CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

EDOXABAN
(Lixiana – SERVIER Canada Inc.)
Indication: Venous Thromboembolic Events

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that edoxaban be reimbursed for the treatment of venous thromboembolism (VTE) (deep vein thrombosis [DVT], pulmonary embolism [PE]) and the prevention of recurrent DVT and PE, if the following condition is met:

Condition:
- Substantial reduction in price.

Reasons for the Recommendation:
1. One double-blind, double-dummy, non-inferiority, randomized controlled trial (RCT) (Hokusai-VTE; N = 8,292) demonstrated that edoxaban (60 mg once daily, or dose-adjusted edoxaban 30 mg once daily) was non-inferior to warfarin for the primary outcome of symptomatic recurrent VTE during the 12-month study period (3.2% versus 3.5% in the edoxaban and warfarin groups, respectively; hazard ratio [HR] 0.89; 95% confidence interval [CI], 0.703 to 1.128; pre-specified non-inferiority margin 1.5).
2. In the same trial, edoxaban was statistically superior to warfarin for the primary safety outcome of clinically relevant bleeding (8.5% versus 10.3% in the edoxaban and warfarin groups respectively, HR 0.81; 95% CI 0.705 to 0.936; p = 0.004).
3. Based on the submitted economic model and network meta-analysis (NMA), the manufacturer reported that edoxaban was not cost-effective when compared with warfarin, with an incremental cost per quality-adjusted life year (QALY) of $94,352. Edoxaban was dominated by rivaroxaban and apixaban (edoxaban was associated with fewer QALYs and was more costly). Based on a probabilistic analysis of the economic model, among available DOACs indicated for the treatment and prevention of VTE, CDR estimated that edoxaban had a 0% probability of being the most cost-effective strategy at thresholds of up to $100,000 per QALY. As edoxaban is less effective than apixaban, a substantial price reduction would be required for the incremental cost-effectiveness of apixaban relative to edoxaban to exceed $50,000 per QALY.

Of Note:

- CDEC noted that edoxaban is the fourth DOAC available for the treatment and prevention of VTE and, in contrast to apixaban and rivaroxaban, edoxaban requires initial bridging with low molecular weight heparin.
- CDEC noted that at a price reduction of at least 80%, edoxaban, compared to apixaban, represents both a net loss of health and a corresponding decrease in costs.

Discussion Points:

- CDEC recognized that there were no head-to-head trials comparing edoxaban with other Direct Oral Anticoagulants (DOACs) for the treatment and prevention of VTE. Two manufacturer-submitted NMAs and five NMAs identified by CDR suggested that there were no statistically significant efficacy differences between edoxaban and other DOACs (apixaban, dabigatran, and rivaroxaban) in treating and preventing recurrent VTE. In six out of the seven NMAs it was suggested that edoxaban was associated with statistically significantly more major bleeding than apixaban, and statistically significantly more major and clinically relevant non-major bleeding than apixaban and dabigatran. However, the small number of studies available, the relative rarity of the events that were analyzed, and the high level of heterogeneity among studies (including blinding and variation in the duration of treatment across the studies) result in uncertainty in interpreting the comparative safety and efficacy of edoxaban to other DOACs.

Background:

Edoxaban has two Health Canada-approved indications: treatment of VTE (DVT and PE) and the prevention of recurrent DVT and PE; and for the prevention of stroke and systemic embolic events in patients with atrial fibrillation, in whom anticoagulation therapy is appropriate. The recommended dose of edoxaban for the treatment of VTE and prevention of recurrent DVT and PE is 60 mg once daily following the initial use of a parenteral anticoagulant for five to ten days. Edoxaban 30 mg once daily is recommended in patients with one or more of the following clinical factors: a) Moderate renal impairment (creatinine clearance (CrCL) 30- 50 mL/min; b) Low body weight ≤ 60 kg, and c) Concomitant use of P-glycoprotein (P-gp) inhibitors except amiodarone and verapamil. Duration of therapy should be individualized after careful assessment of the treatment benefit against the individual risk of bleeding. Patients with transient risk factors (e.g., surgery, trauma, immobilisation) should receive treatment for at least three months, while extended duration therapy is recommended for patients with permanent risk factors or idiopathic DVT or PE.

Summary of CDEC Considerations

CDEC considered the following information prepared by CDR: a systematic review of RCTs and pivotal studies, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to individuals with VTE.

Patient Input Information

No patient input was received from any patient group for this submission. The key information provided from one patient group presented below was adapted from the patient input received October 2014, for the CDR review of apixaban (Eliquis) for the treatment of VTE (DVT, PE) and prevention of recurrent DVT and PE.

