# CDEC FINAL RECOMMENDATION

## APIXABAN
## (Eliquis — Bristol-Myers Squibb Canada and Pfizer Canada)
## Indication: Venous Thromboembolic Events

**Recommendation:**
The Canadian Drug Expert Committee (CDEC) recommends that apixaban be listed for the treatment of venous thromboembolic events (VTE) (deep vein thrombosis [DVT] and pulmonary embolism [PE]) and prevention of recurrent DVT and PE, for a duration of up to six months, if the following condition is met:

**Condition:**
- Drug plan costs for apixaban should provide cost savings relative to drug plan costs for other new oral anticoagulants (NOACs).

**Reasons for the Recommendation:**
1. One randomized controlled trial (RCT) (AMPLIFY; N = 5,400) demonstrated that apixaban was non-inferior, but not superior, to enoxaparin plus warfarin for reducing the risk of recurrent VTE or VTE-related death after six months of treatment (relative risk [RR] 0.84; 95% confidence interval [CI], 0.60 to 1.18).
2. There are no studies directly comparing apixaban against other NOACs for the treatment and prevention of VTE. The results of seven indirect comparisons demonstrated no added clinical benefit with apixaban versus other NOACs for both acute and extended VTE treatment.
3. Because of the use of placebo as a comparator in the AMPLIFY-EXT trial (N = 2,486), the comparative clinical benefit of apixaban over alternative treatments is uncertain for the treatment of VTE for a duration greater than six months.
4. Apixaban was statistically superior to enoxaparin plus warfarin for major bleeding over six months in AMPLIFY (RR 0.31; 95% CI, 0.17 to 0.54); however, the comparative major bleeding risk of apixaban compared with other NOACs is uncertain due to inconsistency and limitations in the available indirect comparisons.
5. Reanalysis of the manufacturer's pharmacoeconomic model conducted by the CADTH Common Drug Review (CDR) suggested that apixaban is associated with similar quality-adjusted life-years (QALYs) and costs to both rivaroxaban and enoxaparin plus warfarin for six months of treatment. CDR reanalysis suggested that the incremental cost-utility ratio (ICUR) for apixaban versus enoxaparin plus warfarin could exceed $100,000 per QALY, when both treatments are used for 18 months; therefore, apixaban is not considered to be cost-effective versus enoxaparin plus warfarin beyond six months of treatment.

**Background:**
Apixaban has a Health Canada indication for the treatment of VTE (DVT and PE) and prevention of recurrent DVT and PE. The recommended dose of apixaban for the treatment of acute DVT or PE is 10 mg twice daily for seven days, followed by 5 mg twice daily; the recommended dose for continued prevention of recurrent VTE is 2.5 mg twice daily after at least six months of treatment for DVT or PE. Duration of therapy should be individualized after careful assessment of the balance between anticoagulant treatment benefit and individual risk of bleeding; patients with transient risk factors should receive treatment for at least three months, while extended duration therapy is recommended for patients with permanent risk factors or idiopathic VTE.

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

***Patient Input Information***
The following is a summary of key information provided by one patient group, consisting of patients and caregivers, which responded to the CDR call for patient input:

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

***Clinical Trials***
The CDR systematic review included two RCTs. AMPLIFY (N = 5,400) evaluated the non-inferiority of apixaban to a regimen of warfarin and enoxaparin in patients with confirmed symptomatic DVT or PE with a risk of recurrence. The primary efficacy outcome was the incidence of symptomatic recurrent VTE or VTE-related death at six months. Non-inferiority (NI) would be demonstrated if the upper bound of the corresponding 95% CI was below the NI margins of 1.8 for the RR and 0.035 for the risk difference (RD). If NI was demonstrated, then superiority for major bleeding, the primary safety outcome, would be tested, followed by superiority for VTE or VTE-related death.

AMPLIFY-EXT (N = 2,486) evaluated the superiority of apixaban over placebo for extended VTE treatment in patients who were previously diagnosed with symptomatic DVT or PE, had completed approximately six to 12 months of anticoagulation therapy, and did not experience a VTE recurrence during that treatment period. Patients who had participated in AMPLIFY were eligible for enrolment in AMPLIFY-EXT and represented 34% of the study population.

***Outcomes***

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

- Recurrent VTE or VTE-related death — defined as the adjudicated composite of symptomatic recurrent non-fatal DVT or PE, or VTE-related death
- Recurrent VTE or all-cause mortality — defined as the adjudicated composite of symptomatic recurrent non-fatal DVT or PE, or all-cause mortality
- Major bleeding — defined as acute clinically overt bleeding associated with a fall in the hemoglobin level of 2 g/dL or more; or transfusion of two or more units of packed red blood cells or 1,000 mL or more of whole blood; or bleeding in a critical site or that was fatal
- Serious adverse events, total adverse events, withdrawals due to adverse events, and notable harms.

