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

1. Purpose of Application

The submission sought an Authority Required listing for dabigatran for prevention of venous thromboembolic events in adult patients undergoing total hip replacement (THR) and total knee replacement (TKR).

2. Background

At the March 2009 meeting, the PBAC deferred its consideration of dabigatran as an Authority Required listing for the prevention of venous thromboembolic events in an adult patient undergoing elective total hip replacement. Although, PBAC concluded that oral dabigatran 220 mg once daily was no more effective, but possibly less safe than subcutaneous enoxaparin 40 mg once daily, the Committee considered that a comparison with rivaboxaban was also relevant. The Committee also considered there was insufficient data to support subsidy of the dabigatran 150 mg daily dose. Rivoxaban was not listed at the time of submission. *(See also March 2009 Public Summary Document)*

3. Registration Status

Dabigatran was TGA registered on 24 November 2008 for the 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

Authority Required
Prevention of venous thromboembolic events in a patient undergoing total hip replacement surgery.

Authority Required
Prevention of venous thromboembolic events in a patient undergoing total knee replacement surgery.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Venous thromboembolic events (VTE) represent a major cause of morbidity and a significant cause of mortality in hospitalised patients. Total hip replacement and total knee replacement are high risk factors for VTE, affecting around 50% of patients if no thromboprophylaxis is given.

Dabigatran would provide an alternative oral treatment for prevention of venous thromboembolic events in patients undergoing total hip replacement and total knee replacement surgery.

6. Comparator

The submission nominated enoxaparin 40 mg once daily as the comparator. The PBAC had previously requested a comparison with rivaroxaban 10 mg. noting that rivaroxaban had been recommended for listing at its March 2009 meeting.

The submission stated that no head-to-head trials are available for dabigatran and rivaroxaban, and argued that an indirect analysis between the two drugs was inappropriate on methodological grounds. The submission stated that the results presented consider only the comparisons between dabigatran versus enoxaparin and rivaroxaban versus enoxaparin. No formal statistical indirect comparison was made between dabigatran and rivaroxaban because this was considered inappropriate.

7. Clinical Trials

Total hip replacement

The submission presented one three arm randomised trial comparing dabigatran 220 mg once daily for 28-35 days and dabigatran 150 mg once daily for 28-35 days with enoxaparin 40 mg once daily for 28-35 days (RE-NOVATE), and one randomised trial comparing rivaroxaban 10 mg once daily for 35 days with enoxaparin 40 mg once daily for 35 days (RECORD 1).

Total knee replacement

The submission presented one three arm randomised trial comparing dabigatran 220 mg once daily for 8±2 days and dabigatran 150 mg once daily for 8±2 days with enoxaparin 40 mg once daily for 8±2 days (RE-MODEL), and one randomised trial comparing rivaroxaban 10 mg once daily for 10-14 days with enoxaparin 40 mg once daily for 10-14 days (RECORD 3).

The key trials published at the time of the submission are shown in the table below:

Trial ID/First author	Protocol title/ Publication title	Publication citation
Common reference enoxaparin		
Dabigatran vs enoxaparin trials		
Total hip replacement		
RE-NOVATE Eriksson BI, Dahl OE, Rosencher N, 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 BI, Dahl OE, Buller HR, et al.	A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial.	J Thromb Haemost 2005; 3(1): 103-11.
Total knee replacement		
Eriksson BI, Dahl OE, Rosencher N, et al.	Oral dabigatran etexilate vs subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial.	Haemostasis 2007; 5: 2178-2185.
BISTRO II	As above	
The RE-MOBILIZE Writing Committee (2008).	The oral thrombin inhibitor dabigatran etexilate vs the North American Enoxaparin Regimen for the prevention of venous thromboembolism after knee arthroplasty surgery.	The Journal of Arthroplasty 2009;24(1): 1-9.