- Patients reported that their day-to-day lives have been affected, mostly due to the requirement of having to take medications at specific times or multiple times during the day.

- Although the majority of patients have indicated that their ability to perform activities has not changed, some reported that they are limited in some activities they had done previously, such as exercise or lifting items. A small number reported an inability to return to work.
- The condition also has an impact on caregivers. Some indicated that they faced no additional challenges, while others reported new challenges, including feeling more overwhelmed, busy, anxious, or stressed, and needing to take time off work.

Clinical Trials

The CDR systematic review included one RCT. Hokusai-VTE (N=8,292) evaluated the non-inferiority (NI) of edoxaban to warfarin in patients with documented acute symptomatic DVT and/or PE. All patients received initial therapy with open-label unfractionated heparin or enoxaparin for at least 5 days. Edoxaban or warfarin was administered in a double-blind, double-dummy fashion. Edoxaban (or placebo) was started after discontinuation of initial heparin in the edoxaban treatment group. Edoxaban was administered at a dose of 60 mg orally once daily (QD), or at a dose of 30 mg QD in patients with a creatinine clearance (CrCL) between 30 to 50 ml/minute, a body weight of 60 kg or less, or in patients who were receiving concomitant treatment with potent P-gp inhibitors. Warfarin (or placebo) was started at the same time as heparin. The intended treatment duration for edoxaban or warfarin of 3, 6, and 12 months were determined by the investigator. The primary efficacy outcome was symptomatic recurrent VTE during the 12-month study period. Non-inferiority was demonstrated if the upper bound of the corresponding 95% CI was below the NI margin of 1.5 for the HR. If NI was demonstrated, then superiority for the secondary efficacy endpoint of the composite of symptomatic recurrent VTE and all-cause mortality during the 12-month study period was tested. The primary safety outcome was clinically relevant bleeding.

Outcomes

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

- Symptomatic recurrent VTE — defined as the adjudicated composite endpoint of DVT, non-fatal PE, and fatal PE during the 12-month study period. The events that were counted in this analysis were those events that occurred from the date of randomization through the end of the 12-month study period, regardless of whether the patient was taking the study drug.
- Symptomatic recurrent VTE and all-cause mortality — defined as the adjudicated composite clinical outcome of non-fatal symptomatic recurrent PE, symptomatic recurrent DVT, and all-cause mortality during the 12-month study period. The events that were counted in this analysis were those events that occurred from the date of randomization through the end of the 12-month study period, regardless of whether the patient was taking the study drug.
- Major bleeding — defined as overt bleeding associated with a fall in the hemoglobin level of 2 g/dL or more; or transfusion of 2 or more units of packed red blood cells or whole blood; or bleeding at a critical site, including intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal; or contributing to death.
- Clinically relevant bleeding — defined as major bleeding or clinically relevant non-major bleeding which occurred when a patient was receiving treatment or within three days after interrupting or stopping the study drug.
- Serious adverse events (SAE), total adverse events, withdrawals due to adverse events, and notable harms.

Efficacy
Edoxaban was shown to be non-inferior, but not superior, to warfarin for the primary efficacy outcome of symptomatic recurrent VTE during the 12-month study period. Treatment with edoxaban was associated with the following HRs compared with warfarin:

- Modified intention-to-treat population: 0.89 (95% CI, 0.703 to 1.128);
- Per-protocol population: 0.87 (95% CI 0.688 to 1.107)

The proportion of patients who experienced individual events classified as DVT only, non-fatal PE, fatal PE, and unexplained death (and VTE cannot be ruled out) were as follows (edoxaban versus warfarin):

- DVT only: 1.4% versus 1.5%
- Non-fatal PE: 1.2% versus 1.4%
- Fatal PE: <0.1% versus <0.1%
- Unexplained Death (and VTE cannot be ruled out): 0.5% versus 0.5%.

The secondary efficacy endpoint (the composite endpoint of recurrent VTE and all-cause mortality) occurred in 228 patients (5.5%) in the edoxaban group and in 228 patients (5.5%) in the warfarin group (HR: 1.00; 95% CI: 0.832, 1.200, p=0.9933), indicating that superiority was not established.

The proportion of patients requiring hospitalization due to AEs during the on-treatment period was slightly lower in the edoxaban treatment group compared to warfarin treatment group ([redacted]). The duration of hospital stay due to recurrent VTE and due to bleeding was approximately two days shorter on average for patients in the edoxaban treatment group than warfarin treatment group. However, no statistical analysis was reported.

