Common Drug Review
Pharmacoeconomic Review Report

June 2017

Drug	Edoxaban (Lixiana)
Indication	Treatment of venous thromboembolism (VTE) (deep vein thrombosis [DVT], pulmonary embolism [PE]) and the prevention of recurrent DVT and PE.
Reimbursement request	As per indication
Dosage form(s)	15 mg, 30 mg, and 60 mg oral tablets
NOC Date	November 4, 2016
Manufacturer	SERVIER Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in hematology who provided input on the conduct of the review and the interpretation of findings.

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TABLE OF CONTENTS

Tables

Figures

ABBREVIATIONS

CDR	CADTH Common Drug Review
CEAC	cost-effectiveness acceptability curve
ACTEPH	chronic thromboembolic pulmonary hypertension
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICH	intracranial hemorrhage
NMA	network meta-analysis
NOAC	non-vitamin K antagonist oral anticoagulant
PE	pulmonary embolism
PTS	post-thrombotic syndrome
QALY	quality-adjusted life-year
VTE	venous thromboembolism

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Edoxaban (Lixiana)
Study Question	What is the cost-effectiveness of edoxaban compared with warfarin and other DOACs (dabigatran, rivaroxaban, and apixaban) for the treatment of VTE and the prevention of recurrent VTE in Canadian patients?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with an acute symptomatic VTE (iVTE) who require anticoagulation treatment
Treatment	Edoxaban 60 mg daily
Outcome	QALYs
Comparators	Warfarin Rivaroxaban 20 mg daily Apixaban 5 mg twice daily Dabigatran 150 mg twice daily
Perspective	Health care system
Time Horizon	Lifetime (50 years)
Results for Base Case	• The incremental cost per QALY for edoxaban versus warfarin is $27,924 based on results of the Hokusai–VTE trial, and $94,352 based on the results of the manufacturer-submitted NMA. • Based on the NMA, edoxaban is dominated by rivaroxaban and apixaban (i.e., edoxaban is costlier and less effective). Dabigatran is both costlier and more effective than edoxaban, with an incremental cost per QALY of $69,284 when compared with edoxaban.
Key Limitations	• Sequential analysis of all comparators was not conducted; rather, edoxaban was compared pairwise with other NOACs. • Results of the manufacturer-submitted NMA are uncertain due to limitations, such as heterogeneity between trials and rarity of some analyzed events. • There was inappropriate specification of uncertainty around some transition probabilities. • Inappropriate construction of cost-effectiveness acceptability curves led to incorrect probabilities of cost-effectiveness. • Analysis could not be stratified by iVTE (PE or DVT). • Model does not distinguish between recurrent PE or DVT (treated as a single outcome of recurrent VTE).
CDR Estimate(s)	Based on the preferred approach of incorporating all comparators into a sequential analysis using the results of the NMA, edoxaban is not cost-effective. Apixaban is the optimal strategy (incremental cost per QALY vs. warfarin of $21,358). • Edoxaban is not cost-effective compared with warfarin with an incremental cost per QALY of $94,352. • Edoxaban is dominated by rivaroxaban and apixaban (costlier and less effective), but may be cost-effective compared with dabigatran. In probabilistic analyses, apixaban has a 91.7% probability 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. A price reduction of at least 80% for edoxaban would be required for it to be considered the optimal strategy.

CDR = CADTH Common Drug Review; DOAC = direct oral anticoagulant; iVTE = index VTE; NMA = network meta-analysis; NOAC = non-vitamin K antagonist oral anticoagulant; PE = pulmonary embolism; QALY = quality-adjusted life-year; vs. = versus; VTE = venous thromboembolism.

EXECUTIVE SUMMARY

Background

Edoxaban (Lixiana) is indicated for the treatment of venous thromboembolism (VTE) and the prevention of recurrent VTE.[1] The dose is 60 mg once daily. The cost per day of treatment with edoxaban is $2.84.[2]

The manufacturer submitted a cost-utility analysis conducted using a simple Markov model with eight health states: on-treatment after VTE; off-treatment; recurrent VTE; treatment after recurrent VTE; clinically relevant non-major (CRNM) bleed; intracranial hemorrhage (ICH); non-ICH major bleed; and death.[2] In addition, three concomitant events were incorporated to capture complications related to VTE: chronic thromboembolic pulmonary hypertension (CTEPH); severe post-thrombotic syndrome (PTS); and post-ICH. Analysis did not distinguish between deep vein thrombosis (DVT) and pulmonary embolism (PE). Rather, a hybrid state of VTE was used, with results weighted by the proportion of VTE events that were DVT and PE.

There are five comparators 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). Analysis comparing edoxaban versus warfarin is conducted through a direct comparison based on the Hokusai–VTE trial.[3] Further comparison with warfarin, rivaroxaban, apixaban, and dabigatran was conducted through a network meta-analysis (NMA) provided by the manufacturer.[4]

Costs for both therapy[5-9] and events[8-14] were largely obtained from appropriate published articles or relevant databases from Ontario. Utility estimates for health states and events were obtained from relevant published literature.[2,15-18]

Summary of Identified Limitations and Key Results

There were several limitations within the manufacturer's economic evaluation, a number of which were related to the modelling:

- A sequential analysis comprising all comparators simultaneously was not reported; rather, edoxaban was compared with warfarin and other non-vitamin K oral antagonist anticoagulants (NOACs) in a pairwise manner.
- CADTH Common Drug Review (CDR) clinical reviewers concluded there was considerable uncertainty regarding the comparative efficacy and safety results reported in the manufacturer's NMA (and in other published NMAs identified in a literature search) due to the small number of available trials, heterogeneity across trials, and the rarity of some events. This translates into uncertainty regarding the comparative cost-effectiveness of edoxaban versus warfarin and other direct oral anticoagulants (DOACs) in the analysis based on the NMA.
- 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. This may have affected the cost-effectiveness results. The manufacturer was asked to address this limitation, but declined. As such, no further examination of the impact of this limitation was possible.
- 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.[3] The manufacturer was asked to address this limitation, but declined. As such, no further examination of the impact of this limitation was possible. The model also assumed a consistent rate of mortality post-PE regardless of treatment, which may not be appropriate.

