Common Drug Review
Pharmacoeconomic Review Report

June 2016

Drug	apixaban (Eliquis)
Indication	Treatment of venous thromboembolic events (deep vein thrombosis, pulmonary embolism) and prevention of recurrent deep vein thrombosis and pulmonary embolism.)
Listing request	Treatment of venous thromboembolic events (deep vein thrombosis and pulmonary embolism) and prevention of recurrent deep vein thrombosis and pulmonary embolism.
Manufacturer	Bristol-Myers Squibb Canada and Pfizer Canada

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.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update – Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

The information in this report is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment with respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this document to ensure that its contents are accurate, complete, and up-to-date as of the date of publication, CADTH does not make any guarantee to that effect. CADTH is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in the source documentation. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the information in this document or in any of the source documentation.

This document is intended for use in the context of the Canadian health care system. Other health care systems are different; the issues and information related to the subject matter of this document may be different in other jurisdictions and, if used outside of Canada, it is at the user's risk. This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

CADTH takes sole responsibility for the final form and content of this document, subject to the limitations noted above. The statements and conclusions in this document are those of CADTH and not of its advisory committees and reviewers. The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada or any Canadian provincial or territorial government. Production of this document is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon.

TABLE OF CONTENTS

Tables

Figure

ABBREVIATIONS

CDR	CADTH Common Drug Review
CRNM	clinically relevant, non-major
CUA	cost-utility analysis
DVT	deep vein thrombosis
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
INR	international normalized ratio
NMA	network meta-analysis
PE	pulmonary embolism
QALY	quality-adjusted life-year
RR	relative risk
VTE	venous thromboembolic event

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Apixaban (Eliquis)
Study Question	What are the long-term clinical and economic benefits of apixaban in the treatment of VTE and prevention of recurrent VTE events for a duration of 6 months compared with treatment with standard of care (enoxaparin plus warfarin) or other NOACs, rivaroxaban or dabigatran? What are the health economic benefits of extending treatment with apixaban to patients with VTE who have already completed at least 6 months of anticoagulation therapy and for whom treating physicians may be uncertain about continuing therapy as per the traditional practice?
Type of Economic Evaluation	CUA
Target Population	Patients who require anticoagulation for treatment of the index VTE and subsequent treatment for the prevention of recurrent events.
Treatment	Acute-treatment phase • apixaban 10 mg b.i.d. × 7 days, followed by 5 mg b.i.d. for up to 6 months. Extended-treatment phase • apixaban 10 mg b.i.d. × 7 days, followed by 5 mg b.i.d. for up to 6 months, followed by 2.5 mg b.i.d. for up to 18 months.
Outcome(s)	QALYs and overall survival in life-years.
Comparators	Acute-treatment phase • enoxaparin × 8 days, warfarin × 6 months • rivaroxaban 15 mg b.i.d. × 21 days, then 20 mg q.d. × 6 months • enoxaparin × 8 days, then dabigatran 150 mg b.i.d. × 6 months. Extended-treatment phase • enoxaparin × 8 days, warfarin x 6 months, no treatment × 12 months • rivaroxaban 15 mg b.i.d. × 21 days, then 20 mg q.d. × 18 months • enoxaparin × 8 days, then dabigatran 150 mg b.i.d. × 18 months.
Perspective	Canadian provincial government payer
Time Horizon	Lifetime
Results for Base Case	Acute-treatment phase • apixaban versus enoxaparin plus warfarin: apixaban is dominant • apixaban versus rivaroxaban: apixaban is dominant • apixaban versus dabigatran: apixaban is dominant. Extended-treatment phase • apixaban versus enoxaparin plus warfarin followed by no treatment: incremental ICUR: $4,827.78 per QALY • apixaban versus rivaroxaban: apixaban is dominant • apixaban versus dabigatran: apixaban is dominant.
Key Limitations	CDR noted a number of limitations with the manufacturer's model: • Any conclusions regarding the relative effects of apixaban and other NOACs on outcomes such as major bleeding are uncertain due to limitations with the available data. Long-term comparative bleeding rates of apixaban with enoxaparin plus warfarin obtained from the NMA are also limited by the low event rates.

	• The extended-treatment phase compares 18 months of apixaban with 6 months of enoxaparin plus warfarin and 12 months of no treatment: this comparison is unfair and results in an overestimation of incremental QALYs with apixaban. • Administration costs for enoxaparin and INR monitoring with warfarin were likely overestimated, which will bias the results in favour of apixaban. • The assumption that patients using enoxaparin plus warfarin have a higher utility decrement compared with apixaban (and rivaroxaban) (0.013 vs. 0.002) is not supported by strong evidence.
CDR Estimate(s)	Based on combined analysis assuming: • Equal recurrent VTE for all treatments; equal major bleeds for apixaban and rivaroxaban at 6 months, and the lower bound of the CrI from the NMAs for rivaroxaban (18 months) and enoxaparin plus warfarin (6 and 18 months) • Equal treatment discontinuation across apixaban, rivaroxaban, and enoxaparin plus warfarin • The proportion of patients able to do INR monitoring at home is 25% (instead of 50%), and the proportion of patients able to successfully self-administer enoxaparin is 92% (instead of 75%) • Equal utility decrement for enoxaparin plus warfarin and apixaban • Utilities for other VTE events from an alternative source • In the extended-treatment phase, anticoagulation is extended during 18 months for all treatments. For the acute-treatment phase (6 months of treatment), apixaban is likely to provide similar QALYs at similar costs to both rivaroxaban and enoxaparin plus warfarin. For the extended-treatment phase (18 months of treatment), apixaban resulted in small QALY gains (0.007) but an incremental cost of $831 when compared with enoxaparin plus warfarin, leading to an ICUR higher than $100,000 per QALY.

b.i.d. = twice daily; CDR = CADTH Common Drug Review; CrI = credible interval; CUA = cost-utility analysis; DVT = deep vein thrombosis; ICUR = incremental cost-utility ratio; INR = international normalized ratio; NMA = network meta-analysis; NOACs = new oral anticoagulants; PE = pulmonary embolism; QALY = quality-adjusted life-year; vs = versus; VTE = venous thromboembolic event.

EXECUTIVE SUMMARY

Background

Apixaban (Eliquis) is being reviewed for the treatment of venous thromboembolic events (VTEs); i.e., deep vein thrombosis (DVT), pulmonary embolism (PE), and the prevention of recurrent DVT and PE. The requested listing criteria are as per indication.[1] Apixaban is available as 2.5 mg and 5 mg tablets at a flat price of $1.60 per tablet. The recommended dose for the treatment of acute DVT or PE is 10 mg twice daily for seven days ($6.40 daily), followed by 5 mg twice daily ($3.20 daily). The recommended dose for the continued prevention of recurrent DVT and PE is 2.5 mg twice daily after at least six months of treatment for DVT or PE ($3.20 daily).[1,2]

The manufacturer submitted a cost-utility analysis (CUA) comparing apixaban to low-molecular-weight heparin (enoxaparin) followed by a vitamin K antagonist (warfarin) or new oral anticoagulants (NOACs) including rivaroxaban and dabigatran over a lifetime horizon in patients who require anticoagulation for the treatment of an index VTE and subsequent treatment for the prevention of recurrent events. Two base-case analyses are presented: anticoagulation during six months (acute treatment) or during 18 months (extended treatment). Patients enter the model having just experienced an index PE or DVT event and are placed in the health states "index PE" (30%) or "index DVT" (70%).[3]

Summary of Identified Limitations and Key Results

The key limitations with the submitted model were the uncertainty surrounding the network meta-analysis (NMA) findings, overestimation of administration and monitoring costs of enoxaparin plus warfarin, use of different treatment-related disutilities for enoxaparin plus warfarin and comparison of 18 months of apixaban to only six months of anticoagulation therapy with enoxaparin plus warfarin in the extended-treatment phase.

