CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

RIVAROXABAN
(Xarelto® – Bayer Inc.)

Description:
Rivaroxaban is an oral antithrombotic agent that directly inhibits Factor Xa. Rivaroxaban is indicated for the prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement (THR) or total knee replacement (TKR) surgery.

Dosage Forms:
10 mg tablet. The recommended dose is 10 mg once daily, started 6 to10 hours after surgery.

Recommendation:
The Canadian Expert Drug Advisory Committee recommends that rivaroxaban, at a dose of 10 mg daily, be listed for prophylaxis of venous thromboembolism following total knee replacement or total hip replacement surgery, for up to two weeks, as an alternative to low molecular weight heparins.

Reasons for the Recommendation:
1. In one large trial in THR patients and two large trials in TKR patients, rivaroxaban, compared with enoxaparin, was associated with a statistically significantly lower incidence of the composite primary outcome of venographic deep vein thrombosis, non-fatal pulmonary embolism and all-cause deaths. Rivaroxaban was associated with a similar, or lower incidence of composite outcomes that included clinically relevant events (major VTE and symptomatic VTE), compared to enoxaparin.

2. In the manufacturer's economic evaluation in TKR patients, rivaroxaban was associated with better clinical outcomes and lower overall costs relative to enoxaparin, assuming both agents are used for 14 days. The results were robust to extensive sensitivity analysis.

3. In the manufacturer's economic evaluation in THR patients, the manufacturer reports that rivaroxaban was associated with a cost per quality adjusted life year (QALY) gained of $40,000 if rivaroxaban is used for 35 days and enoxaparin is used for 14 days, which are reflective of the treatment durations in one of the clinical trials. Based on CDR re-analyses using clinical and costing assumptions which the Committee felt were more likely, the incremental cost per QALY for 35 days of rivaroxaban prophylaxis compared with a 14 day course of enoxaparin (the duration commonly funded by many drug plans at present), may be significantly less attractive. No studies have addressed whether there is additional clinical benefit gained by using rivaroxaban for 35 days, compared with using it for a

shorter duration. The Committee felt that the cost effectiveness of prolonged prophylaxis with rivaroxaban in THR was uncertain and as such, that there was insufficient evidence to justify recommending prophylaxis beyond 14 days.

Summary of Committee Considerations:

The Committee considered a systematic review of five double blind randomized controlled trials (RCTs) evaluating the effects of rivaroxaban compared to enoxaparin in patients who underwent elective THR (N=7923, 3 trials) or TKR surgery (N=5679, 2 trials). One of these trials was a phase II THR study (N=873), the other four were phase III trials. The primary outcome for all trials was a composite of the incidence of deep vein thrombosis (DVT) assessed by venography, non-fatal pulmonary embolism (PE) and all-cause deaths. Major VTE was a secondary composite outcome that included proximal DVT, PE and VTE-related deaths. Symptomatic VTE was also evaluated as a composite outcome and included symptomatic DVT, PE or death due to PE. Only one TKR trial used the Canadian approved enoxaparin dose (30 mg twice daily) initiated post-operatively; all other trials used enoxaparin 40 mg once daily initiated pre-operatively. Duration of rivaroxaban therapy was 35 days in the two largest THR studies, 12 days in both TKR studies and 10 days in the smaller phase II THR study. Duration of enoxaparin therapy was the same as rivaroxaban in all studies except one THR study, in which it was given for 14 days and rivaroxaban was given for 35 days. Three of the four phase III trials were designed to accept non-inferiority of rivaroxaban compared to enoxaparin for the primary outcome if the upper limit of the 95% confidence interval for the absolute treatment difference was below 3.5 to 4%. A non-inferiority margin of 1.5% was selected for the outcome of major VTE for these three trials. The fourth phase III trial was designed to test the superiority of rivaroxaban over enoxaparin in THR patients.