Based on the preferred approach of incorporating all comparators in a sequential analysis using the results of the NMA, CDR found that edoxaban is not cost-effective. Apixaban is the optimal strategy (incremental cost per quality-adjusted life-year [QALY] versus warfarin: $21,358). Edoxaban is not cost-effective compared with warfarin with an incremental cost per QALY of $94,352, and is dominated by rivaroxaban and apixaban (costlier and less effective). In probabilistic analyses, apixaban has a 91.7% probability 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. A price reduction of at least 80% for edoxaban would be required for it to be considered the optimal strategy at a threshold of $50,000 per QALY gained.

Conclusions

Edoxaban was dominated (less effective and costlier) by both apixaban and rivaroxaban, and unlikely to be considered cost-effective versus warfarin (incremental cost-utility ratio [ICUR]: $94,352 per QALY). However, there is considerable uncertainty associated with these results due to uncertainty regarding the findings of the manufacturer-submitted NMA and structural issues with the model that could not be addressed by CDR. Based on a $50,000 per QALY threshold and list prices for other NOACs, the price of edoxaban would need to be reduced by 80% for it to be considered cost-effective.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis of edoxaban compared with other approved therapies in Canada (e.g., warfarin, other non-vitamin K antagonist oral anticoagulants [NOACs]) for the treatment of venous thromboembolism (VTE) and the prevention of recurrent VTE conducted from the perspective of a Canadian health care payer over a lifetime horizon.

The analysis was based on a simple Markov model with eight health states. All patients were assumed to start the model with acute symptomatic VTE leading to initial treatment of six months. The cohort then moves within the remaining seven states (recurrent VTE, treatment after recurrent VTE, clinically relevant non-major [CRNM] bleed, intracranial hemorrhage [ICH], non-ICH major bleed, off-treatment, and death) based on the underlying probability of events on warfarin and the relative effects (odds ratios) for each direct oral anticoagulant (DOAC) versus warfarin. In addition, three concomitant events are incorporated to capture complications related to VTE (chronic thromboembolic pulmonary hypertension [CTEPH], severe post-thrombotic syndrome [PTS], and post-ICH; i.e., permanent disability due to ICH). The manufacturer did not distinguish between deep vein thrombosis (DVT) and pulmonary embolism (PE); rather, a hybrid state of VTE was used, with results weighted by the proportion of VTE events that were DVT and PE.

Monthly transition probabilities for patients on warfarin were derived from the Hokusai–VTE trial.[3] For edoxaban versus warfarin, the odds ratios from the Hokusai–VTE trial were applied to the warfarin transition probabilities.[3] A further comparison was conducted that compared all DOACs with warfarin in a pairwise manner. For this analysis, a network meta-analysis (NMA) was conducted to derive odds ratios compared with warfarin, which were then used to derive transition probabilities for patients treated with each of the other DOACs.[4] The overall findings of the NMA were that there were no significant differences between edoxaban and the other DOACs on efficacy outcomes. Findings for bleeding outcomes varied across analyses, although the risk of major bleeding was significantly higher with edoxaban than with apixaban in the manufacturer's analysis, as well as in most other analyses identified in the literature.

Costs are presented in 2015 Canadian dollars and include treatment costs, event costs, and post-event costs. Drug costs were obtained from the Ontario Drug Benefit (ODB) formulary, with resource use and costs relating to warfarin management derived from a recent CADTH Health Technology Assessment (HTA).[5-9] Acute event costs, such as for recurrent PE/DVT and bleeding events, were derived from the Ontario Case Costing Initiative and the Ontario Schedule of Benefits.[9,10] The proportions of VTEs that were PE or DVT were derived from the Hokusai–VTE trial.[3] Costs of disease outcomes such as CTEPH and PTS were derived from the literature.[11-14]

Utility values by age for the general population were obtained from Alberta and applied to stable disease.[2] Utility values for events were derived from a recent Canadian study and from other literature sources.[15-18]

A probabilistic sensitivity analysis (PSA) and a vast array of deterministic analyses were conducted.

2. MANUFACTURER'S BASE CASE

For the analysis based on the Hokusai–VTE study, edoxaban was associated with more quality-adjusted life-years (QALYs) (12.149 versus 12.068) and higher costs ($16,702 versus $14,440) than warfarin, leading to an incremental cost per QALY of $27,924.

TABLE 2: MANUFACTURER'S BASE RESULTS BASED ON THE HOKUSAI–VTE TRIAL

	Edoxaban Versus Warfarin (Scenario A)
Incremental costs	$2,261.93
Incremental QALYs	0.0810
ICER	$27,924.48

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; VTE = venous thromboembolism.
Source: Manufacturer's submission.[2]

Pairwise cost-effectiveness comparisons based on the NMA found edoxaban unlikely to be cost-effective compared with warfarin, with a much higher incremental cost per QALY of $94,352 than the analysis based on the Hokusai–VTE study. Dabigatran was more effective than edoxaban, but more costly and unlikely to be cost-effective given an incremental cost per QALY of $69,284. Edoxaban was dominated by both rivaroxaban and apixaban in that it was less effective and more costly. The manufacturer did not conduct a sequential cost-effectiveness analysis incorporating all comparators simultaneously, which would have been a more informative way of presenting the results.