CADTH Common Drug Review (CDR) reanalyses suggest that for the acute-treatment phase (six months), apixaban is likely to provide similar quality-adjusted life-years (QALYs) at similar costs to both rivaroxaban (same QALYs, incremental cost of $25 over lifetime) and enoxaparin plus warfarin (incremental QALYs = 0.007, incremental cost = $45, incremental cost-utility ratio [ICUR] = $6,425 per QALY). For the extended-treatment phase (18 months), the ICUR of apixaban versus enoxaparin plus warfarin could be higher than $100,000 per QALY.

Conclusions

CDR found a number of limitations with the manufacturer's submission. For the treatment of VTE (DVT and PE) and prevention of recurrent VTE events, there is a high degree of uncertainty related to interpreting the comparative bleeding risks associated with apixaban compared with other NOACs. CDR reanalysis of the six-month scenario, assuming similar rates of VTE and smaller differences in rates of major bleeding, suggests that apixaban is likely to provide similar QALYs at similar costs to both rivaroxaban and enoxaparin plus warfarin.

CDR reanalysis of the 18-month comparison in which apixaban was compared with 18 months of enoxaparin plus warfarin suggests that the ICUR of apixaban versus enoxaparin plus warfarin could be higher than $100,000 per QALY.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer conducted a cost-utility analysis (CUA) comparing apixaban to low-molecular-weight heparin (LMWH; enoxaparin) followed by vitamin K antagonists (warfarin), and new oral anticoagulants (NOACs) including rivaroxaban and dabigatran, in patients requiring anticoagulation for the treatment of venous thromboembolism (VTE).[3] The model population was assumed to have similar characteristics to those recruited into the AMPLIFY[4] and AMPLIFY-EXT[5] studies, which are key sources for the model evidence. The base-case time horizon was the patient's lifetime, using a Canadian provincial public-payer perspective where costs are reported in 2014 Canadian dollars.

Two base-case analyses are presented: apixaban for an acute-treatment phase (six months of treatment), and an extended-treatment period for up to 18 months overall. In the acute-treatment phase analysis, the comparators are the other drugs for six months. However, for the extended 18-month comparison, the comparators are rivaroxaban and dabigatran for 18 months, or enoxaparin plus warfarin for six months followed by no treatment for 12 months.

A Markov model is used to simulate patients over the lifetime of their disease using a three-cycle length. Patients enter the model having just experienced an index PE or DVT event and are placed in the health states "index PE" (30%) or "index DVT" (70%). The model includes 13 health states: Index PE; Index DVT; Recurrent PE; Recurrent DVT; Chronic Thromboembolic Pulmonary Hypertension (CTEPH); Intracranial Bleed (all intracranial bleeds are assumed to be major bleeds); Non-Intracranial Major Bleed; Clinically Relevant, Non-major (CRNM) Bleed; PE Second-Line Treatment; DVT Second-Line Treatment; PE Off Treatment; DVT Off Treatment; and Death. The transitions differ between treatments based on evidence from a series of sources, but are based primarily on the results of two manufacturer-funded network meta-analyses (NMAs): one for acute treatment of VTE (zero to six months)[6] and one for extended treatment of VTE (beyond six months of treatment duration).[7] Results of the two NMAs were used to inform the risk of VTE and VTE-related death, and the risk of major bleeding and CRNM bleeding, as well as treatment discontinuation in the economic model. A summary and critical appraisal of the NMAs is presented in Appendix 6 of the CADTH Common Drug Review (CDR) clinical review.

The NMA is based on a series of clinical trials, but the key sources for apixaban are the AMPLIFY[4] trial (acute treatment) and the AMPLIFY-EXT[5] (extended treatment) trial. The results of the NMA suggest apixaban reduces the risk of VTE recurrence and has a lower risk of causing major bleeds and CRNM bleeds versus comparators (although NMA estimates were not always statistically significant). The impact of these risks is accounted for in the model by assigning VTEs, bleeds, and other events utilities and costs. Patients are assumed to have a base-case utility of 0.85, and then assigned disutilities for events from external sources based on the treatment used (not from the AMPLIFY trials). The costs for each event were taken primarily from the Ontario Case Costing Initiative. The unit costs of drugs were taken from the Ontario Ministry of Health Drug Benefit Formulary. Costs of monitoring and administration were based on assumptions regarding the number of patients who would be able to self-inject enoxaparin and who would be able to perform international normalized ratio (INR) monitoring at home. Costs and health outcomes (VTE, bleeding events, life-years [LYs], and quality-adjusted life-years [QALYs]) are presented for each treatment, along with the incremental cost-utility ratio (ICUR).

2. MANUFACTURER'S BASE CASE

As recurrent VTE, major bleeds, and CRNM bleeds are assumed to be reduced in the first six months and have similar anticoagulant-related costs, the six-month base-case analysis reports that apixaban incurs higher QALYs (7.855 versus 7.845, 7.831, and 7.824, for rivaroxaban, dabigatran, and enoxaparin plus warfarin, respectively) and lower costs ($6,804 versus $6,822, $7,207, and $6,931 for rivaroxaban, dabigatran, and enoxaparin plus warfarin, respectively) versus its comparators, and so it is the dominant option (Table 12 in Appendix 4).

In the 18-month analysis, apixaban is again expected to provide more QALYs (7.938 versus 7.819, 7.910, and 7.824 for rivaroxaban, dabigatran, and enoxaparin plus warfarin, respectively). Rivaroxaban and dabigatran are expected to cost more than apixaban ($7,959 and $7,898 versus $7,481, respectively) and so are again dominated. Apixaban is expected to cost more than enoxaparin plus warfarin (as only six months of treatment are used, and it is inexpensive after the first three months), with an incremental cost of $550 ($7,481 versus 6,931, respectively). The resultant ICUR is $4,310 per QALY (Table 13 in Appendix 4).

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

In the six-month analysis, univariate sensitivity analysis showed that the only change from dominance was when the relative risk (RR) of a major bleed in zero to six months with rivaroxaban was changed from the base-case RR of 1.83 to 0.92. This changed the result from dominant to $9,212 per QALY.

Probabilistic analysis found that 94% of samples were dominant versus enoxaparin plus warfarin (all others were cost-effective at $50,000 per QALY), and 69% of samples were dominant versus rivaroxaban (15% of samples were cost-effective at $50,000 per QALY and 15% of samples were not cost-effective).

In the 18-month analysis, univariate sensitivity analysis versus enoxaparin plus warfarin, in no scenarios was the ICUR above $8,338 per QALY. When compared with rivaroxaban, the only change from dominance was for the RR of a major bleed beyond six months with rivaroxaban and the risk of a major bleed beyond six months with apixaban, both moving to approximately $10,000 per QALY.

Probabilistic analysis found that 100% of samples were cost-effective versus enoxaparin plus warfarin (at $50,000 per QALY), and 82% of samples were dominant versus rivaroxaban (16% of samples were cost-effective at $50,000 per QALY and 2% were not cost-effective).

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Interpretation of the evidence from the NMAs:** The NMAs were based on a limited number of trials, each with small numbers of events. As stated in the CDR clinical report, for the acute treatment and extended prevention of VTE, there were no statistically significant differences between apixaban, dabigatran, and rivaroxaban in terms of efficacy; however, there was a high degree of uncertainty related to interpreting the comparative bleeding risks associated with apixaban compared with other NOACs. If the same risk of recurrent VTE is applied for all treatments, and if a more conservative comparative risk of a major bleed between apixaban and other NOACs is assumed, the incremental QALYs and savings associated with apixaban will be considerably reduced.

