CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

Edoxaban
(Lixiana — SERVIER Canada Inc.)
Indication: Prevention of Stroke and Systemic Embolic Events in Patients With Nonvalvular Atrial Fibrillation

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends edoxaban be reimbursed for the prevention of stroke and systemic embolic events (SEE) in nonvalvular atrial fibrillation if the following conditions and criteria are met:

Clinical Criterion:
List in a manner similar to other direct oral anticoagulants (DOACs) reimbursed for nonvalvular atrial fibrillation.

Condition:
- The drug plan cost of treatment with the drug under review should not exceed the drug plan cost of treatment with the least costly alternative DOAC.

Reasons for the Recommendation:
1. In one phase III, non-inferiority, double-blind, randomized, active-controlled, parallel-group trial (ENGAGE AF-TIMI 48), edoxaban was shown to be noninferior to warfarin for prevention of SEEs, with a lower rate of SEEs compared with warfarin (hazard ratio [HR] = 0.79 [95% CI, 0.63 to 0.99]). Subgroup analyses related to baseline characteristics (age, gender, race, bodyweight, creatinine clearance, $CHADS_2$ score, dose reduction, prior vitamin K antagonist status, and various comorbidities) were consistent with the primary results, although these analyses fell outside the chain of hierarchical statistical analysis.
2. In ENGAGE AF-TIMI 48, the incidence of major bleeding was lower with edoxaban than warfarin (418 patients, 2.75% versus 524 patients, 3.43%; HR = 0.80 [95% CI, 0.71 to 0.91]). Fatal bleeding and hemorrhagic stroke occurred less frequently with edoxaban than warfarin, but gastrointestinal bleeding occurred more frequently. In all harms comparisons, the absolute numerical difference between groups was small.

3. The CADTH Common Drug Review (CDR) analysis of the submitted economic model found that edoxaban was cost-effective compared with warfarin (incremental cost per quality-adjusted life-year $12,672). However, a probabilistic analysis incorporating other available DOACs demonstrated that edoxaban had a low probability of being the most cost-effective strategy at the submitted price. CDEC considered that there was no justification for a price premium for edoxaban based on the information provided by the manufacturer.

Other Discussion Points:

- CDEC noted that Canadian clinical practice guidelines currently recommend DOACs over warfarin for most patients with atrial fibrillation. CDEC discussed this in the context of the current reimbursement criteria in Canada and the evaluation of the included clinical evidence and cost-utility analysis submitted by the manufacturer.
- In ENGAGE AF-TIMI-48, patients were enrolled if they had a $CHADS_2$ score ≥ 2, which is a higher risk group than those recommended for anticoagulation with DOACs in clinical practice guidelines and previous CDEC recommendations for reimbursement with other DOACs. However, CDEC noted there was no rationale to provide a more restrictive reimbursement recommendation for edoxaban than other DOACs based on stroke risk scoring.

Background:

Edoxaban has two Health Canada indications. One of the indications is for the prevention of stroke and SEEs in patients with nonvalvular atrial fibrillation in whom anticoagulation is an appropriate treatment. The second indication is for the treatment of venous thromboembolism (deep vein thrombosis [DVT] and pulmonary embolism [PE]) and the prevention of recurrent DVT and PE. The recommended dose of edoxaban for the prevention of stroke and SEEs in patients with nonvalvular atrial fibrillation is 60 mg once daily. Edoxaban 30 mg once daily is recommended in patients with one or more of the following clinical factors: moderate renal impairment (creatinine clearance 30 mL/min to 50 mL/min); low body weight ≤ 60 kg; or concomitant use of P-glycoprotein inhibitors, except amiodarone and verapamil.

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of randomized controlled trials (RCTs) of edoxaban and a critique of the manufacturer's pharmacoeconomic evaluation. No patient input was received for this submission.

Clinical Trials

The systematic review included one RCT of patients with nonvalvular atrial fibrillation. ENGAGE AF-TIMI 48 (N = 21,105) evaluated the non-inferiority (NI) of edoxaban to warfarin in patients with atrial fibrillation. Patients in the ENGAGE AF-TIMI 48 study were randomized to warfarin, edoxaban 60 mg once daily, or edoxaban 30 mg once daily. Patients randomized to the warfarin group received dose-adjusted warfarin to maintain a monthly measured international normalized ratio (INR) at 2.0 to 3.0. Patients randomized to edoxaban 60 mg or 30 mg groups received the allocated dose unless one of the following criteria was present, in which case the edoxaban dose was halved: creatinine clearance of 30 mL to 50 mL per minute, body weight of 60 kg or less, or verapamil or quinidine use. All patients received two medications — the active allocated

drug, and a matched placebo for the non-allocated drug. To maintain blinding, sham INR values were generated to patients who were randomized to edoxaban. The intended duration depended on collecting a total of 672 events of the primary outcome; the end-result median duration of treatment was 2.5 years. Upon the completion of the study, patients went through a transition period to an anticoagulant chosen by the treating physician. The primary efficacy outcome was a composite of stroke and SEE (time to first adjudicated ischemic or hemorrhagic stroke, or SEE).

NI would be demonstrated if the upper boundary of the one-sided 97.5% CI of edoxaban compared with warfarin was below the NI margin of 1.38 for the HR. If NI was achieved, the primary outcome of stroke/SEE was then tested at an alpha of 0.01 for superiority; if superiority was achieved, the secondary outcome of stroke/SEE/ CV mortality was tested for superiority at an alpha of 0.01; if superiority was achieved, the secondary outcome of major adverse cardiovascular events, which includes myocardial infarction, stroke, SEE, or CV mortality was tested for superiority at an alpha of 0.01; and if superiority was achieved, the secondary outcome of stroke/SEE/ all-cause mortality was tested for superiority.