TABLE 3: MANUFACTURER'S BASE RESULTS BASED ON THE NETWORK META-ANALYSIS

	Edoxaban vs. Warfarin (NMA)	Edoxaban vs. Dabigatran	Edoxaban vs. Rivaroxaban	Edoxaban vs. Apixaban
Incremental costs	$2,470.62	−$698.95	$480.29	$150.27
Incremental QALYs	0.0262	−0.0101	−0.0425	−0.0825
ICER	$94,352.44	$6,928.72	Dominated	Dominated

ICER = incremental cost-effectiveness ratio; NMA = network meta-analysis; QALY = quality-adjusted life-year; vs. = versus.
Source: Manufacturer's submission.[2]

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

A thorough range of univariate sensitivity analyses for each variable in the model were conducted for the comparisons with warfarin, but not for the comparisons with the other DOACs.

For the analysis based on the Hokusai–VTE trial, the results were sensitive to the underlying rate of ICH and the relative effects of edoxaban with respect to ICH. For the analysis based on the NMA, the results were only sensitive to the relative effects of edoxaban with respect to ICH. The interpretation of results was not sensitive to any other parameters.

A further range of scenarios was considered relating to time horizon, discount rate, and baseline probability of events on warfarin. In these analyses, the factor that had the greatest impact on the results was the use of baseline probabilities from the CADTH HTA,[8] increasing the incremental cost per QALY for edoxaban versus warfarin to $145,338.

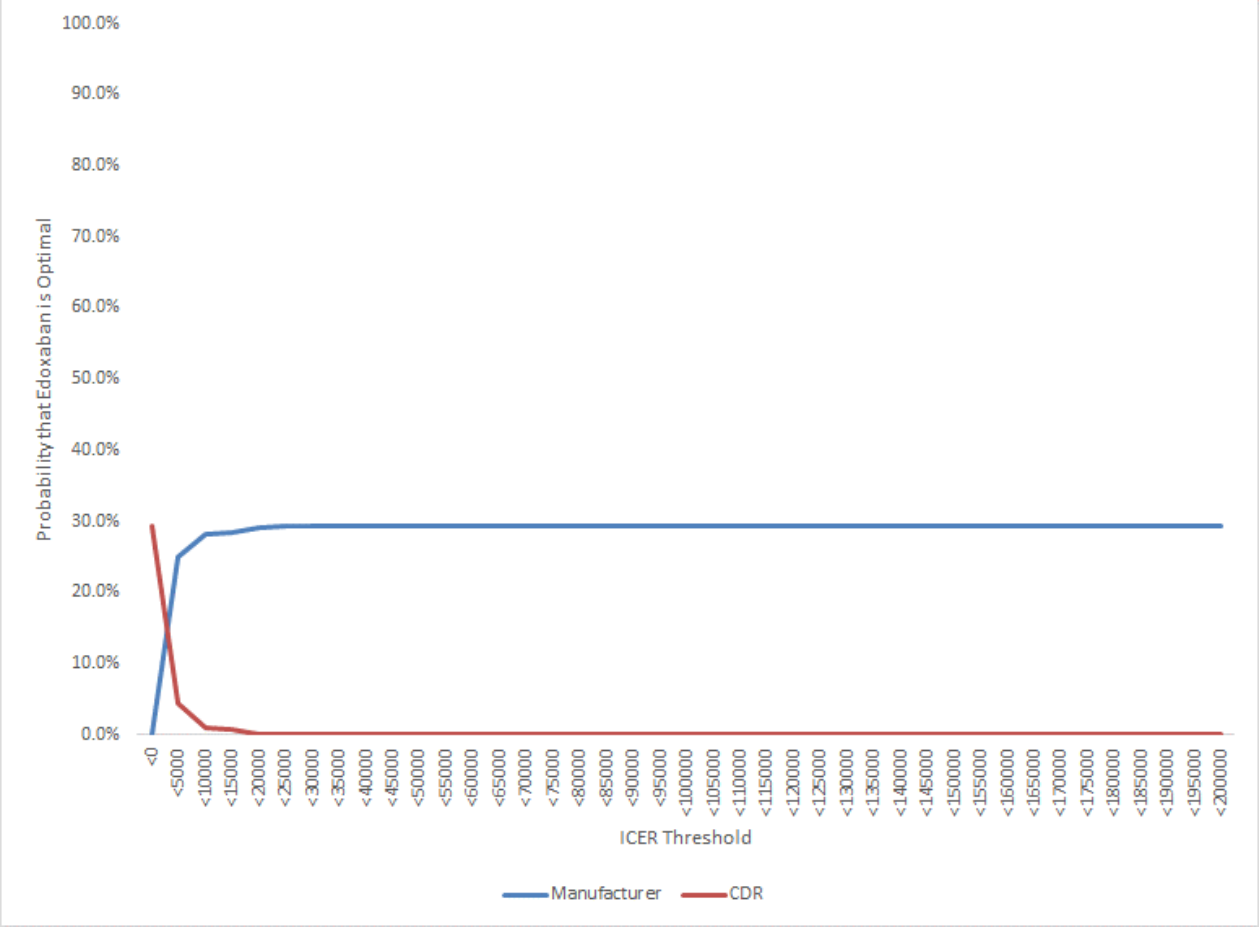
Within the PSA, at a threshold of $50,000 per QALY, there was a 57% probability that edoxaban was cost-effective compared with warfarin based on the trial-based comparison, and an 11% probability according to the NMA-based comparison. Corresponding figures for the comparison with the DOACs were not provided; only the cost-effectiveness acceptability curves (CEACs) were presented. However, as discussed in the following section, the CEACs were incorrectly formulated.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