- **For the 18-month analysis, the comparison with six months of enoxaparin plus warfarin followed by 12 months without treatment is not representative of current practice:** The manufacturer compared 18 months of apixaban with six months of enoxaparin plus warfarin followed by 12 months without treatment, instead of 18 months of anticoagulation. This appears questionable, as enoxaparin plus warfarin provides benefit from six to 18 months at a very low incremental cost (the main cost of enoxaparin plus warfarin occurs in its first six months). The clinical expert involved in the review indicated that if clinicians believe that the risk-benefit ratio favours pursuing anticoagulation beyond six months, then the same duration of treatment with enoxaparin plus warfarin should be applied. Comparing an 18-month anticoagulation period with a six-month treatment duration likely underestimates the QALYs in the comparator group, and thus overestimates the incremental QALYs associated with apixaban.
- **Differential rates of drug withdrawal:** The manufacturer assumed differential rates of drug discontinuation, particularly in the extended phase of treatment in which patients receiving apixaban are assumed to have a lower rate of withdrawal compared with other treatments. This is based on the NMA, in which no statistical difference in rates was observed. This assumption can increase the QALYs for apixaban, but can also increase its cost.
- **Proportion of patients able to do home INR monitoring: The true cost of INR monitoring is uncertain.** The manufacturer assumes that 50% of patients can do INR monitoring at home, whereas evidence from Alberta suggests that as few as 6% of patients could be candidates and willing to accept home monitoring.[8] Home INR monitoring is more expensive, so this assumption increases the incremental costs proportionally. The manufacturer's base case results in an annual cost for INR monitoring of $371.11. Lower annual costs have been used in previous economic evaluations.[9] In the CADTH therapeutic review on New Oral Anticoagulants Compared With Warfarin in Preventing Stroke and Other Cardiovascular Events in Patients With Atrial Fibrillation, an annual cost of $240.69 was used, which corresponds to an annual cost of $252 ($0.70 daily) when inflated to 2015 dollars.
- **Proportion of patients able to self-administer enoxaparin:** The manufacturer assumes that 75% of patients can self-administer enoxaparin, whereas other evidence from the UK suggests this might be higher (92% was assumed in National Institute for Health and Care Excellence [NICE] guidance).[10] Self-administering enoxaparin is less expensive, so this assumption potentially increases the cost of enoxaparin.
- **Utility decrement of enoxaparin plus warfarin:** The manufacturer assumes patients using enoxaparin plus warfarin have a higher utility decrement compared with patients using apixaban (and rivaroxaban) (0.013 versus 0.002). The source of these utilities is a paper by Gage et al.[11] (1996), which used direct elicitation procedures (time trade-off and standard gamble). While there might be some plausibility for this assumption, there is limited evidence to support it. If enoxaparin plus warfarin is assumed to have equal utility decrement to apixaban, similar to what was done in other reviews,[9] the incremental QALYs associated with apixaban versus enoxaparin plus warfarin will be reduced.
- **Other utilities:** The utility values for events were taken from various sources, but mostly from a study by Hogg et al. (2013)[12] that used direct elicitation approaches (standard gamble). Because CADTH recommends indirect utility approaches, which can provide smaller estimates, if alternative sources of utilities from a previous CADTH report are used on NOACs for atrial fibrillation,[9] the incremental QALYs will be reduced but apixaban still dominates.

5. CADTH COMMON DRUG REVIEW ANALYSES

CDR reanalyses were focused on the comparisons to rivaroxaban and enoxaparin plus warfarin. Although indicated for the treatment of VTE and the prevention of recurrent VTE events, at the time of the apixaban review, dabigatran had not been reviewed by CDR and therefore was not listed on any CDR-participating drug plan for this indication.

For the extended-treatment phase, a comparison with six months of enoxaparin plus warfarin followed by 12 months of aspirin is also presented in Appendix 4, although the use of this regimen for the extended prevention of VTE is still controversial.[13,14] Results of various analyses explained above when applied one by one are shown in Table 14, Table 15, and Table 16, in Appendix 4.

A conservative analysis that combines the following assumptions was performed for both six-month and 18-month analyses:

- Assumes equal VTE across apixaban, rivaroxaban, and enoxaparin plus warfarin
- Assumes equal major bleeds for apixaban and rivaroxaban for the first six months, and the lower credible interval of the NMA estimate for rivaroxaban beyond six months, and enoxaparin plus warfarin at both first six months and beyond (because AMPLIFY reported a significantly lower risk of major bleedings with apixaban versus enoxaparin plus warfarin). Note: CRNM bleeds were not changed, as the NMA results found credible intervals did not overlap 1 and CRNM bleeds did not significantly affect costs and QALYs
- Assumes equal treatment discontinuation across apixaban, rivaroxaban, and enoxaparin plus warfarin
- Assumes the proportion of patients able to do INR monitoring at home is 25% (which corresponds to an annual cost of $252, as per the CADTH therapeutic review)[9]
- Assumes the proportion of patients successfully able to self-administer enoxaparin is 92%[10]
- Assumes the utility decrement for enoxaparin plus warfarin is equal to apixaban
- Assumes the sources of utilities for other events are from an alternative source[9]
- For the 18-month analysis only, assumes anticoagulation is extended for all treatments.

The results of this analysis for six months are that apixaban and rivaroxaban have equivalent QALYs (7.898) and similar costs (apixaban costs an additional $25; $6,768 versus $6,744, respectively). While apixaban is estimated to cost slightly more, probabilistic sensitivity analysis performed by CDR suggests the incremental costs and QALYs are close to 0. Compared with enoxaparin plus warfarin, apixaban provides 0.007 additional QALYs (7.898 versus 7.891, respectively) and a small (= $45) incremental cost ($6,768 versus $6,723, respectively). The resultant ICUR is $6,425 per QALY.

The biggest difference in results from the manufacturer's submission comes in the 18-month comparison to enoxaparin plus warfarin. In this, the incremental QALYs are much smaller than those in the manufacturer's submission (as enoxaparin plus warfarin is used in months 6 to 18) and are equal to 0.009 (7.981 versus 7.974, respectively), but the incremental cost remains large (equal to $830, $7,453 versus $6,623, respectively). The resultant ICUR is $111,938 per QALY. While comparisons to rivaroxaban for the 18-month analysis are not as relevant, as rivaroxaban is currently not reimbursed by CDR-participating drug plans for the extended phase, CDR results found that apixaban provides small additional QALYs at small additional costs, resulting in an ICUR of $80,581 per QALY versus rivaroxaban.

The impact of a price reduction on the ICUR is shown in Table 2 below. A price reduction of approximately 30% would be required to bring the ICUR of an 18-month course of apixaban compared with an 18-month course of enoxaparin plus warfarin below commonly accepted thresholds.

TABLE 2: CDR REANALYSIS: PRICE REDUCTION SCENARIOS FOR 18 MONTHS OF APIXABAN VERSUS ENOXAPARIN PLUS WARFARIN

ICURs of Submitted Drug Versus Comparator		
Price	**Base-Case Analysis Submitted By Manufacturer**	**Reanalysis by CDR ($ per QALY)**
Submitted ($1.60)	Dominant	111,938
10% reduction ($1.44)	Dominant	90,538
20% reduction ($1.28)	Dominant	69,140
30% reduction ($1.12)	Dominant	47,741
40% reduction ($0.96)	Dominant	26,343
50% reduction ($0.80)	Dominant	4,943

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

6. ISSUES FOR CONSIDERATION

Rivaroxaban is the only other NOAC currently reimbursed by CDR-participating drug plans for the treatment of VTE and the prevention of recurrent VTE events. Most plans specify that rivaroxaban is to be reimbursed as an alternative to heparin plus warfarin for up to six months. When used for longer than six months, rivaroxaban is more costly than heparin plus warfarin. As such, patients with an intended duration of therapy of longer than six months should be considered for initiation on heparin plus warfarin.

7. PATIENT INPUT

Input was received from the Heart and Stroke Foundation Canada (HSFC). Responses from the 45 survey participants with blood clots indicated 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. Some patients also mentioned having to manage their disease with other forms of therapy, changing their diets, and having to take time off work. More than half of the patients indicated that their ability to perform activities has not changed, but some reported that they are unable to do the activities they have done in the past, 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. There was no comment regarding the impact of monitoring on quality of life.