***Efficacy***

<u>Acute Treatment of Venous Thromboembolic Events (AMPLIFY)</u>

- Apixaban was shown to be non-inferior, but not superior, to enoxaparin plus warfarin for the primary efficacy outcome of recurrent VTE or VTE-related death after six months of treatment. The use of apixaban was associated with the following RRs compared with enoxaparin plus warfarin:
  - Intention-to-treat population: 0.84 (95% CI, 0.60 to 1.18); *P* < 0.0001 for NI [redacted]
- The proportion of patients who experienced individual events classified as non-fatal DVT, non-fatal PE, VTE-related death, or all-cause mortality was low in the AMPLIFY trial and there were no statistically significant differences between apixaban and enoxaparin plus warfarin for these individual end points. The proportion of patients with events and the associated RRs for these events were as follows (apixaban versus enoxaparin plus warfarin):
  - Non-fatal DVT: 0.8% versus 1.3%; [redacted]
  - Non-fatal PE: 1.0% versus 0.9%; [redacted]
  - VTE-related death: 0.4% versus 0.6%; [redacted]
  - All-cause mortality: 1.6% versus 2.0%; 0.79 (95% CI, 0.53 to 1.19).
- The proportion of patients requiring hospitalization while receiving study treatment was slightly lower in the apixaban group compared with the enoxaparin plus warfarin group ([redacted]). The duration of the hospital stay was two days shorter on average for patients in the apixaban group compared with enoxaparin plus warfarin ([redacted]). However, no statistical analysis was reported.

<u>Prevention of Recurrence of Venous Thromboembolic Events (AMPLIFY-EXT)</u>

- Apixaban was statistically superior to placebo for the proportion of patients who experienced VTE or all-cause mortality (3.8% with apixaban versus 11.6% with placebo) and the proportion of patients who experienced VTE or VTE-related death ([redacted]). The RRs for apixaban versus placebo were:
  - VTE or VTE-related death: [redacted]; *P* < 0.0001 for superiority
  - VTE or all-cause mortality: 0.33 (95% CI, 0.22 to 0.48); *P* < 0.0001 for superiority.
- Apixaban was statistically superior to placebo for the proportion of patients who experienced non-fatal DVT (*P* < 0.0001). There was no statistically significant difference between

apixaban and placebo for non-fatal PE, VTE-related death, and all-cause mortality. The RRs for these individual events were:
  - Non-fatal DVT: [redacted]
  - Non-fatal PE: [redacted]
  - VTE-related death: [redacted]
  - All-cause mortality: [redacted].
- The proportion of patients requiring hospitalization was slightly lower in the apixaban treatment group compared with placebo (5.0% versus 7.5%, respectively). The duration of the hospital stay was [redacted] shorter on average for patients in the apixaban group versus placebo ([redacted]). However, no statistical analysis was reported.

***Harms (Safety and Tolerability)***

Acute Treatment of Venous Thromboembolic Events (AMPLIFY)

- Results from AMPLIFY demonstrated the superiority of apixaban over the combination of enoxaparin and warfarin for the primary safety outcome of major bleeding (RR 0.31; 95% CI, 0.17 to 0.54, *P* < 0.0001 for superiority). Apixaban was superior to enoxaparin plus warfarin for clinically relevant non-major (CRNM) bleeding (RR 0.48; 95% CI, 0.38 to 0.60, *P* < 0.0001 for superiority). Notable bleeding events included fatal bleeding (one patient with apixaban versus two patients with enoxaparin plus warfarin), intracranial bleeding (three patients versus six patients, respectively), and gastrointestinal bleeding (six patients versus 17 patients, respectively).
- At least one serious adverse event was reported for 16% of patients in the apixaban group and 15% of patients in the enoxaparin plus warfarin group. The most commonly reported serious adverse events were [redacted].
- At least one adverse event was reported for 67% and 72% of patients in the apixaban and in the enoxaparin plus warfarin treatment groups, respectively.
- Withdrawals due to adverse events were reported for 6.1% and 7.4% of patients in the apixaban and in the enoxaparin plus warfarin treatment groups, respectively.