1. The baseline rates with warfarin from the CADTH HTA may be preferred over the baseline rates from the Hokusai–VTE trial; however, CADTH Common Drug Review (CDR) was unable to reproduce the scenario analysis reported in the manufacturer's report that used the CADTH NMA baseline rates. This may have been due to the lack of transparency within the model design and the automated approach to conducting sensitivity analysis (rather than a more formal description of changes required for accurate implementation of sensitivity analyses).
2. There was an error in the formulation of the CEAC in that the analysts calculated the proportion of incremental cost-effectiveness ratios (ICERs) below a specified threshold. This failed to distinguish between ICERs in the northeast and southwest quadrants and between ICERs in the northwest and southeast quadrants. This is illustrated in Figure 1 for the comparison of apixaban and edoxaban. The manufacturer's estimates imply that the probability that edoxaban is optimal for a threshold of $50,000 is approximately 30% when it is in fact 0%. The correct approach would have been to calculate net monetary benefit with each specific threshold for each replication.
3. For certain transition probabilities and utilities, the method for assuming a standard error around estimates was inappropriate. When data on uncertainty were unavailable for transition probabilities or utility values, the manufacturer's submission assumed the uncertainty could be specified by a standard error equivalent to 20% of the mean value. With both probabilities and utilities, the approach adopted by the manufacturer for specifying uncertainty would yield different levels of uncertainty depending on the specification. For example, if the probability of an event was 10%, the standard error would be 0.02; yet if the specification was the probability of no event, the standard error would be 0.18. This inconsistency is not appropriate, although it is unlikely to affect the results.
4. Stratified analysis by type of index VTE was not possible. This is a limitation, as it is possible that the cost-effectiveness of edoxaban could vary by this factor, given the different results by type of VTE: the primary end point in the Hokusai–VTE trial (the hazard ratio for recurrent VTE for edoxaban versus warfarin) for incident DVT only was 1.02 (95% confidence interval [CI], 0.75 to 1.38) and for incident PE was 0.73 (95% CI, 0.50 to 1.06). CDR requested this feature within the model, but this request was denied by the manufacturer; therefore, the impact of combining DVT and PE as VTE could not be explored. The argument provided was that there was no significant statistical interaction between treatment and type of initial event (DVT or PE) for the primary end point of the Hokusai–VTE trial.[19]
5. Given the significantly different consequences of recurrent DVT and recurrent PE (fatal and non-fatal), CDR requested that the model be designed to distinguish between these outcomes rather than incorporate a single state for recurrent VTE. However, the manufacturer declined this request on the basis that no statistical analyses were planned for the components of the primary end point (recurrent VTE) in Hokusai–VTE, and that the estimates for the individual components (DVT, non-fatal PE, fatal PE) were directionally consistent with the primary end point.[19] The model also assumes a consistent rate of mortality post-PE regardless of treatment, which may not be appropriate.

6. The submitted report highlights the comparisons of edoxaban with each alternative therapy individually. CDR considered the analysis based on the NMA to be more informative, as it allowed direct comparison between all relevant treatment alternatives. The preferred approach to assessing the cost-effectiveness of edoxaban is to consider all alternatives together through a sequential analysis. However, it should be noted that CDR clinical reviewers concluded there was considerable uncertainty regarding the comparative efficacy and safety results reported in the manufacturer's NMA (and in other published NMAs identified in a literature search) due to the small number of available trials, heterogeneity across trials, and rarity of some events. This translates into uncertainty regarding the comparative cost-effectiveness of edoxaban versus warfarin and other DOACs in the analysis based on the NMA.

FIGURE 1: COST-EFFECTIVENESS ACCEPTABILITY CURVES FROM MANUFACTURER'S SUBMISSION



CDR = CADTH Common Drug Review; ICER = incremental cost-effectiveness ratio.
Source: Manufacturer's submission.[2]

CDR was able to address limitations 2 and 6. Limitation 4 did not affect the base-case analysis and only changed the degree of uncertainty within the probabilistic analysis; therefore, it was not addressed specifically in a CADTH reanalysis. Although CDR attempted to address limitation 1, CDR could not replicate the scenario analysis results contained within the manufacturer's report. The other limitations could not be addressed, but should be considered with respect to reimbursement decisions for edoxaban.

5. CADTH COMMON DRUG REVIEW REANALYSES

5.1 Inability to Replicate Sensitivity Analysis Based on CADTH NMA Baseline Rates (Limitation 1)

Table 4 shows the results of the CDR attempt to adopt the event rates on warfarin from the CADTH HTA, and the corresponding scenario analysis by the manufacturer based on the CADTH HTA event rates. Given the divergence in results and the inability to identify its cause, CDR did not focus on this reanalysis.

TABLE 4: COMPARISON OF CADTH COMMON DRUG REVIEW AND MANUFACTURER SENSITIVITY ANALYSES BASED ON CADTH HEALTH TECHNOLOGY ASSESSMENT EVENT RATES

	Incremental Cost Per QALY	
	Manufacturer's Report	CDR Attempt to Replicate
Edoxaban versus warfarin	$145,338	$152,448
Dabigatran versus edoxaban	$181,052	$244,607
Rivaroxaban versus edoxaban	Dominated	Dominated
Apixaban versus edoxaban	$9,389	$2,054

CDR = CADTH Common Drug Review; QALY = quality-adjusted life-year.

5.2 Focus on Full Sequential Analysis of All Relevant Comparators (Limitation 6)

CDR wishes to give prominence to the full analysis of all comparators based on the submitted model design but using relative effects from the submitted NMA, and to produce an appropriate cost-effectiveness acceptability curve.

Results are presented first as a sequential analysis of cost-effectiveness (Table 5).