8. CONCLUSIONS

CDR found a number of limitations with the manufacturer's submission. For the treatment of VTE (DVT and PE) and the prevention of recurrent VTE events, there is a high degree of uncertainty related to interpreting the comparative bleeding risks associated with apixaban compared with other NOACs. CDR reanalysis of the six-month scenario assuming similar rates of VTE and smaller differences in major bleedings suggests that apixaban is likely to provide similar QALYs at similar costs to both rivaroxaban and enoxaparin plus warfarin.

CDR reanalysis of the 18-month comparison in which apixaban was compared with 18 months of enoxaparin plus warfarin suggests the ICUR of apixaban versus enoxaparin plus warfarin could be higher than $100,000 per QALY.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 3 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may also be devices or procedures. Costs are manufacturer's list prices, unless otherwise specified. Product Listing Agreements are not reflected in the table, and as such may not represent the actual costs to public drug plans.

TABLE 3: THERAPIES FOR THE TREATMENT AND PREVENTION OF RECURRING VENOUS THROMBOEMBOLISM

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Average Daily Drug Cost ($)	Total Cost of a 6-Month Course
Apixaban (Eliquis)	**2.5 mg** **5.0 mg**	**Tablet**	**1.6000**[a]	***Treatment of acute DVT and/or PE*:** Apixaban 10 mg PO b.i.d. × 7 days, followed by 5 mg PO b.i.d. ***Continued prevention of recurrent DVT and/or PE*:** Apixaban 2.5 mg PO b.i.d. after at least 6 months of treatment for DVT or PE.	**First 7 days** **6.40** **Thereafter** **3.20**	604.80
Rivaroxaban (Xarelto)	10 mg 15 mg 20 mg	Tablet	2.8400	15 mg b.i.d. for first 3 weeks, followed by 20 mg q.d. for the continued treatment and prevention of recurrent DVT and PE	First 3 weeks: 5.68. Thereafter: 2.84	576.52
Dabigatran (Pradaxa)	110 mg 150 mg	Capsule	1.6000 1.6000	150 mg b.i.d. following treatment with a parenteral anticoagulant for 5 to 10 days	3.20[b]	861.84
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 q.d.	0.07 to 0.12	292.18 to 301.28

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Average Daily Drug Cost ($)	Total Cost of a 6-Month Course
Low-molecular-weight heparin SC						
Enoxaparin sodium (Lovenox)	30 mg/0.3 mL 40 mg/0.4 mL 60 mg/0.6 mL 80 mg/0.8 mL 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	6.3600 8.4800 12.7200 19.9600 21.2000 63.6000 25.4400 31.8000	1 mg/kg SC b.i.d. for approximately 7 days	39.92[d]	NA
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 12,500 IU/0.5 mL 15,000 IU/0.6 mL 18,000 IU/0.72 mL	Syringe	5.3460 10.6910 16.0340 21.3820 26.7260 32.0700 38.4840	200 IU/kg SC q.d. for approximately 5 days	32.07[d]	NA
Nadroparin calcium (Fraxiparine)	0.3 mL 0.4 mL 0.6 mL 0.8 mL 1.0 mL	9,500 anti-Xa IU/mL Syringe	9.1290	171 anti-XA IU/kg SC q.d. for up to 10 days	18.26[d]	NA
	0.6 mL 0.8 mL 1.0 mL	19,000 anti-Xa IU/mL Syringe	18.2580			
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	4.6800 6.5450 8.4170 18.5580 26.7490 34.3880	175 anti-Xa IU/kg SC q.d., average duration is 7 days	26.75[d]	NA
	20,000 IU/2 mL 40,000 IU/2 mL	Vial	37.0980 75.3600		22.72[d]	NA

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Average Daily Drug Cost ($)	Total Cost of a 6-Month Course
Other anticoagulants						
Fondaparinux sodium (generics)	2.5 mg /0.5 mL 7.5 mg/0.6 mL	Syringe	11.1944 17.5000[e]	2.5 mg to 10 mg SC q.d., average duration is 7 days	17.50 to 33.58[d]	NA
Heparin sodium (Heparin Leo)	10,000 IU/1 mL 50,000 IU/5 mL	Injection	1.1000[e] 5.0100[e]	333 IU/kg SC initially, followed by 250 IU/kg every 12 hours	Initial dose: 2.34.[d] Daily thereafter: 3.51.[d]	NA

b.i.d. = twice daily; DVT = deep vein thrombosis; IU = international units; NA = not applicable; PE = pulmonary embolism; PO = orally; q.d. = once daily; SC = subcutaneously.
[a] Manufacturer's submitted price, also Ontario Drug Benefit list price.
[b] Ontario Drug Benefit list price for the prevention of stroke and systemic embolism in at-risk patients with non-valvular atrial fibrillation. Dabigatran had not been submitted for this indication to CDR at the time of the apixaban review (although it has a Notice of Compliance from Health Canada for this indication).
[c] Concomitant treatment with warfarin is normally started immediately. Treatment with low-molecular-weight heparin 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.
[d] Assumes 70 kg patient weight.
[e] Quebec formulary list price (February 2015).
Source: Ontario Drug Benefit list prices (February 2015) unless otherwise indicated.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

Six-Month Analysis

TABLE 4: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS APIXABAN RELATIVE TO RIVAROXABAN?

Apixaban Vs. 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 CE ratio or net benefit calculation	Incremental cost = $25 Incremental QALYs = 0					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; vs = versus.
Note: Based on CADTH Common Drug Review reanalysis.

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS APIXABAN RELATIVE TO ENOXAPARIN PLUS WARFARIN?

Apixaban Vs. Enoxaparin plus Warfarin	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)			X			
Drug treatment costs alone		X	X			
Clinical outcomes						
Quality of life		X				
Incremental CE ratio or net benefit calculation	Incremental cost = $45 Incremental QALYs = 0.007 ICUR = $6,425 per QALY					

CE = cost-effectiveness; ICUR = incremental cost-utility ratio; NA = not applicable; QALY = quality-adjusted life-year; vs = versus.
Note: Based on CADTH Common Drug Review reanalysis.

Eighteen-Month Analysis

TABLE 6: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS APIXABAN RELATIVE TO RIVAROXABAN?

Apixaban Vs. Rivaroxaban	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone		X		X		
Clinical outcomes						
Quality of life		X				
Incremental CE ratio or net benefit calculation	Incremental cost = $127 Incremental QALYs = 0.0016 ICUR = $80,581 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; vs = versus.
Note: Based on CADTH Common Drug Review reanalysis.

TABLE 7: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS APIXABAN RELATIVE TO ENOXAPARIN PLUS WARFARIN?

Apixaban Vs. Enoxaparin plus Warfarin	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone		X		X		
Clinical outcomes						
Quality of life		X				
Incremental CE ratio or net benefit calculation	Incremental cost = $831 Incremental QALYs = 0.0.007 ICUR = $111,938 per QALY					

CE = cost-effectiveness; ICUR = incremental cost-utility ratio; NA = not applicable; QALY = quality-adjusted life-year; vs. = versus.
Note: Based on CADTH Common Drug Review reanalysis.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 8: 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"*	None		
Was the material included (content) sufficient?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		
Was the submission well organized and was information easy to locate?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		