Friedman et al (2007).	Dabigatran etexilate versus enoxaparin in preventing venous thromboembolism following total knee arthroplasty.	J Thromb Haemost 2007; 5(Suppl 1): Abstr O-W-051.
Rivaroxaban vs enoxaparin trials		
Total hip replacement		
RECORD 1 Eriksson BI, Borris LC. et al.	Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty.	New England Journal of Medicine 2008, 358(26): 2765-2775.
Eriksson BI, Borris LC, et al.	Oral Rivaroxaban Compared with Subcutaneous Enoxaparin for Extended Thromboprophylaxis after Total Hip Arthroplasty: The RECORD1 Trial.	ASH Annual Meeting Abstracts 2007, vol. 110, no. 11, Abstract 6.
RECORD 2 Kakkar AK et al.	Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial.	Lancet, published online 25th July 2008 Lancet 2008; 372 (9632):31-39
ODIXa-HIP2 Eriksson et al.	Oral, direct Factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement.	J Thromb Haemost 2006; 4: 121-128.
ODIXaHIP-OD Eriksson et al.	A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement.	Circulation, 2006; 114: 2374-2381.
ODIXaHip Eriksson *et al*.	Dose-escalation study of rivaroxaban (BAY 59-7939) – an oral, direct Factor Xa inhibitor – for the prevention of venous thromboembolism in patients undergoing total hip replacement.	Thrombosis Research 2007; 120: 685-693
Total knee replacement		
RECORD 3 Lassen MR, Ageno W, et al.	Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty.	New England Journal of Medicine 2008, 358(26): 2776-2786.
Kamphuisen PW.	Thromboprophylaxis with rivaroxaban or enoxaparin did not differ for major bleeding in knee arthroplasty.	ACP Journal Club, 2008; 149: JC47.
RECORD 4 Turpie AG, Lassen MR, et al.	Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial.	Lancet 2009; 373(9676): 1673-1680.
ODIXa-KNEE Turpie et al.	BAY 59-7939: an oral, direct Factor Xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement. A phase II dose-ranging study.	J Thromb Haemost 2005; 3: 2479-2486.
Meta-analysis		
Wolowacz SE, Roskell NS, et al.	Efficacy and safety of dabigatran etexilate for the prevention of venous thromboembolism following hip or knee arthroplasty.	Thromb Haemost 2009; 101: 77-85

8. Results of Trials

As the PBAC specifically requested a comparison of dabigatran and rivaroxaban, common reference-based indirect comparisons of the effectiveness and safety of dabigatran 220 mg versus rivaroxaban 10 mg, in patients undergoing THR or TKR, were performed during the evaluation. The PBAC agreed that the results of the indirect comparison of dabigatran and rivaroxaban are uncertain and conclusions from these analyses cannot be used for the purposes of comparing these drugs.

9. Clinical Claim

The submission claimed that, when the balance of effectiveness and risk of bleeding events is taken into consideration, dabigatran is no worse than rivaroxaban.

For PBAC's view of this claim, see Recommendation and Reasons.

10. Economic Analysis

The November 2009 submission presented a cost-minimisation analysis, based on the implicit assumption that both dabigatran 220 mg and dabigatran 150 mg are equi-effective to rivaroxaban 10 mg.

The PBAC considered there was insufficient evidence provided to support this assumption. Only drug costs were included in the economic analysis. Neither costs associated with prophylaxis failure (VTEs), nor costs of treating adverse events, were included.

The PBAC accepted the cost analysis provided in the March 2009 submission, a cost-minimisation analysis on the basis that dabigatran 220 mg and dabigatran 150 mg were equi-effective to enoxaparin 40 mg, was reasonable (see also March 2009 Public Summary Document).

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year expected to receive dabigatran was estimated to be in the range of 10,000 to 50,000 in Year 5.

The financial savings per year to the PBS were estimated to be less than $10 million in Year 5. The submission's estimate was considered uncertain due to difficulties in assessing the likely uptake of dabigatran, given the current and future use of enoxaparin and rivaroxaban for this indication are unknown.