TABLE 5: SEQUENTIAL COST-EFFECTIVENESS: CADTH COMMON DRUG REVIEW REANALYSIS

	Total Costs ($)	Total QALYs	Incremental Cost Per QALY Versus Warfarin	Sequential Incremental Cost Per QALY
Warfarin	$14,440	12.068		
Apixaban	$16,760	12.176	$21,358	$21,358
Rivaroxaban	$16,430	12.136	$28,990	Subject to extended dominance through apixaban and warfarin
Dabigatran	$17,610	12.104	$87,380	Dominated by apixaban
Edoxaban	$16,911	12.094	$94,352	Dominated by apixaban and rivaroxaban

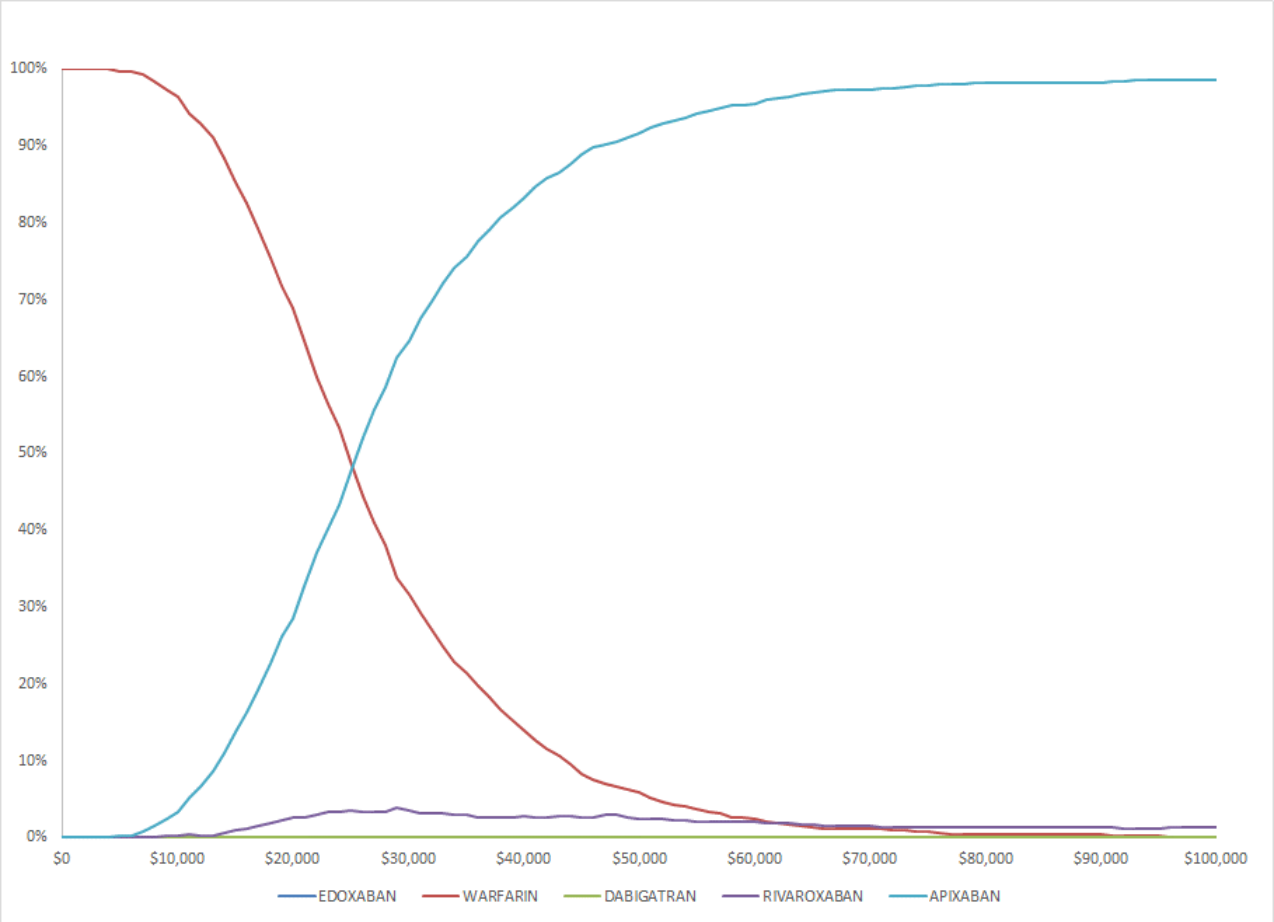
QALY = quality-adjusted life-year.

The results of the sequential analysis illustrate that both edoxaban and dabigatran are dominated by apixaban, while rivaroxaban is subject to extended dominance through warfarin and apixaban. Apixaban is optimal assuming a willingness to pay more than $21,358 per QALY.

5.3 Revised Reporting of Probabilistic Sensitivity Analysis (Limitation 2)

CDR did not correct the flawed approach in the manufacturer's report for creating the CEACs for pairwise comparisons with edoxaban, as inclusion of all comparators within the same CEAC is more informative (Figure 2).

FIGURE 2: COST-EFFECTIVENESS ACCEPTABILITY CURVE FROM CADTH REANALYSIS INCLUDING ALL COMPARATORS



The CEAC illustrates that at a threshold of $50,000 per QALY, apixaban has the highest probability of being optimal (91.7%). The probability that edoxaban is optimal is 0% for all thresholds from $0 to $100,000.

5.4 Price Reduction Scenarios

Given the findings of the CDR analysis, a further analysis was conducted assessing the necessary price reduction for edoxaban to be considered cost-effective at a threshold of $50,000 per QALY (Table 5, Table 6).