Outcomes

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

- composite of stroke and SEE
- ischemic stroke
- hemorrhagic stroke
- systemic thromboembolic event
- major bleeding.

Efficacy

- Edoxaban was shown to be noninferior, but not superior, to warfarin for the primary efficacy outcome of stroke and SEE. The use of 60 mg edoxaban was associated with the following HRs compared with warfarin:
  - Modified, on-treatment period, intention-to-treat population: 0.79 (97.5% CI, 0.63 to 0.99).
  - Overall study period, intention-to-treat population: 0.87 (97.5% CI, 0.73 to 1.04).
- During the treatment period, the proportion of patients (modified intention to treat) who experienced individual events classified as stroke were as follows (60 mg edoxaban versus warfarin):
  - ischemic stroke: 0.87% versus 0.93%
  - hemorrhagic stroke: 0.26% versus 0.49%
  - fatal stroke: 0.29% versus 0.28%
  - disabling stroke: 0.23% versus 0.26%
  - SEE: 0.05% versus 0.08%.

Harms (Safety and Tolerability)

- The safety outcome, major bleeding, was presented in the ENGAGE AF-TIMI 48 study as a pre-specified primary safety outcome. The incidence of major bleeding (modified

International Society on Thrombosis and Haemostasis criteria) was lower with edoxaban 60 mg versus warfarin in (418 patients, 2.75% versus 524 patients, 3.43%; HR = 0.80 [95% CI, 0.71 to 0.91]). The incidences of major bleeding designated as fatal bleeding or hemorrhagic stroke were lower with edoxaban 60 mg versus warfarin, while there were more patients with gastrointestinal hemorrhage in the edoxaban 60 mg group than in the warfarin group.

The incidence of non-bleeding adverse events was similar between edoxaban 60 mg and warfarin groups. Approximately one-third of the patients in the ENGAGE AF-TIMI 48 trial experienced a non-bleeding serious adverse event (SAE). Numerically, 2,315 patients (33.0%) experienced non-bleeding SAEs in the edoxaban 60 mg group, and 2,516 patients (35.9%) experience non-bleeding SAEs in the warfarin group. The number of patients who discontinued the allocated treatment due to adverse events was similar in the edoxaban 60 mg group and in the warfarin group. Overall, there were fewer deaths in the edoxaban 60 mg group (769 patients, 11.0%) than in the warfarin group (836 patients, 11.9%). In both groups, the bulk of the deaths were driven by cardiovascular causes (7.5% in the edoxaban 60 mg groups, and 8.7% in the warfarin group).

Cost and Cost-Effectiveness

Edoxaban (Lixiana) is available as a 30 mg and 60 mg tablet at a submitted price of $2.84, regardless of dosage strength. At a recommended dose of 60 mg once daily, with the potential for dose reduction to 30 mg once daily if required, the daily cost of treatment is $2.84.

The manufacturer submitted a cost-utility analysis based on a Markov model, compared with a lifetime horizon, from the perspective of the publicly funded health care system. Analyses were conducted comparing edoxaban with warfarin (5 mg once daily) and rivaroxaban (60 mg once daily). For the comparison with warfarin, data from the ENGAGE AF-TIMI 48 trial were used; while for the comparison with rivaroxaban, data from a manufacturer-submitted network meta-analysis (NMA) were used. Analyses comparing edoxaban with dabigatran (110 mg twice daily and 150 mg twice daily) and apixaban (5 mg twice daily) are included as sensitivity analyses, with the necessary clinical data obtained from the manufacturer-submitted NMA. The rationale for excluding these comparators from the primary analysis was two-fold: limited comparability of the ENGAGE AF-TIMI 48 trial of edoxaban and the pivotal trials for dabigatran and apixaban; as well as rivaroxaban being the most commonly used DOAC in Canada. According to the manufacturer's base-case analysis, treatment with edoxaban was more effective (quality-adjusted life-year [QALY] gain of 0.1517) and more costly ($1,922) than warfarin leading to an incremental cost per QALY gained of $12,672. Edoxaban was dominant compared with rivaroxaban (i.e., it was less costly and more effective).

No major limitations with respect to the model, assumptions, and data inputs were found. Limitations relate to the context of the decision problem:

- Given the patient population from the ENGAGE AF-TIMI trial, analysis is only relevant to AF patients with $CHADS_2 \geq 2$; whereas edoxaban may be used in patients with $CHADS_2 = 1$.

- The submitted analysis highlights only the comparisons of edoxaban with warfarin and rivaroxaban. Given current funding of DOACs, comparisons with apixaban and dabigatran are also relevant and should have been given equal prominence.

CDR reanalysis incorporating all relevant comparators (warfarin, other DOACs) found, for patients with nonvalvular atrial fibrillation ($CHADS_2 \geq 2$) requiring anticoagulation, apixaban was the most cost-effective DOAC and all other new oral anticoagulant (NOACs) (including edoxaban) were dominated (i.e., less effective and more costly). Apixaban remained cost-effective compared with edoxaban (at a willingness-to-pay threshold of $50,000) unless the price of edoxaban was reduced by at least 33%. It was noted that the relative cost-effectiveness of edoxaban versus apixaban and dabigatran is somewhat uncertain due to limitations of the clinical data.

Patient Input Information
No patient input was received for this submission.

CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

February 15, 2017 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 not requested the removal of confidential information.

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.

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