PUBLIC SUMMARY DOCUMENT
Product: Dabigatran etexilate mesilate, capsules, 75 mg, 110 mg (base), Pradaxa®
Sponsor: Boehringer Ingelheim Pty Limited
Date of PBAC Consideration: March 2009

1. Purpose of Application
The submission sought a restricted benefit listing for dabigatran for prevention of venous thromboembolic events (VTE) in adult patients undergoing total hip replacement (THR) surgery.

2. Background
This was the first time dabigatran had been considered by the PBAC.

3. Registration Status
Dabigatran was registered by the TGA on 24 November 2008 for prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement).

4. Listing Requested and PBAC's View
Restricted Benefit
Prevention of venous thromboembolic events in adult patients undergoing total hip replacement surgery.

In the Pre-Subcommittee Response the sponsor had no objection to an Authority Required listing.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
Dabigatran would provide an alternative treatment for VTE prevention in patients undergoing total hip replacement.

6. Comparator
Enoxaparin 40 mg given 12 hours preoperatively and then once daily for 30 days post surgery.

Although the PBAC accepted that subcutaneous enoxaparin injection was an appropriate main comparator at the time the submission was lodged, the PBAC considered that oral rivaroxaban tablet was a more appropriate comparator given that it is also a new oral therapy for the prevention of VTE in patients undergoing elective total replacement of the hip (or knee).

7. Clinical Trials
The submission presented one three-arm randomised trial (RE-NOVATE) comparing dabigatran 220 mg for 28-35 days and dabigatran 150 mg for 28-35 days with enoxaparin 40 mg 28-35 days in patients undergoing elective total hip replacement surgery.

The trial had been published at the time of the submission, as follows:

Trial/First author	Protocol title	Publication Citation
Direct randomised trials		
Eriksson et al	Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial.	Lancet 2007; 370: 949-56.
Eriksson et al	Dabigatran etexilate is effective and safe for the extended prevention of venous thromboembolism following total hip replacement.	J Thromb Haemost, 2007; 5(S2): Abstr O-W-049.

8. Results of Trials

The submission presented results of the primary composite outcome, total VTE and all cause mortality, the disaggregated components of this outcome and the main secondary outcome, major VTE and VTE related mortality for both dabigatran 200 mg and 150 mg versus enoxaparin.

The RE-NOVATE trial was designed as a non-inferiority trial, with a pre-specified non-inferiority margin of an absolute risk difference of 7.7% for the primary outcome of total VTE and all cause mortality based on preserving two-thirds of the 95% CI difference between enoxaparin and placebo. Non-inferiority was inferred if the upper margin of the 95% confidence interval for the absolute risk difference did not exceed this margin.

The PBAC noted a number of published trials assessing new antithrombotic drugs compared to enoxaparin for the prevention of VTE in patients undergoing THR surgery have considered absolute risk differences in total VTE of 4-5% as being clinically important.

(1). *Dabigatran 220 mg versus enoxaparin 40 mg.*
In the comparison of dabigatran 220 mg and enoxaparin 40 mg, the result for the primary outcome, total VTE and all cause mortality, met both the predefined non-inferiority criterion of an absolute risk difference of no more than 7.7%, and the more stringent criterion on the basis of previous literature (a difference of no more than 4%).

The results were heavily weighted by the large proportion of asymptomatic DVT, the clinical significance of which is still debated, especially distal asymptomatic DVT, which account for > 75% of the observed events in the dabigatran treatment arm and 93% in the enoxaparin arm.

The rates of symptomatic DVT, non-fatal PE and death (VTE not ruled out), were all higher in the dabigatran 220 mg treatment arm than in the enoxaparin arm, although the trial was not sufficiently powered for testing for statistically significant differences in these uncommon events.

(2). *Dabigatran 150 mg versus enoxaparin 40 mg.*
In the comparison of dabigatran 150 mg and enoxaparin 40 mg, the result for the primary outcome, total VTE and all cause mortality (RD 1.9%, 95%CI -0.6%, 4.4%), met the predefined non-inferiority criterion of an absolute risk difference of no more than 7.7%. However, it failed to meet the more stringent non-inferiority criterion of a difference of no

more than 4.0% but was within the 4-5% range, noted by the PBAC to be clinically important in a number of published trials.