TABLE 6: CADTH COMMON DRUG REVIEW REANALYSIS: PRICE REDUCTION SCENARIOS

Incremental Cost Per QALY ($)			
Price	**Edoxaban Versus Warfarin**	**Rivaroxaban Versus Edoxaban[a]**	**Apixaban Versus Edoxaban[a]**
Submitted	$94,352	Rivaroxaban dominates edoxaban	Apixaban dominates edoxaban
10% reduction	$73,961	$1,263	$4,653
20% reduction	$53,570	$13,835	$11,129
30% reduction	$33,179	$26,407	$17,604
40% reduction	$12,788	$38,979	$24,080
50% reduction	Edoxaban dominates warfarin	$51,551	$30,556
60% reduction	Edoxaban dominates warfarin	$64,123	$37,031
70% reduction	Edoxaban dominates warfarin	$76,695	$43,507
80% reduction	Edoxaban dominates warfarin	$89,267	$49,983

QALY = quality-adjusted life-year.
[a] Ratios reflect comparison of rivaroxaban or apixaban versus edoxaban; therefore, for edoxaban to be preferred, the ratio must be greater than the willingness-to-pay threshold.

Based on a willingness to pay of $50,000 per QALY, the cost of edoxaban would have to be reduced by at least 80% for edoxaban to be considered the optimal treatment strategy.

Analysis is based on listed prices. If lower effective prices are in place for either apixaban or rivaroxaban, necessary price reductions for edoxaban will be greater than shown in Table 4.

6. ISSUES FOR CONSIDERATION

The current effective prices for rivaroxaban, apixaban, and dabigatran are unknown, which may limit the ability to accurately interpret the results of the submitted analysis.

7. PATIENT INPUT

No patient-group input was received by CDR for this submission. Therefore, CDR considered input that had been received in October 2014 as part of the review of apixaban (Eliquis) for the treatment and prevention of VTE.[20] Based on responses to a survey conducted by the Heart and Stroke Foundation, patients with VTE described the need to take medications at one or more specific times each day, dietary changes, and having to take time off work. While many patients indicated that their ability to perform activities had not changed, some reported they were unable to perform some tasks such as exercise or lifting items. Symptoms experienced by patients included fatigue, general swelling of the legs and ankles, leg pain or leg cramping, shortness of breath, depression, and bruising. Adverse events from therapy reported by patients included bruising, swelling, bleeding, dizziness, drowsiness, tingling in the hands and feet, and joint pain. Some caregivers reported feeling more overwhelmed and busier, anxious, or stressed. Some caregivers needed to take time off work.

The symptoms and adverse effects experienced by patients are likely to be captured in the health states and corresponding utility values in the economic model submitted by the manufacturer. As the submitted analysis was performed from the public payer perspective, productivity losses (such as those due to patient or caregiver lost time from work) were not captured.

8. CONCLUSIONS

Edoxaban was dominated (less effective and costlier) by both apixaban and rivaroxaban, and was unlikely to be considered cost-effective versus warfarin (incremental cost-utility ratio [ICUR] of $94,352 per QALY). CDR found that the probability that edoxaban was cost-effective was 0% for all QALY thresholds between $0 and $100,000. However, there is considerable uncertainty associated with these results due to uncertainty regarding the findings of the manufacturer-submitted NMA and structural issues with the model that could not be addressed by CDR (such as the inability to model DVT and PE as separate events for both incident and recurrent VTE). Based on a threshold of $50,000 per QALY, the price of edoxaban would need to be reduced by 80% for it to be considered cost-effective, based on current list prices for the other DOACs. The required price reduction for edoxaban would be higher if there are lower effective prices for the other DOACs.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 7 have been deemed appropriate by the clinical expert consulted by CADTH Common Drug Review (CDR). Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 7: ORAL ANTICOAGULANTS FOR THE TREATMENT AND PREVENTION OF VENOUS THROMBOEMBOLISM

Comparator Drug	Strength	Dosage Form	Price ($)	Recommended Daily Use	Average Daily Drug Cost ($)	Total Cost of a 6-Month Course ($)
Edoxaban (Lixiana)	15 mg 30 mg 60 mg	Tablet	2.8400[a]	60 mg once daily following initial use of heparin	2.84	518
Apixaban (Eliquis)	2.5 mg 5.0 mg	Tablet	1.6000	*Treatment of acute DVT and/or PE*: Apixaban 10 mg p.o. b.i.d. for 7 days, followed by 5 mg p.o. b.i.d. *Continued prevention of recurrent DVT and/or PE*: Apixaban 2.5 mg p.o. b.i.d. after at least 6 months of treatment for DVT or PE	First 7 days 6.40 Thereafter 3.20	606
Dabigatran (Pradaxa)	110 mg 150 mg	Capsule	1.6480 1.6480	150 mg twice daily following treatment with a parenteral anticoagulant for 5 to 10 days	3.30	602
Rivaroxaban (Xarelto)	10 mg 15 mg 20 mg	Tablet	2.8400	15 mg twice daily for first three weeks followed by 20 mg daily for the continued treatment and prevention of recurrent DVT and PE	First 3 weeks: 5.68 Thereafter: 2.84	578
Vitamin K Antagonists						
Warfarin (generic)	1 mg 2 mg 2.5 mg 3 mg 4 mg 5 mg 10 mg	Tablet	0.0796 0.0841 0.0674 0.1043 0.1043 0.0675 0.1211	Usual maintenance: 2 mg to 10 mg daily	0.07 to 0.12	292 to 301

b.i.d. = twice daily; DVT = deep vein thrombosis; PE = pulmonary embolism; p.o. = orally.
[a] Manufacturer's submitted price.[22]
Source: Ontario Drug Benefit list prices (November 2016)[21] unless otherwise indicated.

