hemorrhagic stroke, major bleeds, clinically relevant non-major (CRNM) bleeds; or myocardial infarction. Recurrent stroke could also occur in those patients who experienced stroke. Patients who experienced a clinical event had associated costs of medical management, as well as a decrement in quality of life. Clinical inputs were based on data from AVERROES (apixaban versus ASA) and ARISTOTLE (apixaban versus warfarin) for the VKA unsuitable and suitable populations, respectively. For the comparison of apixaban with other antithrombotic agents, including other NOACs, event rates for the comparators were based on a systematic review and network meta-analysis carried out by the manufacturer (ROCKET-AF for rivaroxaban versus warfarin; RE-LY for dabigatran versus warfarin). The manufacturer reported that in the VKA suitable population, apixaban when compared with warfarin was $13,695 per quality-adjusted life-year (QALY) gained. In the VKA unsuitable group, apixaban was $2,986 per QALY compared with ASA. The incremental cost-effectiveness ratios (ICERs) for apixaban versus other NOACs (dabigatran and rivaroxaban) ranged from $551 to $10,177 per QALY.

A number of limitations were noted with the economic submission:

- CDR re-analysis was limited due to constraints placed on the model supplied by the manufacturer, which limited the re-analyses that could be conducted.
- The manufacturer submitted an unpublished indirect comparison and network meta-analysis of apixaban versus other NOACs. The results showed that apixaban had greater efficacy in other major bleed, CRNM bleeds, and intracranial hemorrhage when compared with other NOACs. However, given the small risk reductions and overlapping credible intervals, definitive conclusions on cost-effectiveness could not be made.

The incremental cost-utility ratio (ICUR) for apixaban compared with warfarin is likely to be < $40,000 per QALY gained. Given uncertainty associated with the true differences in benefits and harms among NOACs, the relative cost-effectiveness of apixaban compared with other NOACs is unclear.

Apixaban has a daily cost of $3.20 (2.5 mg or 5 mg twice daily) compared with warfarin $0.07 (2 mg to 10 mg daily); ASA $0.01 (80 mg to 325 mg daily); dabigatran $3.20 (110 mg or 150 mg twice daily); rivaroxaban $2.84 (15 mg or 20 mg daily).

**Other Discussion Points:**

The Committee noted the following:

- The manufacturer requested listing for the prevention of thromboembolic events in at-risk patients with non-valvular AF (i.e., as a first-line option for patients aged ≥ 65 years or with
the two additional risk factors of being female and having vascular disease, or for all patients with a CHADS$_2$ score $\geq 1$).

- In ARISTOTLE, apixaban demonstrated superiority compared with warfarin for both the primary efficacy end point (SSE) and primary safety end point (major bleeding) due to a reduction in bleeding risk: superiority for the primary efficacy outcome was mainly driven by a reduction in hemorrhagic stroke, while superiority for the primary safety outcome was mostly driven by a reduction in intracranial hemorrhage.
- In AVERROES, the observation of fewer ischemic strokes appeared to drive the statistical significance of the primary efficacy end point.
- Although not specifically stated in the patient group input submission, the Committee noted that patients with AF may have a preference for a therapy that does not require INR monitoring.
- There is currently no reliable reversal agent for apixaban.
- Patients with an estimated creatinine clearance level of less than 25 mL/min were excluded from the ARISTOTLE and AVERROES trials; therefore, there is no information regarding the safety and efficacy of apixaban in this patient population.

Research Gaps:
The Committee noted that there is an absence of evidence regarding the following:
- There were no direct comparisons of apixaban against other NOACs.
- There is uncertainty regarding patient compliance with twice daily dosing of drugs for AF.

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.

February 20, 2013 Meeting

Regrets:
Two CDEC members did not attend the meeting.

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 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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