The results were also heavily weighted by the large proportion of asymptomatic DVT cases. The interpretation of the results for the main secondary outcome, major VTE and VTE-related death (RD 0.4%, 95%CI -1.5%, 2.2%) was difficult as no non-inferiority margin was specified for this outcome. However, the narrow confidence interval was suggestive of non-inferiority.

The PBAC noted the trial subjects for this comparison were not representative of those for whom this dose of dabigatran is recommended. A reduced dose of dabigatran, 150 mg daily, is recommended in patients with moderate renal impairment (creatinine clearance 30-50 mL/min). Patients with moderate renal impairment only represented 4.7% of the full analysis set (FAS) and 5.2% of the safety population in the dabigatran 150 mg treatment group.

The PBAC noted in terms of being an alternative in patients with moderate renal impairment, there were insufficient numbers of patients in this subgroup across the trials presented in the pre-PBAC response to assess the comparative benefits and harms of the 150 mg and 220 mg daily doses.

Between 23-26% of randomised participants were excluded from the analysis of the primary outcome in each of the treatment arms. The main reason for exclusion was lack of confirmed VTE data. The PBAC was advised the submission did not adequately address the potential for bias due to such high exclusion rates and the possible effects on the validity of the results. Baseline characteristics for the primary efficacy analysis set were not provided. Due to this, it was difficult to compare the characteristics of patients with and without missing data to assess whether missing data were randomly distributed. Excluded participants were fairly evenly distributed between the three treatment groups and the reasons for exclusion were similar.

The primary safety outcome in the RE-NOVATE trial was incidence of bleeding events, comprising of major bleeding events (MBE), clinically relevant bleeding events (CRBE), and any bleeding events. The results are presented in the following table. The submission also provided a summary of other adverse events.

Summary of bleeding events during the treatment period[a] (safety population)

Trial ID	Dabigatran n (%)	Enoxaparin n (%)	Risk Difference RD % (95%CI)	Relative Risk (95% CI)
Dabigatran 220 mg vs enoxaparin 40 mg				
	N=1146	N=1154		
Major bleeding[b]	23 (2.0)	18 (1.6)	0.45 (-0.63, 1.53)	1.29 (0.70, 2.37)
Clinically relevant bleeding	48 (4.2)	40 (3.5)	0.72 (-0.85, 2.29)	1.21 (0.80, 1.82)
Minor bleeding	70 (6.1)	74 (6.4)	-0.30 (-2.28, 1.68)	0.95 (0.69, 1.31)
Bleeding requiring discontinuation	1 (<0.1)	1 (<0.1)	*0.00 (-0.24, 0.24)*	*1.01 (0.06, 16.1)*
Dabigatran 150 mg vs enoxaparin 40 mg				
	N=1163	N=1154		
Major bleeding[b]	15 (1.3)	18 (1.6)	-0.27 (-1.24, 0.70)	0.83 (0.42, 1.63)
Clinically relevant bleeding	55 (4.7)	40 (3.5)	1.26 (-0.35, 2.88)	1.36 (0.92, 2.03)

Minor bleeding Bleeding requiring discontinuation	72 (6.2) 1 (<0.1)	74 (6.4) 1 (<0.1)	-0.22 (-2.20, 1.76) *0.00 (-0.24, 0.24)*	0.97 (0.71, 1.32) *0.99 (0.06, 15.8)*

CI=confidence interval; CRBE=clinically relevant bleeding events; MBE=major bleeding events; RD=risk difference.

[a] The treatment period was defined as the time from the first administration of study drug until 3 days after the last administration of study drug.

[b] Primary safety outcome.

The rates of treatment-emergent bleeding events in the dabigatran treatment groups were fairly similar to those in the enoxaparin group, although the incidence of more severe bleeding events (MBE and clinically relevant bleeding events) tended to be higher with both doses of dabigatran. There was insufficient statistical power to draw any firm conclusions regarding the incidence of major bleeding events with dabigatran compared to enoxaparin.

The rates of any adverse event (AE) resulting in prophylaxis discontinuation or hospitalisation, and any serious AE, were similar for all three treatment groups.

There was also insufficient data to accurately determine the comparative incidence of AEs of special interest, such as hepatic and cardiac events for the two drugs, although the incidence of cardiac events tended to be higher in both the dabigatran groups compared to enoxaparin. Little information was available regarding the potential for other rare or delayed adverse events.

