CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

DABIGATRAN ETEXILATE
(Pradax® – Boehringer Ingelheim Canada Ltd.)

Description:
Dabigatran, administered as dabigatran etexilate, is an oral antithrombotic agent. It is a reversible direct thrombin inhibitor 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:
Supplied as 75 mg and 110 mg capsules. The recommended initial dose is 110 mg given one to four hours after surgery, followed by 220 mg once daily thereafter.

Recommendation:
The Committee recommends that dabigatran not be listed.

Reasons for the Recommendation:
1. Non-inferiority compared with enoxaparin was not demonstrated in the REMOBILIZE study, which was the only phase III trial which compared dabigatran 220 mg with the Health Canada approved dose of enoxaparin (30 mg twice daily) following TKR. In this study, dabigatran use was associated with a higher incidence of the primary outcome (composite of deep vein thrombosis, non-fatal pulmonary embolism and all-cause deaths) which was statistically significant and clinically important. This finding, the large *a priori* non-inferiority margins, and the wide confidence intervals observed for key analyses reduce confidence in the claim that dabigatran is non-inferior to enoxaparin.

Summary of Committee Considerations:
The Committee considered a systematic review of three double blind randomized controlled trials (RCTs) evaluating the effects of dabigatran compared to enoxaparin in patients who underwent elective THR (n=3494, 1 trial) or TKR surgery (n=4716, 2 trials). A double blind placebo-controlled RCT performed in patients in Japan undergoing TKR was also considered (n=512). The primary outcome for all trials was a composite of the incidence of deep vein thrombosis (DVT) assessed by venography, non-fatal pulmonary embolism and all-cause deaths. Major VTE was a secondary composite outcome that included proximal DVT, PE and VTE-related deaths. Symptomatic DVT events were also evaluated. In one TKR trial, the comparator agent was enoxaparin 30 mg twice daily, initiated post-operatively, while in two trials, the comparator was enoxaparin 40 mg once daily, initiated pre-operatively. Duration of drug prophylaxis was 35 days in the THR study, 8 days and 15 days in the active control TKR studies, and 14 days in the

placebo controlled trial. The three active control studies were designed to accept non-inferiority of dabigatran compared to enoxaparin for the primary outcome if the upper limit of the 95% confidence interval for the absolute treatment difference was below 7.7-9.2% (i.e. favouring enoxaparin). This was interpreted by the Committee as being a large non-inferiority margin. The placebo controlled trial was designed to test the superiority of dabigatran in TKR patients.

Compared to placebo, dabigatran 220 mg daily was associated with statistically significant reductions in the primary outcome and major VTE. Compared to enoxaparin 30 mg twice daily (the Health Canada approved dose), dabigatran 220 mg daily was associated with a statistically significant increase in the incidence of the primary outcome in the REMOBILIZE study. The primary outcome was heavily influenced by asymptomatic DVT identified through screening venograms in approximately 70% of patients. While asymptomatic DVTs were numerically the majority of primary outcome composite events, the Committee did not discount it as a surrogate measure of symptomatic events and therefore it provided a basis for the recommendation. The incidence of the primary outcome was similar in the dabigatran 220 mg daily and enoxaparin 40 mg daily treatment arms in the other TKR study and the only THR study. As such, dabigatran 220 mg met the predefined criteria for non-inferiority in these two studies. The rates of major VTE were similar in the dabigatran 220 mg and enoxaparin treatment groups in all three active comparator studies. A venogram was required to assess the primary outcome, but 25 to 30% of patients in the studies did not have evaluable venograms and while this is a common shortcoming of VTE trials, it reduces confidence in the results. The incidence of symptomatic DVT in the trials was between 1 to 2% and was similar between the dabigatran and enoxaparin treatment arms.

There were no statistically significant differences between dabigatran and enoxaparin in the incidence of death or pulmonary embolism, though the studies were not powered to detect such a difference. Major bleeding occurred at a rate of 1 to 2% in all trials and the differences between dabigatran and enoxaparin were small and not statistically significant. Serious adverse events occurred at a similar rate in the dabigatran and enoxaparin treatment groups.

The manufacturer submitted a cost utility analysis comparing dabigatran to enoxaparin in patients undergoing THR or TKR surgery. Several scenarios considered in the cost-utility analysis performed by the manufacturer reported differences in quality adjusted life years (QALYs) that favoured enoxaparin, although these gains were very small. In these scenarios, there were some cost savings associated with dabigatran use compared with enoxaparin. However, these cost savings were not considered sufficient to offset the higher incidence of venous thrombosis seen in the REMOBILIZE trial.

The daily cost of dabigatran ($7.85) is greater than warfarin (approximately $0.40), but less than enoxaparin ($12.38 for 30mg twice daily or $8.20 for 40mg daily), dalteparin ($9.45) 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 dabigatran 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.

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.

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