TABLE 8: PARENTERAL TREATMENTS FOR THE TREATMENT AND PREVENTION OF VENOUS THROMBOEMBOLISM

Comparator Drug	Strength	Dosage Form	Price ($)	Recommended Daily Use	Average Daily Drug Cost ($)
Low-Molecular-Weight Heparins[a]					
Enoxaparin sodium (Lovenox)	30 mg/0.3mL 40 mg/0.4mL 60 mg/0.6mL 80 mg/0.8mL 100 mg/1 mL 100 mg/mL 120 mg/0.8 mL 150 mg/1 mL	Syringe Syringe Syringe Syringe Syringe 3 mL vial Syringe Syringe	6.6170 8.8220 13.2330 17.6450 22.0560 63.6000 26.4670 33.0850	1 mg/kg SC twice daily for approximately 7 days	35.29[b]
Dalteparin sodium (Fragmin)	2,500 IU/0.2 mL 5,000 IU/0.2 mL 7,500 IU/0.3 mL 10,000 IU/0.4 mL 12,500I U/0.5 mL 15,000 IU/0.6 mL 18,000 IU/0.72 mL	Syringe	5.4529 10.9048 16.3547 21.8096 27.2605 32.7114 39.2537	200 IU/kg SC once daily for approximately 5 days	32.71[b]
Nadroparin calcium (Fraxiparine)	0.3 mL 0.4 mL 0.6 mL 1.0 mL	9,500 anti-Xa IU/mL syringe	5.4150 6.8400 9.0580 9.0580	171 anti-Xa IU/kg SC once daily for up to 10 days	18.12[b]
	0.6 mL 0.8 mL 1.0 mL	19,000 anti-Xa IU/mL syringe	18.1170		
Tinzaparin sodium (Innohep)	2,500 IU/0.25 mL 3,500 IU/0.35 mL 4,500 IU/0.45 mL 10,000 IU/0.5 mL 14,000 IU/0.7 mL 18,000 IU/0.9 mL	Syringe	4.9140 6.8720 8.8380 20.0430 28.0860 36.1070	175 anti-Xa IU/kg SC once daily, average duration of 7 days	28.09[b]
	20,000 IU/2 mL 40,000 IU/2 mL	Vial	38.9530 79.1300		38.95[b]
Other Anticoagulants					
Fondaparinux sodium (generics)	2.5 mg /0.5 mL 7.5 mg/0.6 mL	Syringe	11.1944 18.1356	2.5 mg to 10 mg SC once daily; average duration is 7 days	11.19 to 29.33
Heparin sodium (Heparin Leo)	10,000 IU/1 mL 50,000 IU/5 mL	Injection	1.1000[c] 5.0100[c]	333 IU/kg SC initially, followed by 250 IU/kg every 12 hours	Initial dose: 2.34 Daily thereafter: 3.51

IU = international units; SC = subcutaneously.

[a] Concomitant treatment with warfarin is normally started immediately. Treatment with low-molecular-weight heparins should be continued until the levels of the prothrombin complex factors have decreased to a therapeutic level, in general for approximately 5 to 10 days.

[b] Assumes 70 kg patient weight. Assumes extra medication in syringes or vials is wasted.

[c] Quebec formulary list price (November 2016).[23]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 9: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS EDOXABAN RELATIVE TO WARFARIN (BASED ON NMA)?

	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
ICER or net benefit calculation	Incremental cost per QALY gained for edoxaban versus warfarin = $94,352					

ICER = incremental cost-effectiveness ratio; NMA = network meta-analysis; QALY = quality-adjusted life-year.

TABLE 10: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS EDOXABAN RELATIVE TO RIVAROXABAN?

	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone			X			
Clinical outcomes				X		
Quality of life				X		
Incremental cost-effectiveness ratio or net benefit calculation	Edoxaban is dominated by rivaroxaban.					

TABLE 11: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS EDOXABAN RELATIVE TO DABIGATRAN 150 MG?

	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)		X				
Drug treatment costs alone			X			
Clinical outcomes				X		
Quality of life				X		
ICER or net benefit calculation	Incremental cost per QALY gained for dabigatran versus edoxaban = $69,284					

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

TABLE 12: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS EDOXABAN RELATIVE TO APIXABAN?

	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone		X				
Clinical outcomes					X	
Quality of life					X	
Incremental cost-effectiveness ratio or net benefit calculation	Edoxaban is dominated by apixaban.					

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 13: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments *Reviewer to provide comments if checking "no"*	The model is unnecessarily complex, which made it impossible to replicate some key sensitivity analyses.		
Was the material included (content) sufficient?			X
Comments *Reviewer to provide comments if checking "poor"*	CDR requested a stratified analysis and the model to distinguish between DVT and PE, but the manufacturer declined to address these issues.		
Was the submission well organized and was information easy to locate?		X	
Comments *Reviewer to provide comments if checking "poor"*	None		

CDR = CADTH Common Drug Review.