TABLE 9: AUTHOR INFORMATION

Authors	Affiliations
Peter L. Quon Hoa H Le	Evidera

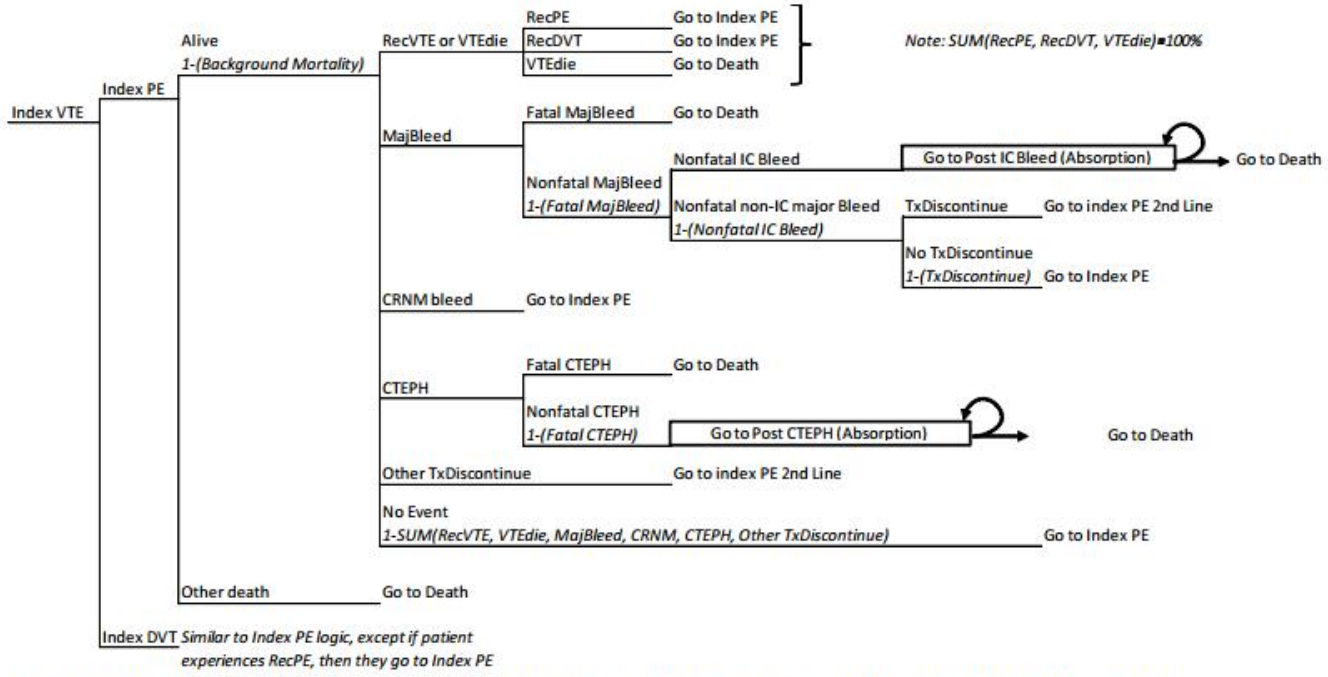
	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The model considers the cost-effectiveness and cost-utility of anticoagulant treatments on long-term costs and outcomes. A Markov model is used to simulate patients over the lifetime of their disease using a three-month cycle length. Patients enter the model having just experienced an index pulmonary embolism (PE) or deep vein thrombosis (DVT) event, and are placed in the health states "index PE" (30%) or "index DVT" (70%). The model includes 13 health states: Index PE; Index DVT; Recurrent PE; Recurrent DVT; Chronic Thromboembolic Pulmonary Hypertension; Intracranial Bleed (all intracranial bleeds are assumed to be major bleeds); Non-intracranial Major Bleed; Clinically Relevant, Non-major (CRNM) Bleed; PE Second-Line Treatment; DVT Second-Line Treatment; PE Off Treatment; DVT Off Treatment; and Death. The transitions differ between treatments based on the results of a network meta-analysis (NMA). Costs and health outcomes (venous thromboembolic event [VTE]), bleeding events, life-years (LYs), and quality-adjusted life-years (QALYs) are presented for each treatment, along with the incremental cost-effectiveness ratio (ICER).

FIGURE 1: MANUFACTURER'S MODEL STRUCTURE



Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; IC, intracranial; PE, pulmonary embolism; tmt, treatment

Note: PTS is modeled in the background in patients with index DVT.

Source: Manufacturer's pharmacoeconomic submission.[3]

TABLE 10: DATA SOURCES

Data Input	Description of Data Source	Comment
Distribution of index VTE event PE (30%) and DVT (70%)	Canadian study by Kahn et al. (2012)[15]	Patients who experience an index PE or DVT are tracked separately due to the different underlying costs, utilities, and comorbidities (CTEPH and PTS).
Efficacy	An NMA is conducted using key data from AMPLIFY and AMPLIFY-EXT for the efficacy of apixaban. • [redacted] • Distributed across VTE-related death (21.54%), recurrent PE (37.69%), recurrent DVT (40.77%). Results from AMPLIFY.	None of these differences are statistically significant and based on small number of events. Unclear whether these are meaningfully differences.
Natural history	Transitions between other health states are from various sources.	
Utilities	Utilities are taken from various sources. The baseline value is 0.85 from the CCHS. Decrements for events (PE, DVT, bleed, anticoagulation) are taken from various papers. Decrements are also related to treatment (0.002 for apixaban, rivaroxaban, and dabigatran, 0.013 for enoxaparin plus warfarin).	The types of utilities are not described — likely a mix of preference based measures (different instruments, some with Canadian weights others not) and direct utility methods. Using enoxaparin plus warfarin is assumed to have a lower decrement than other treatments.
Resource use		
AEs (Indicate which specific adverse events were considered in the model.)	An NMA is conducted using key data from AMPLIFY and AMPLIFY-EXT for the efficacy of apixaban. • [redacted] 13.5% of major bleeds are assumed to be fatal (Linkins et al. 2010) • [redacted] • CTEPH (0.0125 rate, mortality = 0%) and post-thrombotic syndrome (rate = 0).	Based on small number of events. Unclear whether these are meaningfully differences.
Mortality	Other deaths are based on Canadian life-tables adjusted to exclude mortality due to VTE and bleeding events.	
Costs		
Drug	Costs were taken from ODB program, with the exception of warfarin, whose costs were taken from the CDEC report. Unit cost • apixaban 2.5 mg $1.60 per tablet, 5 mg $1.60 per tablet	

Data Input	Description of Data Source	Comment
	• rivaroxaban 15 mg $2.84 per tablet, 20 mg $2.84 per tablet • dabigatran 150 mg $1.60 per tablet Daily price (induction) • enoxaparin $35.87 • warfarin $0.11 • apixaban $6.40 • Rivaroxaban $5.68 • dabigatran — none Daily price (long-term and extended) • enoxaparin $35.87 • warfarin $0.11 • apixaban $3.20 • rivaroxaban $2.84 • dabigatran $3.20	
Administration	Injection • It is assumed 75% of patients taking enoxaparin self-inject, based on an observational study in Ontario. Costs for training are included, as well as costs for nurse delivery in the other 25% of patients. INR tests • Monitoring of 50% of warfarin patients is assumed to be done at home, based on a study in Quebec. Other drugs • Six monitoring visits are required in the first three months, followed by three visits every three months, based on the opinion of clinical experts received during an Eliquis National Advisory Board Meeting.	This seems high, and increases the costs of warfarin substantially.
VTE event	Event costs are taken from the OCCI reference costs in 2010–2011 by relevant ICD-10 codes.	

AE = adverse event; CCHS = Canadian Community Health Survey; CDEC = Canadian Drug Expert Committee; CTEPH = chronic thromboembolic pulmonary hypertension; DVT = deep vein thrombosis; ICD = International Classification of Diseases; NMA = network meta-analysis; OCCI = Ontario Case Costing Initiative; ODB = Ontario Drug Benefit; PTS = post-thrombotic syndrome; RR = relative risk; VTE = venous thromboembolic event.

TABLE 11: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Compared with other NOACs, apixaban offers a lower risk of recurrent VTE, as well as CRNM bleeds and major bleeds.	Likely inappropriate. There are no statistically significant differences between apixaban, dabigatran, and rivaroxaban in terms of efficacy. High levels of uncertainty preclude any definite conclusion regarding potentially meaningful differences between apixaban and the other NOACs in terms of bleeding risk.
Patients at higher risk of VTE beyond 6 months of treatment would not use enoxaparin plus warfarin.	Inappropriate. If clinicians believe that the risk-benefit ratio favours pursuing anticoagulation beyond 6 months, then the same duration of treatment with enoxaparin plus warfarin should be applied.
75% of patients taking enoxaparin self- inject.	Higher rates reported in the literature. This might overestimate the costs of enoxaparin.
50% of warfarin self-monitoring is assumed to be done by patients at home.	Much lower rates reported in the literature. This might overestimate warfarin monitoring costs.
Treatment discontinuation assumed to differ across treatments.	Likely inappropriate. NMA found no significant difference in discontinuation rates.
Patients using enoxaparin have a higher utility decrement compared with apixaban (and rivaroxaban) (–0.013 vs. –0.002).	Potentially inappropriate. No evidence to support this assumption.