There was minimal information on the safety of dabigatran 150 mg in patients with moderate renal impairment, the population for which this dose is recommended. Analyses of the incidence of adverse events in different subgroups of patients, such as different ages, patients with specific co-morbidities, or patients with risk factors for VTE or bleeding, was not provided in the submission.

For further PBAC comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that both dabigatran 220 mg and dabigatran 150 mg is non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety to enoxaparin 40 mg for short term prophylaxis of VTE in patients undergoing elective total hip replacement.

For PBAC comments on these results, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis on the basis that dabigatran 220 mg and dabigatran 150 mg were equi-effective to enoxaparin 40 mg.

The PBAC concluded that oral dabigatran 110 mg twice daily was no more effective, but possibly less safe, than subcutaneous enoxaparin 40 mg once daily.

The submission claimed a cost saving for dabigatran 220 mg/day over enoxaparin 40 mg/day taking account of drug, home visits, preoperative administration and heparin-induced thrombocytopenia (HIT) costs, as appropriate, over a 30-day therapy duration.

The result of the cost analysis presented in the submission relied on the acceptance of the estimated cost-offsets related to the provision of other healthcare resources.

The result suggested that use of dabigatran 220 mg/day produced a cost saving when compared to enoxaparin 40 mg/day when both the costs of medication and other healthcare resources were considered, however this was reliant on cost-offsets and assumptions with respect to their value, which were considered uncertain.

11. Estimated PBS Usage and Financial Implications

The submission estimated a financial cost/year to the PBS of< $10 million in up to Year 5 of listing.

The validity of these estimates was unclear due to uncertainty regarding the uptake rate of dabigatran, and the current level of use of enoxaparin for this indication was unknown.

12. Recommendation and Reasons

The PBAC deferred its consideration of dabigatran as Authority Required for the prevention of venous thromboembolic events in an adult patient undergoing elective total hip replacement in order to give the applicant an opportunity to compare dabigatran with rivaroxaban, another new oral therapy available for the same patient population.

Although the PBAC accepted that subcutaneous enoxaparin injection was an appropriate main comparator at the time the submission was lodged, the PBAC considered that oral rivaroxaban tablet was a more appropriate comparator given that it is also a new oral therapy for the prevention of venous thromboembolic events in patients undergoing elective total replacement of the hip (or knee). Although the sponsor of dabigatran comments briefly on this new alternative in its pre-PBAC response, it argues that an indirect comparison involving enoxaparin as the common reference would be inappropriate because of methodological differences in the trials.

As a separate issue, the PBAC did not accept that the 150 mg daily dose was adequately justified. In terms of being a dosing alternative, noninferiority was not clearly established compared with enoxaparin 40 mg daily if using the more stringent noninferiority margin of 4% absolute risk difference in the primary outcome of total VTE and all cause mortality. In terms of being an alternative in patients with moderate renal impairment, there were insufficient numbers of patients in this subgroup across the trials presented in the pre-PBAC response to assess the comparative benefits and harms of the 150 mg and 220 mg daily doses.

The primary outcome analysed in the enoxaparin-controlled randomised trial was a composite measure, which was dominated by a relatively large number of asymptomatic events detected by venography that had no direct patient relevance (especially asymptomatic distal deep vein thromboses). Across the trial, there were about 25% of patients who were not assessed for this primary outcome mainly due to problems with venography, but loss to follow-up was similar across the arms of the trial. Thus the conclusion for non-inferiority rested on an interpolation that the composite outcome results reflected the results for each of the rarer and directly patient-relevant types of events included in the composite outcome.

The PBAC was concerned that the point estimates for treatment-emergent bleeding, although not statistically significant, tended to favour enoxaparin over dabigatran. This is of concern

because of the small therapeutic window between reducing clinically important thrombotic events and increasing clinically important bleeding; the paucity of evidence available in the extended assessment of harms and the likelihood that these trials were underpowered to detect this outcome.

The PBAC concluded that oral dabigatran 220 mg once daily was no more effective, but possibly less safe, than subcutaneous enoxaparin 40 mg once daily in the restriction requested for PBS listing.

The PBAC considered that a comparison with rivaroxaban was relevant, given the concurrent PBAC consideration of rivaroxaban. The PBAC therefore deferred its consideration of dabigatran to give the applicant an opportunity to compare the two new oral therapies for the prevention of venous thromboembolic events.

Recommendation:
Defer

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Boehringer Ingelheim has sought the advice of the PBAC on a new submission to enable dabigatran to be listed on the PBS.