Compared to enoxaparin, rivaroxaban was associated with statistically significant reductions in the incidence of the primary outcome in all five studies. The difference between treatment arms was largely attributable to reductions in asymptomatic DVT measured by venography at the end of the treatment period. The incidence of major VTE was statistically significantly reduced compared to enoxaparin 40 mg once daily in two of the phase III THR studies and one of the TKR studies. There was no statistically significant difference between rivaroxaban and enoxaparin 30 mg twice daily in major VTE in the other TKR trial. Given that measurement of the primary outcome required a venogram, it is noteworthy that 30 to 40% of patients in each of the studies did not have evaluable venograms. While this is a common shortcoming of VTE trials, it reduces confidence in the results. The incidence of symptomatic VTE was statistically significantly lower in the rivaroxaban treatment arm, compared to enoxaparin, in one of the TKR trials and one of the THR trials.

There were no statistically significant differences between rivaroxaban and enoxaparin in the incidence of death or pulmonary embolism, though studies were not powered to detect such a difference. Major bleeding occurred at a rate less than 1% in all trials, and while numerically higher with rivaroxaban than enoxaparin in four of five trials, the differences were small and not statistically significant. In a pooled analysis of all five trials, serious adverse events occurred at a lower rate in the rivaroxaban group than the enoxaparin group.

The manufacturer submitted a cost-utility analysis comparing rivaroxaban to enoxaparin. For TKR, the manufacturer reported that rivaroxaban is less costly and associated with more QALYs than enoxaparin if both agents are used for 14 days. The results of the analyses for TKR were robust to extensive sensitivity analyses. In the manufacturer's economic evaluation in THR patients, the manufacturer reports that rivaroxaban was associated with cost per quality adjusted life year (QALY) gained of $40,000 if rivaroxaban is used for 35 days and enoxaparin is used for 14 days, which are reflective of the treatment durations in one of the clinical trials. Based on CDR re-analyses using clinical and costing assumptions which the Committee felt were more likely, the incremental cost per QALY for 35 days of rivaroxaban

prophylaxis compared with a 14 day course of enoxaparin, may be significantly less attractive. No studies have addressed whether there is additional clinical benefit gained by using rivaroxaban for 35 days, compared with using it for a shorter duration. The Committee felt that the cost effectiveness of prolonged prophylaxis with rivaroxaban in THR was uncertain and as such, that there was insufficient evidence to justify recommending prophylaxis beyond 14 days.

The daily cost of rivaroxaban ($9.92) is greater than enoxaparin 40 mg daily ($8.00), dalteparin ($9.45), and warfarin (approximately $0.40), but lower than enoxaparin 30 mg twice daily ($12.06) and fondaparinux ($15.08).

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.
2. There is potential for use of rivaroxaban in conditions outside the approved indication. The Committee had concerns about the possible off-label use for indications such as treatment of VTE, acute coronary syndrome and cardioembolic prophylaxis for non-valvular atrial fibrillation, in the absence of adequate clinical trial data to support such use.
3. Given that there is uncertainty regarding the cost-effectiveness of VTE prophylaxis beyond 14 days, CEDAC recommends that reimbursement of other agents for extended prophylaxis of VTE after 14 days of rivaroxaban use should not be provided.
4. Rivaroxaban is contraindicated in patients receiving concomitant systemic treatment with inhibitors of CYP3A4 and P-glycoprotein since this may lead to an increased bleeding risk. Rivaroxaban is not recommended for use in patients with severe renal impairment.
5. Low molecular weight heparins are considered appropriate comparators to rivaroxaban and are the most frequently used agents for prophylaxis of VTE following THR and TKR surgery in Canada. Warfarin is another oral agent used for prophylaxis of VTE following THR and TKR surgery - this agent requires laboratory monitoring. Given that its use has declined significantly since the introduction of the low molecular weight heparins, the Committee felt that comparison of rivaroxaban with the low molecular weight heparins was appropriate.

Background:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.