CRNM = clinically relevant, non-major; NOAC = new oral anticoagulant; NMA = network meta-analysis; vs. = versus; VTE = venous thromboembolic event.

Manufacturer's Results

TABLE 12: MANUFACTURER'S BASE-CASE RESULTS FOR THE ACUTE-TREATMENT PHASE (SIX MONTHS)

	Apixaban	Enoxaparin/ Warfarin	Rivaroxaban	Dabigatran
Total cost	6,804.20	6,930.85	$6,821.63	$7,207.17
Total LY	9.344	9.316	9.334	9.318
Total QALY	7.855	7.824	7.845	7.831
Incremental cost (compared with apixaban)	-	–126.65	–17.43	–402.97
Incremental LY (compared with apixaban)	-	0.028	0.010	0.026
Incremental QALY (compared with apixaban)	-	0.031	0.010	0.024
ICER $/LY	-	Dominant	Dominant	Dominant
ICUR $/QALY	-	Dominant	Dominant	Dominant

ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; LY = life-year; QALY = quality-adjusted life-year.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[3]

Univariate sensitivity analysis showed that the only change from dominance was for the RR of a major bleed in 0 to six months with rivaroxaban (from base case RR of 1.83 to 0.92), resulting in a change from dominant to $9,212 per QALY.

Probabilistic analysis found that 94% of samples are dominant versus enoxaparin plus warfarin (all others were cost-effective at $50,000 per QALY), and 69% of samples were dominant versus rivaroxaban (the other 15% of samples were cost-effective at $50,000 per QALY).

TABLE 13: MANUFACTURER'S BASE-CASE RESULTS FOR THE EXTENDED-TREATMENT PHASE (18 MONTHS)

	Apixaban	Enoxaparin/ Warfarin	Rivaroxaban	Dabigatran
Total cost	7481	6930.85	7959	7898.3
Total LY	9.444	9.316	9.314	9.412
Total QALY	7.938	7.824	7.819	7.91
Incremental cost (compared with apixaban)	-	–126.65	–17.43	–402.97
Incremental LY (compared with apixaban)	-	0.028	0.010	0.026
Incremental QALY (compared with apixaban)	-	0.031	0.010	0.024
ICER $/LY	-	4827.78	Dominant	Dominant
ICUR $/QALY	-	4309.79	Dominant	Dominant

ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; LY = life-year; QALY = quality-adjusted life-year.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[3]

A univariate sensitivity analysis versus enoxaparin plus warfarin found no scenarios in which ICER was above $8338 per QALY. Compared with rivaroxaban, the only change from dominance was for the RR of a major bleed beyond six months with rivaroxaban and the risk of a major bleed beyond six months with apixaban, both moving to approximately $10,000 per QALY.

A probabilistic analysis found that 100% of samples were cost-effective versus enoxaparin plus warfarin (at $50,000 per QALY), and 82% of samples were dominant versus rivaroxaban (the other 16% of samples were cost-effective at $50,000 per QALY).

CADTH Common Drug Review Reanalysis

CDR undertook a number of reanalyses to assess the impact of some of the limitations identified with the manufacturer's model:

1. **Assuming equal VTE across apixaban, rivaroxaban, and enoxaparin plus warfarin**
2. **Assuming equal major bleeds for apixaban and rivaroxaban at six months, and the lower credible interval for rivaroxaban (18 months) and enoxaparin plus warfarin, as AMPLIFY reported a significantly lower risk with apixaban versus enoxaparin plus warfarin (six months and 18 months)**
   For major bleeds, if the risk for apixaban is assumed to be equal to the risk for rivaroxaban, the incremental costs are reduced sufficiently that it no longer remains dominant but still has a favourable ICUR $6,028 per QALY. The NMA does find the risk of major bleeds to be significantly

greater for enoxaparin plus warfarin than apixaban, but if the risk is changed to the lower credible interval (1.89), the incremental costs and QALYs also reduce but apixaban remains dominant.
In the 18-month analysis: assuming equal VTE increases the incremental costs and QALYs for apixaban (since the NMA suggests that patients on apixaban have slightly more events). However, assuming the risk of major bleeds decreased for both rivaroxaban and enoxaparin plus warfarin beyond six months (lower credible intervals of the NMA) compared with apixaban results in ICURs of $27,760 per QALY versus rivaroxaban and $29,227 per QALY versus enoxaparin plus warfarin.

3. **Assuming equal treatment discontinuation across apixaban, rivaroxaban, and enoxaparin plus warfarin**
   Six-month analysis: apixaban still dominates rivaroxaban and enoxaparin plus warfarin.
   Eighteen-month analysis: apixaban still dominates rivaroxaban. ICUR versus enoxaparin plus warfarin nearly doubles from $4,828 per QALY to $9,446 per QALY.
4. **Assuming the proportion of patients able to do INR monitoring at home is 6% or 25%**
   Changing from 50% to 6% does not change the dominance of apixaban, although it decreases the savings associated with apixaban.
   Changing from 50% to 25% has little influence on the results, although it decreases the savings associated with apixaban.
5. **Assuming the proportion of patients successfully able to self-administer enoxaparin is 92%**
   While changing from 75% to 92% does not change the dominance of apixaban, it does decrease incremental costs.
6. **Assuming the utility decrement for enoxaparin plus warfarin is equal to apixaban**
   If enoxaparin plus warfarin is assumed to have an equal utility decrement to apixaban, the incremental QALYs associated with apixaban versus enoxaparin plus warfarin are reduced substantially, although apixaban remains dominant.
7. **Assuming the sources of utilities for other events are from an alternative source**
   When alternative sources of utilities from a previous CADTH report (NOACs for atrial fibrillation) are used, the incremental QALYs are reduced, but apixaban still dominates.
8. **For the 18-month analysis only, assuming anticoagulation is extended during 18 months instead of six months for all treatments**
   The ICUR for apixaban versus enoxaparin plus warfarin nearly doubles, from $4,828 per QALY to $9,449 per QALY.

TABLE 14: CADTH COMMON DRUG REVIEW REANALYSES OF SIX-MONTH TREATMENT (ACUTE)

		Total Cost ($)			QALYs			ICUR ($ per QALY)		Recurrent VTE and VTE-Related Death			Major Bleeds			Anticoagulant-Related Costs($)		
	Scenario Description	**API**	**RIV**	**Warf**	**API**	**RIV**	**Warf**	**Vs. RIV**	**Vs. Warf**	**API**	**RIV**	**Warf**	**API**	**RIV**	**Warf**	**API**	**RIV**	**Warf**
	Reference	6,804	6,822	6,931	7.8546	7.8452	7.8238	Dominant	Dominant	606	606	607	137	141	149	815	788	821
1	Equal incidence of VTE-related death and recurrent VTE compared with API	6,804	6,814	6,912	7.8546	7.8482	7.8311	Dominant	Dominant	606	605	604	137	141	149	815	788	821
2	Equal risk of bleed compared with API for RIV and lower confidence interval for Lenox/warf (RIV from RR = 1.83 to 1.0. Enox/warf from RR = 3.33 to 1.89)	6,804	6,787	6,871	7.8546	7.8517	7.8349	6,028	Dominant	606	607	609	137	137	141	815	789	823
3	Equal risk of bleed compared with API (RIV from RR = 1.83 to 1.0. Enox/warf from RR = 3.33 to 1.0)	6,804	6,787	6,833	7.8546	7.8517	7.8419	6,028	Dominant	606	607	609	137	137	136	815	789	824
4	Combination of 1 and 2	6,804	6,780	6,815	7.8546	7.8546	7.8492	Dominated	Dominant	606	605	606	137	137	137	815	789	824
5	Equal discontinuation	6,804	6,821	6,931	7.8546	7.8452	7.8238	Dominant	Dominant	606	606	607	137	141	149	815	787	822
6	Reduced proportion of patients able to do INR monitoring at home from 50% to 6%[8]	6,757	6,774	6,761	7.8546	7.8452	7.8238	Dominant	Dominant	606	606	607	137	141	149	767	741	651
7	Reduced proportion of patients able to do INR monitoring at home from 50% to 25%	6,777	6,795	6,835	7.8546	7.8452	7.8238	Dominant	Dominant	606	606	607	137	141	149	788	761	725
8	Increased proportion of patients successfully able to self-administer enox from 75% to 92% (NICE)[10]	6,795	6,813	6,899	7.8546	7.8452	7.8238	Dominant	Dominant	606	606	607	137	141	149	806	779	789
9	Utility decrement of enox/warf equal to API (from 0.013 to 0.002)	6,804	6,822	6,931	7.8566	7.8473	7.8311	Dominant	Dominant	606	606	607	137	141	149	815	788	821
10	Alternative utility decrements (PE from 0.1 to 0.022. Bleeds from	6,804	6,822	6,931	7.8962	7.8869	7.8653	Dominant	Dominant	606	606	607	137	141	149	815	788	821