Harms (Safety and Tolerability)
Results from the Hokusai-VTE study demonstrated the superiority of edoxaban over warfarin for the primary safety outcome of clinically relevant bleeding (HR: 0.81; 95% CI: 0.705, 0.936; p = 0.004 for superiority). The statistical significance of this composite outcome was mainly driven by the reduction of CRNM bleeding (298 patients [7.2%] in the edoxaban treatment group vs. 368 patients [8.9%] in the warfarin treatment group). Edoxaban also had numerically fewer major bleeds than warfarin (56 [1.4%] vs. 66 [1.6%]). Notable bleeding events included fatal bleeding (3 [0.1%] patients with edoxaban versus 10 [0.2%] patients with warfarin), intracranial bleeding (5 [0.1%] patients versus 18 [0.4%] patients, respectively), and GI bleeding (27 [0.7%] patients versus 18 [0.4%] patients, respectively).

At least one SAE was reported for 12.2% of patients in the edoxaban group and 13.2% of patients in the warfarin group. The most common SAE in the edoxaban treatment group was pneumonia (0.7% and 0.4%, edoxaban versus warfarin, respectively). The most common SAE in the warfarin group was increased INR (<0.1% and 1.9%, edoxaban versus warfarin, respectively). At least one adverse event was reported for 68.5% and 71% of patients in the edoxaban and in the warfarin treatment groups, respectively. Withdrawals due to adverse events were reported for 4.7% and 4.5% of patients in the edoxaban and in the warfarin treatment groups, respectively.

Cost and Cost-Effectiveness

Edoxaban is available as a 60 mg tablet at a submitted price of $2.84. At a recommended dose of 60 mg once daily, the daily cost of treatment is $2.84.

The manufacturer submitted a cost utility analysis based on a Markov model, over a lifetime horizon, from the perspective of the publicly funded health care system. Five comparators were considered within the model: edoxaban, warfarin (5 mg once daily), rivaroxaban (60 mg once daily), dabigatran (150 mg twice daily) and apixaban (5 mg twice daily). For the comparison with warfarin, data from the Hokusai-VTE trial were used. Further comparison with warfarin, rivaroxaban, apixaban and dabigatran was conducted through an NMA provided by the manufacturer. According to the manufacturer's base case analyses, for the analysis based on the Hokusai–VTE study, edoxaban was associated with greater QALYs (12.149 versus 12.068) and greater costs ($16,702 versus $14,440) than warfarin, leading to an incremental cost per QALY of $27,924. Pairwise cost effectiveness comparisons based on the NMA found edoxaban unlikely to be cost effective compared to warfarin with a much higher incremental cost per QALY of $94,352; dabigatran was more effective than edoxaban with an incremental cost per QALY of $69,284. Edoxaban was dominated by both rivaroxaban and apixaban (i.e., less effective and more costly).

CDR identified several limitations with the manufacturer's economic evaluation:

- A sequential analysis comprising all comparators simultaneously was not reported; rather edoxaban was compared to warfarin and other DOACs in a pairwise manner.
- CDR clinical reviewers concluded there was considerable uncertainty regarding the comparative efficacy and safety results reported in the manufacturer's NMA due to the small number of available trials, heterogeneity across trials, and rarity of some events.
- There were a number of instances where the uncertainty around transition probabilities and utilities were inappropriately specified.
- Stratified analysis could not be conducted based on index VTE, i.e., DVT only versus PE.
- The manufacturer assumed recurrent VTE is a single state without distinguishing between fatal PE, non-fatal PE and DVT, despite the different consequences of each event.

Based on the preferred approach of incorporating all comparators in a sequential analysis using the results of the NMA, CDR found that apixaban is the optimal strategy (incremental cost per QALY vs. warfarin of $21,358). Edoxaban is not cost effective compared to warfarin with an incremental cost per QALY of $94,352, and is dominated by rivaroxaban and apixaban (i.e., more costly and less effective). In probabilistic analyses, apixaban has a 91.7% of being the optimal strategy at a threshold of $50,000 per QALY gained, while edoxaban has a probability of 0% for thresholds between $0 and $100,000 per QALY gained. As edoxaban was associated with fewer QALYs compared with apixaban, a price reduction of at least 80% for edoxaban would be required so that the added benefit from apixaban would not be considered cost effective as the incremental cost would be too high at a cost-effectiveness threshold of $50,000 per QALY.

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.

Regrets:

February 15, 2017 Meeting: None
May 17, 2017 Meeting: None

Conflicts of Interest: None

About This Document:

CDEC provides formulary reimbursement 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 requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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