TABLE 14: AUTHORS' INFORMATION

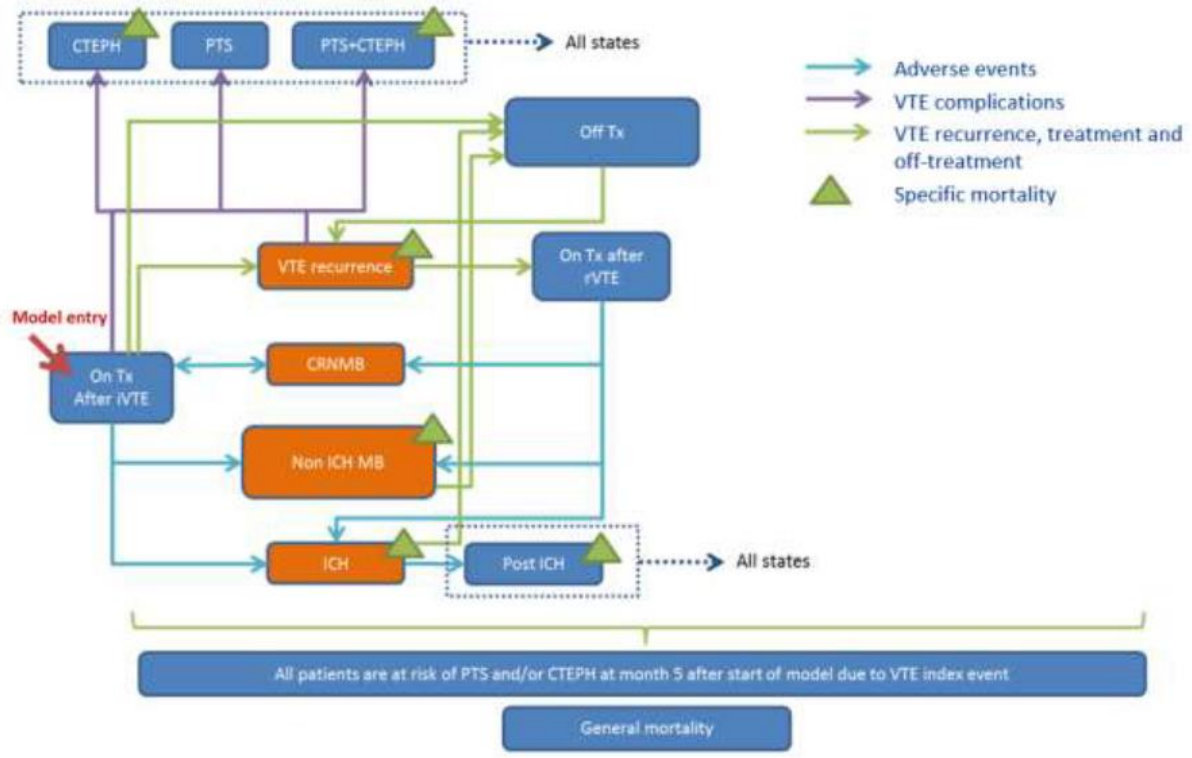
Authors of the Pharmacoeconomic Evaluation Submitted to CDR			
☐ Adaptation of global model/Canadian model done by the manufacturer ☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)			
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis			X

CDR = CADTH Common Drug Review.

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

FIGURE 3: MANUFACTURER'S MODEL SCHEMATIC: FIGURE 3.3



CRNMB = clinically relevant non-major bleed; CTEPH = chronic thromboembolic pulmonary hypertension; ICH = intracranial hemorrhage; iVTE = index VTE; MB = majour bleed; rVTE = recurrent venous thromboembolism; PTS = post-thrombotic syndrome; VTW = venous thromboembolism; Tx = treatment.
Source: Manufacturer's submission.[22]

TABLE 15: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Hokusai–VTE trial[3] Manufacturer-submitted NMA[4]	Appropriate Appropriate, although clinical review identified important limitations, such as between-trial heterogeneity
Natural History	Probability of events (VTE and bleeds) on warfarin: Hokusai–VTE trial[3] Probability of CTEPH – Pengo et al.[24] Probability of PTS – Kahn et al.[25]	CADTH HTA baseline rates may be preferable, but results based on these could not be replicated with manufacturer's sensitivity analysis employing CADTH HTA rates Appropriate Appropriate
Utilities	Health Quality Council of Alberta (specific reference indecipherable in manufacturer's report),[2] Hogg et al.,[15] Lenert et al.,[16] Meads et al.,[17] Luengo-Fernandez et al.[18]	Appropriate
Mortality	Background mortality: Statistics Canada (2011)[26,27] Probability of death post-ICH – Poon et al.[28] Probability of death post-CTEPH – Delcroix et al.[12]	Appropriate Appropriate Appropriate
Costs		
Drug	Rivaroxaban, warfarin, apixaban, and dabigatran: Ontario Drug Benefit formulary (2016)[5] Edoxaban: Daiichi Sankyo[22]	Appropriate
Administration	Warfarin administration: CADTH HTA[8]	Appropriate
Event	OCCI,[10] Ontario SoB,[9] Rubens et al.,[11] Delcroix et al.[12]	Appropriate
Post-Event Health State	CADTH HTA,[8] Caprini et al.,[13] Goeree et al.[14]	Appropriate

CTEPH = chronic thromboembolic pulmonary hypertension; HTA = health technology assessment; ICH = intracranial hemorrhage; NMA = network meta-analysis; OCCI = Ontario Case Costing Initiative; PTS = post-thrombotic syndrome; VTE = venous thromboembolism.

TABLE 16: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Can compare DOACs through NMA.	Appropriate and should be primary analysis.
DVT and PE modelled as a single outcome of VTE. Risks of subsequent VTE after incident event and relative effects of treatment are the same regardless of whether incident event was DVT or PE. Mortality after recurrent PE consistent regardless of treatment.	May not be appropriate given HR for recurrent VTE after incident DVT was 1.02 (95% CI, 0.75 to 1.38), while HR for recurrent VTE after incident PE was 0.73 (95% CI, 0.50 to 1.06) in Hokusai–VTE trial.[3] May not be appropriate, as mortality was different between treatments in Hokusai–VTE trial.[3]
Baseline demographics and baseline event rates from Hokusai–VTE trial are reflective of Canadian population with VTE.	Likely appropriate.
Six-month efficacy from NMA reflects long-term efficacy.	Likely appropriate; tested through sensitivity analysis in which ORs for all NOACs vs. warfarin were set to 1 after 6 months.

CI = confidence interval; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; HR = hazard ratio; OR = odds ratio; NMA = network meta-analysis; NOAC = non-vitamin K antagonist oral anticoagulant; PE = pulmonary embolism; vs. = versus; VTE = venous thromboembolism.

Manufacturer's Results

No additional information.

CADTH Common Drug Review Reanalyses

No additional information.

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