		Total Cost ($)			QALYs			ICUR ($ per QALY)		Recurrent VTE and VTE-Related Death			Major Bleeds			Anticoagulant-Related Costs($)		
	0.2, 0.058 and 0.07 to 0.092, 0.013, 0.013)																	
11	Assume 100% of baseline events are DVT (change % to 100%)	4,292	4,313	4,439	7.8601	7.8507	7.8292	Dominant	Dominant	613	613	614	139	144	151	817	790	835
12	Assume 100% of baseline events are PE (change %PE to 100%)	12,619	12,629	12,699	7.8414	7.8321	7.8107	Dominant	Dominant	589	590	591	131	135	143	809	783	791
13	**CDR-combined reanalysis (combination of 1, 2, 5, 6, 8, 9, and 10)**	**6,768**	**6,744**	**6,723**	**7.8983**	**7.8983**	**7.8913**	**NA**	**$6,425**	**606**	**606**	**605**	**137**	**137**	**141**	**779**	**753**	**693**

API = apixaban; CDR = CADTH Common Drug Review; DVT = deep vein thrombosis; enox = enoxaparin; ICUR = incremental cost-utility ratio; INR = international normalized ratio; NA = not applicable; NICE = National Institute for Health and Care Excellence; PE = pulmonary embolism; QALY = quality-adjusted life-year; RIV = rivaroxaban; RR = relative risk; vs = versus; VTE = venous thromboembolic event; warf = warfarin.

TABLE 15: CDR REANALYSES OF 18-MONTH TREATMENT (EXTENDED): ASSUMING 18 MONTHS OF WARFARIN

		Total Cost ($)			QALYs			ICUR ($ per QALY)		Recurrent VTE and VTE-Related Death			Major Bleeds			Anticoagulant-Related Costs($)		
	Scenario Description	**API**	**RIV**	**Warf**	**API**	**RIV**	**Warf**	**Vs. RIV**	**Vs. Warf**	**API**	**RIV**	**Warf**	**API**	**RIV**	**Warf**	**API**	**RIV**	**Warf**
	Reference	7,481	7,959	6,931	7.9377	7.8189	7.8238	Dominant	4,828	521	512	607	136	18	149	1,764	1,584	821
1	18 months warf instead of 6 months	7,481	7,959	6,980	7.9377	7.8189	7.8847	Dominant	9,449	521	512	515	136	218	162	1,764	1,584	1,051
2	Assume equal incidence of VTE-related death & recurrent VTE vs API (18 months)	7,481	7,952	6,986	7.9377	7.8217	7.8850	Dominant	9,387	521	510	518	36	18	162	1,764	1,584	1,054
3	Assume lower CrI for enox/warf (RR = 1.09) and RIV (RR = 1.54)	7,481	7,35	6,817	7.9377	7.9332	7.9150	27,760	29,227	521	522	517	136	136	141	1,764	1,618	1,057
4	Assume equal risk of bleed vs API (18 months)	7,481	7,346	6,778	7.9377	7.9351	7.9224	51,766	45,705	521	522	517	136	136	136	1,764	1,618	1,059
5	Combination of 2 and 3	7,481	7,348	6,824	7.9377	7.9361	7.9151	79,179	29,098	521	521	521	136	136	141	1,764	1,618	1,060
6	Assume equal discontinuation	7,481	7,967	6,984	7.9377	7.8185	7.8851	Dominant	9,446	521	511	514	136	218	162	1,764	1,590	1,056

		Total Cost ($)			QALYs			ICUR ($ per QALY)		Recurrent VTE and VTE-Related Death			Major Bleeds			Anticoagulant-Related Costs($)		
7	Reduced proportion of patients able to do INR monitoring at home (6%)	7,444	7,923	6,680	7.9377	7.8189	7.8847	Dominant	14,407	521	512	515	136	218	162	1,727	1,548	752
8	Reduced proportion of patients able to do INR monitoring at home (25%)	7,460	7,939	6,811	7.9377	7.8189	7.8847	Dominant	12,244	521	512	515	136	218	162	1,743	1,564	882
9	Increased proportion of patients successfully able to self-administer enox/warf	7,474	7,952	6,950	7.9377	7.8189	7.8847	Dominant	9,891	521	512	515	136	218	162	1,757	1,577	1,021
10	Utility decrement of enox/warf equal to API	7,481	7,959	6,980	7.9393	7.8205	7.9006	Dominant	12,953	521	512	515	136	218	162	1,764	1,584	1,051
11	Alternative utility decrements	7,481	7,959	6,980	7.9819	7.8625	7.9430	Dominant	12,901	521	512	515	136	218	162	1,764	1,584	1,051
12	Assume 100% of baseline events are DVT	4,924	5,437	4,444	7.9434	7.8242	7.8903	Dominant	9,037	528	519	522	138	221	164	1,768	1,588	1,065
13	Assume 100% of baseline events are PE	13,398	13,795	12,848	7.9242	7.8064	7.8715	Dominant	10,428	504	496	498	129	212	155	1,754	1,575	1,020
14	**CDR-combined reanalysis (combination of 1, 2, 3, 6, 8, 9, 10, and 11)**	**7,453**	**7,326**	**6,623**	**7.9813**	**7.9797**	**7,9739**	**80,581**	**111,938**	**521**	**520**	**520**	**136**	**137**	**141**	**1,736**	**1,596**	**861**

API = apixaban; CDR = CADTH Common Drug Review; CrI = credible interval; DVT = deep vein thrombosis; enox = enoxaparin; ICUR = incremental cost-utility ratio; INR = international normalized ratio; PE = pulmonary embolism; QALY = quality-adjusted life-year; RIV = rivaroxaban; VTE = venous thromboembolic event; warf = warfarin.