12. Recommendation and Reasons

The PBAC recommended the Authority Required PBS listing of dabigatran for prevention of venous thromboembolic events in adult patients undergoing total hip replacement (THR) and total knee replacement (TKR) on a cost minimisation basis compared with enoxaparin. The equi-effective doses are dabigatran 220 mg is equivalent to enoxaparin 40 mg.

The PBAC accepted that the cost analysis provided at the March 2009 PBAC meeting was reasonable. Dabigatran is more expensive than enoxaparin when only drugs costs are compared, but it is overall likely to be cost saving in terms of health care resources because it is an oral anticoagulant. The PBAC noted that the proposed price of dabigatran did not claim the full extent of savings, which is conservative.

The PBAC agreed that the results of the indirect comparison of dabigatran and rivaroxaban are uncertain and conclusions from these analyses cannot be used for the purposes of comparing these drugs. The concerns with the indirect comparison of dabigatran versus rivaroxaban are:

- The potential influence of different adjudication committees on the reported frequency of asymptomatic DVT;
- The different duration of treatment in the two trials in patients undergoing TKR (RE-MODEL and RECORD 3);

- Differences in the definition of the primary safety outcome, major bleeding, including differences on how the incidences of major bleeding were collected;
- The inability to determine whether patients in the rivaroxaban trials received other aids, such as support stockings; and
- The difference in event rates for the common comparator, enoxaparin, which may be due to differences in baseline risk in the two trials, or a reflection of the methods and quality of the trials.

Further, the PBAC did not accept the submission's claim that dabigatran is no worse than rivaroxaban. Although a head-to-head trial of dabigatran and rivaroxaban would be required to provide a definitive comparison., the PBAC considered that in all likelihood dabigatran is less efficacious than rivaroxaban, but noted that it is also less expensive.

The PBAC expressed concerns about the comparison of 150 mg dabigatran versus 40 mg enoxaparin, as follows:

- The relative risk of 1.28 and the 95% confidence interval (0.93, 1.78) for the primary outcome does not support the claim of non-inferiority based on the PBAC's view of the non-inferiority margin of 4% absolute risk difference noting that this margin was not the study non-inferiority margin. The upper limit of the confidence interval for dabigatran 150 mg is close to double the relative risk of enoxaparin for the primary outcome. Given that the 150 mg daily dose is recommended as the dose for patients with moderate renal impairment, the use of a population without renal impairment in the trial means that the data are of very limited relevance.
- The lack of evidence for the equi-effectiveness of dabigatran 150 mg and enoxaparin 40 mg in the population for which this dose of dabigatran is recommended ie. moderate renal impairment.

Nevertheless, the PBAC recommended the listing of the 75 mg strength to provide clinicians with a lower dose option. The National Prescribing Service (NPS) was requested to produce a RADAR document to alert prescribers to issues around dosage and length of therapy and to raise awareness about the risk of haemorrhage in all patients taking anti-thrombotic products.

Recommendation:

DABIGATRAN ETEXILATE MESYLATE, capsules, 75 mg (base) and 110 mg (base), 60 tablet packs of 75 mg and 110 mg

Restriction:	<u>Authority Required</u> Prevention of venous thromboembolism in a patient undergoing total hip replacement. <u>NOTE:</u> No applications for increased maximum quantities and/or repeats will be authorised for the pack of 60 tablets.	
Maximum quantity:	20 ‡1	(75 mg, 110 mg) (75 mg (60) and 110 mg (60))
Repeats:	1 0	(75 mg, 110 mg) (75 mg (60) and 110 mg (60))

Restriction:	Authority Required Prevention of venous thromboembolism in a patient undergoing total knee replacement. NOTE: No applications for increased maximum quantities and/or repeats will be authorised.
Maximum quantity:	20 (75 mg and 110 mg)
Repeats:	0

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 welcomes the availability of dabigatran for patients undergoing THR and TKR.