Prevention of Recurrence of Venous Thromboembolic Events (AMPLIFY-EXT)

- The comparison between apixaban and placebo for the continued prevention of VTE in the AMPLIFY-EXT study yielded inconclusive results for the primary safety outcome of major bleeding. The small number of events reported in both the apixaban (n = 2) and the placebo (n = 4) treatment groups leads to substantial uncertainty surrounding the results.
- At least one serious adverse event was reported for 13% of patients in the apixaban group and 19% of patients in the placebo group. The most commonly reported serious adverse events were [redacted].
- At least one adverse event was reported for 71% and 73% of patients in the apixaban and in the placebo groups, respectively.
- Withdrawals due to adverse events were reported for 8.0% and 16.2% of patients in the apixaban and in the placebo groups, respectively. The most commonly reported reasons were [redacted].

***Cost and Cost-Effectiveness***

The manufacturer submitted a cost-utility analysis comparing apixaban with low-molecular-weight heparins (LMWHs) (enoxaparin) plus vitamin K antagonist (warfarin), and NOACs including rivaroxaban and dabigatran over a lifetime horizon in patients who require anticoagulation for treatment of VTE and prevention of recurrent events, from a public payer perspective. Two base-case analyses were presented: an acute treatment phase of six months, and an extended treatment period of 18 months. In the acute treatment phase, all the comparators were used for six months, while in extended analysis, the NOACs were used for 18 months, but enoxaparin plus warfarin was used for six months only, followed by no treatment for the remaining 12 months. A Markov model including 13 health states (such as type of index VTE event, recurrent VTE, adverse events, and death) and a three-month cycle length was used. Patients entered the model following a VTE event and were classified as "index PE" or "index DVT." Results of two manufacturer-funded network meta-analyses (NMAs) — one for acute treatment and one for extended treatment of VTE — were used to inform the risk of VTE and VTE-related death, major bleeding, and CRNM bleeding, as well as treatment discontinuation. Patients were assigned disutilities for events from external published sources (not from the AMPLIFY trials). Costs for each event were taken primarily from the Ontario Case Costing Initiative. The unit costs of drugs were from the Ontario Ministry of Health Drug Benefit Formulary. Costs of international normalized ratio (INR) monitoring and enoxaparin administration were based on assumptions regarding the number of patients who would perform INR monitoring at home and would self-administer LMWH.

In the manufacturer's base case, apixaban was dominant (less costly, more QALYs) over other NOACs for both six-month and 18-month analyses. Compared with enoxaparin plus warfarin, apixaban was dominant in the six-month analysis, and resulted in an ICUR of $4,310 per QALY in the 18-month analysis.

CDR identified a number of limitations with the submitted pharmacoeconomic evaluation, such as uncertainty regarding the findings from the NMA; overestimation of administration and monitoring costs for 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 enoxaparin plus warfarin in the extended treatment phase. CDR reanalyses accounting for the above limitations suggest that for the acute treatment phase (six months), apixaban is likely to provide similar QALYs at similar costs to both rivaroxaban and enoxaparin plus warfarin. For the extended treatment phase (18 months), the ICUR for apixaban compared with enoxaparin plus warfarin could be higher than $100,000 per QALY.

Apixaban is priced at $1.60 per tablet regardless of strength (2.5 mg or 5 mg). When only drug costs are considered, at the recommended daily doses, the cost of a six-month course of apixaban is estimated at $604.80, which is more expensive than a six-month course of rivaroxaban ($576.52) or a six-month course of enoxaparin plus warfarin (ranging between $292.18 and $301.28, assuming seven days of enoxaparin at $39.92 daily based on a 70 kg patient, and treatment with warfarin at $0.07 to $0.12 daily, not including monitoring and administration costs).

**Other Discussion Points:**

CDEC noted the following:

- Uncertainty remains regarding the optimal treatment duration for VTE. Recommendations from major guidelines and experience from clinical practice suggest that the decision to extend anticoagulation should be based upon an individual risk-versus-benefit profile.
- CDR reviewed two indirect comparisons submitted by the manufacturer, as well as five published indirect comparisons that assessed the efficacy and safety of apixaban with other anticoagulants including NOACs, for the acute treatment and continued prevention of VTE. The NMAs suggested that apixaban has similar efficacy to other NOACs for acute and extended VTE treatment, and that apixaban is at least as safe as the other NOACs with respect to the risk of bleeding.

**Research Gaps:**

CDEC noted that there is insufficient evidence regarding the following:

- There are no studies directly comparing apixaban against other NOACs for the treatment and prevention of VTE.
- The comparative efficacy of apixaban versus extended warfarin therapy for the prevention of recurrent VTE.

**CDEC Members:**

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**April 8, 2015 Meeting**
**Regrets:**

None

**Conflicts of Interest:**

None

**About This Document:**

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The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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