TABLE 16: CDR REANALYSES OF 18-MONTH TREATMENT (EXTENDED): ASSUMING SIX MONTHS OF WARFARIN FOLLOWED BY 12 MONTHS OF ASPIRIN

		Total Cost ($)			QALYs			ICUR ($ per QALY)		Recurrent VTE and VTE-Related Death			Major Bleeds			Anticoagulant-Related Costs ($)		
	Scenario Description	**API**	**RIV**	**Warf**	**API**	**RIV**	**Warf**	**Vs. RIV**	**Vs. Warf**	**API**	**RIV**	**Warf**	**API**	**RIV**	**Warf**	**API**	**RIV**	**Warf**
	Reference	7,481	7,959	6,931	7.9377	7.8189	7.8238	Dominant	4,828	521	512	607	136	218	149	1,764	1,584	821
1	6 months of warf followed by 12 months of Aspirin	7,481	7,959	6,980	7.9377	7.8189	7.8847	Dominant	9,449	521	512	515	136	218	162	1,764	1,584	1,051
2	Assume equal incidence of VTE-related death and recurrent VTE compared with API (18 months)	7,481	7,952	6,912	7.9377	7.8217	7.8311	Dominant	5,332	521	510	604	136	218	149	1,764	1,584	821
3	Assume lower CrI for enox/warf (RR = 1.89) and RIV (RR = 1.54)	7,481	7,355	6,871	7.9377	7.9332	7.8349	27,760	5,939	521	522	609	136	136	141	1,764	1,618	823
4	Assume equal risk of bleed compared with API (18 months)	7,481	7,346	6,833	7.9377	7.9351	7.8419	51,766	6,756	521	522	609	136	136	136	1,764	1,618	824
5	Combination of 2 and 3	7,481	7,348	6,852	7.9377	7.9361	7.8423	79,179	6,588	521	521	605	136	136	141	1,764	1,618	823
6	Equal discontinuation	7,481	7,967	6,931	7.9377	7.8185	7.8238	Dominant	4,825	521	511	607	136	218	149	1,764	1,590	822
7	Reduced proportion of patients able to do INR monitoring at home (6%)	7,444	7,923	6,761	7.9377	7.8189	7.8238	Dominant	5,998	521	512	607	136	218	149	1,727	1,548	651
8	Reduced proportion of patients able to do INR monitoring at home (25%)	7,460	7,939	6,835	7.9377	7.8189	7.8238	Dominant	5,487	521	512	607	136	218	149	1,743	1,564	725
9	Increased proportion of patients successfully able to self-administer enox/warfarin	7,474	7,952	6,899	7.9377	7.8189	7.8238	Dominant	5,050	521	512	607	136	218	149	1,757	1,577	789
10	Utility decrement of enox/warf equal to API	7,481	7,959	6,931	7.9393	7.8205	7.8311	Dominant	5,083	521	512	607	136	218	149	1,764	1,584	821
11	Alternative utility decrements	7,481	7,959	6,931	7.9819	7.8625	7.8726	Dominant	5,035	521	512	607	136	218	149	1,764	1,584	821

		Total Cost ($)			QALYs			ICUR ($ per QALY)		Recurrent VTE and VTE-Related Death			Major Bleeds			Anticoagulant-Related Costs ($)		
12	Assume 100% of baseline events are DVT	4,924	5,437	4,439	7.9434	7.8242	7.8292	Dominant	4,252	528	519	614	138	221	151	1,768	1,588	835
13	Assume 100% of baseline events are PE	13,398	13,795	12,699	7.9242	7.8064	7.8107	Dominant	6,159	504	496	591	129	212	143	1,754	1,575	791
14	**CDR-combined reanalysis (combination of 1, 2, 3, 6, 7, 9, 10, and 11)**	**7,453**	**7,326**	**6,584**	**7.9813**	**7.9797**	**7.9354**	**80,581**	**18,927**	**521**	**521**	**554**	**136**	**137**	**144**	**1,736**	**1,591**	**693**

API = apixaban; CDR = CADTH Common Drug Review; DVT = deep vein thrombosis; enox = enoxaparin; ICUR = incremental cost-utility ratio; INR = international normalized ratio; PE = pulmonary embolism; QALY = quality-adjusted life-year; RIV = rivaroxaban; RR = relative risk; VTE = venous thromboembolic event; warf = warfarin.

REFERENCES

1. CDR submission: Eliquis™ (apixaban) 2.5 mg and 5 mg tablets. Company: Bristol-Myers Squibb Canada and Pfizer Canada Alliance [**CONFIDENTIAL** manufacturer's submission]. Montreal (QC): Bristol-Myers Squibb Canada and Pfizer Canada Alliance; 2014 Sep.
2. [Pr]Eliquis® (apixaban): 2.5 mg and 5 mg tablets [product monograph]. Montreal (QC): Bristol-Myers Squibb Canada and Pfizer Canada Alliance; 2015 Feb 20.
3. Pharmacoeconomic evaluation. In: CDR submission: Eliquis™ (apixaban) 2.5 mg and 5 mg tablets. Company: Bristol-Myers Squibb Canada and Pfizer Canada Alliance. [**CONFIDENTIAL** manufacturer's submission]. Montreal (QC): Bristol-Myers Squibb Canada and Pfizer Canada Alliance; 2014 Sep.
4. Clinical Study report: AMPLIFY (NCT00643201): a safety and efficacy trial evaluating the use of apixaban in the treatment of symptomatic deep vein thrombosis and pulmonary embolism [**CONFIDENTIAL** internal manufacturer's report]. New York: Pfizer; 2013 Sep 17.
5. Clinical Study report: AMPLIFY-EXT (NCT00633893): a safety and efficacy trial evaluating the use of apixaban for the extended treatment of deep vein thrombosis and pulmonary embolism [**CONFIDENTIAL** internal manufacturer's report]. New York: Pfizer; 2013 Sep 26.
6. Abacus International. Systematic review/meta-analysis of novel oral anti-coagulants (NOACs) in the initial/long-term treatment of venous thromboembolism (VTE). In: CDR submission: Eliquis™ (apixaban) 2.5 mg and 5 mg tablets. Company: Bristol-Myers Squibb Canada and Pfizer Canada Alliance [**CONFIDENTIAL** manufacturer's submission]. Montreal (QC): Bristol-Myers Squibb Canada and Pfizer Canada Alliance; 2014 Sep 3.
7. Abacus International. Systematic review/meta-analysis of novel oral anti-coagulants (NOACs) in the extended treatment of venous thromboembolism (VTE). In: CDR submission: Eliquis™ (apixaban) 2.5 mg and 5 mg tablets. Company: Bristol-Myers Squibb Canada and Pfizer Canada Alliance [**CONFIDENTIAL** manufacturer's submission]. Montreal (QC): Bristol-Myers Squibb Canada and Pfizer Canada Alliance; 2014 Sep 3.
8. Cepoiu M, Fyie K, Higgins L, Rose S, Lorenzetti D, Youssefi M, et al. Point-of-care testing for oral anticoagulant management with portable prothrombin time systems [Internet]. Calgary: University of Calgary; 2010 Mar 19. [cited 2015 Feb 11]. Available from: http://www.health.alberta.ca/documents/AHTDP-PPTS2-UofC-STE.pdf
9. Wells G, Coyle D, Cameron C, Steiner S, Coyle K, Kelly S, et al. Safety, effectiveness, and cost-effectiveness of new oral anticoagulants compared with warfarin in preventing stroke and other cardiovascular events in patients with atrial fibrillation [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2012 Apr 9. [cited 2015 Feb 11]. (Therapeutic review). Available from: http://www.cadth.ca/media/pdf/NOAC_Therapeutic_Review_final_report.pdf
10. Rivaroxaban for treating pulmonary embolism and prevention of recurrent venous thromboembolism: costing template [Internet]. London: National Institute for Health and Care Excellence; 2013 Jun. [cited 2015 Feb 11]. (NICE TA287). Available from: http://www.nice.org.uk/guidance/ta287/resources/ta287-pulmonary-embolism-and-recurrent-venous-thromboembolism-rivaroxaban-costing-template
11. Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. Arch Intern Med. 1996 Sep 9;156(16):1829-36.
12. Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating quality of life in acute venous thrombosis. JAMA Intern Med. 2013 Jun 24;173(12):1067-72.

13. Brighton TA, Eikelboom JW, Mann K, Mister R, Gallus A, Ockelford P, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. N Engl J Med. 2012 Nov 22;367(21):1979-87.

14. Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini E, Silingardi M, et al. Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med. 2012 May 24;366(21):1959-67.

15. Kahn SR, Springmann V, Schulman S, Martineau J, Stewart JA, Komari N, et al. Management and adherence to VTE treatment guidelines in a national prospective cohort study in the Canadian outpatient setting. The Recovery Study. Thromb Haemost. 2012 Sep;108(3):493-8.