

Recommendations and Reasons

Committee to Evaluate Drugs (CED)

Rivaroxaban

Product:

RIVAROXABAN (Xarelto®) 10mg tablet

Class of drugs:

Anticoagulant

Indication:

Prevention of venous thromboembolic events (blood clots)

Manufacturer:

Bayer Inc.

CED Recommendation-

The CED recommended that rivaroxaban (Xarelto®) 10 mg tablet be listed on the Ontario Drug Benefit (ODB) Formulary for the prevention of blood clots for 14 days following total knee replacement surgery and total hip replacement surgery.

Executive Officer Decision

Given the CED's recommendation and based on a subsequent listing agreement that addresses utilization, the Executive Officer decided to list rivaroxaban as a General Benefit on the ODB Formulary.

Status

Funding available on the Ontario Drug Benefit Formulary.

Highlights of Recommendation:

- ◆ Rivaroxaban is an oral anti-clotting agent, used to prevent venous thromboembolic events (VTE), or blood clots, in patients who have undergone elective total hip replacement (THR) or total knee replacement (TKR) surgery. Blood clots that travel from veins in the leg to the lungs, known as pulmonary embolism, can be fatal.
- ◆ The CED reviewed 5 studies that compared rivaroxaban to enoxaparin. No statistical difference in adverse events and in post-discharge hospitalizations were found.
- ◆ The manufacturer did not submit any studies comparing rivaroxaban to dalteparin, the low molecular weight heparin most commonly prescribed in Ontario, or comparing rivaroxaban to warfarin, an oral drug that has been available for a long time and is commonly prescribed to prevent blood clots.
- ◆ Because patients can take rivaroxaban orally, and do not require home care visits or laboratory processing of blood test results, as compared to warfarin, this medication could reduce overall health-care costs.
- ◆ However, there is no data on whether the risk of bleeding with rivaroxaban, as compared to warfarin, would result in additional doctor visits or hospitalizations, which could increase overall health-care costs and offset the lower laboratory monitoring costs.
- ◆ Rivaroxaban costs less than enoxaparin per day, but is much more expensive than warfarin. Its cost-effectiveness is unclear when taken longer than 14 days post-hospital discharge, which is likely for patients following total hip replacement surgery.
- ◆ The CED expressed concerns about the significant potential for physicians to prescribe rivaroxaban for other conditions where its use has not been approved, such as for patients with irregular heart beats, who require anti-clotting medication.

- ◆ Overall, the CED acknowledged that rivaroxaban is at least as clinically effective as enoxaparin for preventing blood clots following total knee replacement surgery and total hip replacement surgery. Using rivaroxaban for 14 days post-hospital discharge to prevent blood clots demonstrates value-for-money when compared with enoxaparin.

Background:

Major orthopaedic surgery, such as total hip replacement and total knee replacement, is associated with a high risk of developing blood clots. A small number of those patients (< 2%) who experience a blood clot will have a clot in the lungs which is fatal if not on preventative therapy.

Other drugs that may be used to prevent blood clots include oral warfarin and low molecular weight heparin (LMWH) given by injection such as enoxaparin, fondaparinux and dalteparin.

Rivaroxaban is a new oral anti-clotting agent, taken once daily to prevent blood clots in patients who have undergone elective total hip or total knee replacement surgery.

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Detailed Discussion:

- ◆ The CED considered 5 double-blinded randomized controlled trials comparing enoxaparin to rivaroxaban in elective surgery patients: RECORD-1 (Eriksson, 2008), RECORD-2 (Kakkar, 2008), RECORD-3 (Lassen, 2008), RECORD-4 (Turpie, 2008) and study 11527 (Eriksson, 2006).
- ◆ Despite the design differences of the 5 studies, the results were similar across all of them. No clinically significant differences in hospitalizations post-discharge, non-fatal lung clots, serious adverse events, major bleeding, non-major bleeding, and withdrawals were noted between rivaroxaban and enoxaparin treatment groups. There was no statistically significant difference between rivaroxaban and enoxaparin 30 mg injected twice daily in major VTE (proximal deep vein clots, lung clots, and VTE-related death).
- ◆ There were no trials comparing rivaroxaban to dalteparin, the most commonly prescribed low molecular weight heparin in Ontario.
- ◆ There are no trials comparing rivaroxaban to warfarin, the only other oral comparator.
- ◆ The optimal duration of blood clot prevention therapy post-orthopaedic surgery has not been determined. While rivaroxaban could be used up to 35 days after hip surgery, it remains unclear if this long-term approach is required for all patients given the diminishing risk of VTE as the patient gets further from the date of surgery.
- ◆ There is no antidote for rivaroxaban overdose and long-term post-marketing safety data were not provided. The CED noted that there is also no antidote for low molecular weight heparins and the half-life of rivaroxaban is relatively short.
- ◆ As an oral medication, rivaroxaban is more convenient to take than enoxaparin, which is given by subcutaneous injection, and has the potential to reduce other health-care costs such as costs associated with home care.
- ◆ Laboratory monitoring is not required with rivaroxaban, which would reduce the cost for laboratory monitoring and/or home care associated with warfarin therapy. There were no available data on the risk of bleeding with rivaroxaban, as compared to warfarin, which would lead to patient safety concerns and could offset the lower laboratory costs.

- ◆ Rivaroxaban costs less per day than 30 mg of enoxaparin subcutaneously injected twice daily, but is much more expensive than warfarin.
- ◆ The cost-effectiveness of rivaroxaban depends on the duration of prevention therapy and the cost-effectiveness beyond 14 days is unclear, particularly in total hip replacement surgery.
- ◆ The CED expressed concerns about the high potential for off-label use of rivaroxaban, particularly in patients with atrial fibrillation, a type of irregular heart rhythm who may require anti-clotting medication.
- ◆ **Overall, the CED noted that rivaroxaban is at least as clinically effective as enoxaparin for blood clot prevention following total knee replacement and total hip replacement surgery. Prevention therapy with rivaroxaban for 14 days post-hospital discharge is cost-effective when compared to enoxaparin but the cost-effectiveness beyond 14 days is unclear.**

CEDAC Recommendation:

(<http://www.cadth.ca/index.php/en/cdr/recommendations>)

The Canadian Expert Advisory Committee (CEDAC) recommended listing rivaroxaban (Xarelto®), at a dose of 10 mg daily, to prevent blood clots following total knee replacement or total hip replacement surgery, for up to two weeks after discharge from hospital, as an alternative to low molecular weight heparins.



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