

PTAC and Cardiovascular Subcommittee Minutes for Dabigatran in Orthopaedics and AF

November 2008 PTAC minutes

Dabigatran Etexilate for the Prevention of Venous Thromboembolic Events in Patients Undergoing Orthopaedic Surgery

The Committee reviewed an application from Boehringer Ingelheim for the listing of dabigatran etexilate (Pradaxa) on the Pharmaceutical Schedule for the prevention of venous thromboembolic events in patients undergoing orthopaedic surgery.

The Committee noted that without prophylaxis the incidence of venographically demonstrated venous thromboembolism is 40% to 60% after joint replacement surgery to the lower limb. However the Committee considered that a large number of these events are asymptomatic and do not impact on either morbidity or mortality. The Committee noted that information submitted by the supplier indicated mortality rates resulting from pulmonary embolism ranged between 0.1% and 7.5% after lower limb joint replacement surgery. The Committee considered that there is a historical aspect to these high rates and that recent data (2006/2007) from the Scottish Arthroplasty Registry indicated lower overall morbidity and mortality in a country where aspirin and mechanical prophylaxis predominated over low molecular weight heparin (LMWH) prophylaxis. Complete Scottish data for 2006/2007 showed symptomatic venous thromboembolism within 90 days and all cause mortality within 90 days occurring in 1.3% and 0.7% of patients undergoing a total hip replacement and 1.3% and 0.5% of patients undergoing a total knee replacement.

The Committee noted the RE-MOBILIZE, RE-MODEL, and RE-NOVATE Phase III clinical trials which compared the efficacy and safety of dabigatran to enoxaparin in the prevention of venous thromboembolism following hip and knee orthopaedic surgery. The Committee noted that the studies showed that the efficacy, adverse effect profile including hepatotoxicity, and the risk of bleeding of dabigatran was non-inferior to that of enoxaparin.

The Committee considered that the studies were of good quality, but noted that there were a number of exclusion criteria which could affect the studies' generalisability to clinical practice, and the studies were not powered adequately for safety outcomes. The Committee also noted that the primary endpoint was the incidence of total VTE and all-cause mortality however there is some debate as to whether total VTE is an appropriate endpoint.

The Committee noted that current venous thromboembolism prophylaxis practice varies between New Zealand hospitals in both duration and the type of pharmaceutical agent used. The Committee noted that low molecular weight heparin, warfarin and aspirin are used to varying degrees in clinical practice. The Committee noted that concern regarding bleeding and infection rates partially accounted for the reluctance of some centres to use low molecular weight heparins. Therefore the Committee considered that there was a question as to whether dabigatran, if made available, would be used by surgeons for the same reasons.

The Committee considered that the most appropriate comparator to dabigatran was low molecular weight heparin as this was the comparator used in the clinical trials;

however, aspirin or warfarin are often used in clinical practice in New Zealand. The Committee considered that dabigatran and low molecular weight heparin had the same or similar clinical effect and that they could be reference priced for thromboprophylaxis following elective orthopaedic surgery.

The Committee noted that dabigatran was a tablet and considered that it would therefore be preferred to enoxaparin which was an injection and could result in significant local bruising. The Committee considered that the current market would grow if dabigatran became available and also wondered if it might be used for unregistered indications.

The Committee considered that dabigatran would be especially useful in elderly patients but noted that there was no antidote to dabigatran and that this could be an issue if there is a major bleeding complication.

The Committee noted that dabigatran was cheaper than the MIMS price of enoxaparin.

The Committee **recommended** that dabigatran be declined for a listing in Section B of the Pharmaceutical Schedule but that it be listed on the Discretionary Community Supply (DCS) list with a low priority following knee and hip orthopaedic surgery for a duration of up to 10 days and 35 days respectively.

The Committee **recommended** that PHARMAC staff write to orthopaedic surgeons to determine what current practice is, and what place in therapy, if any, they considered dabigatran would occupy. The Committee also **recommended** that PHARMAC monitors further safety signals.

The Decision Criteria particularly relevant to this recommendation are: *(iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; and (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

November 2009 PTAC minutes

Rivaroxaban (Xarelto) for Venous Thromboembolism (VTE) Prophylaxis

Application

The Committee reviewed an application from Bayer New Zealand Ltd for the listing of rivaroxaban (Xarelto) on the Pharmaceutical Schedule for the treatment of venous thromboembolism prophylaxis after major orthopaedic surgery.

Recommendation

The Committee recommended that rivaroxaban for the treatment of venous thromboembolism prophylaxis after major orthopaedic surgery be listed in the Pharmaceutical Schedule with a medium priority.

The Decision Criteria particularly relevant to this recommendation are: *(iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; and (v) The cost-effectiveness of meeting health*

needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.

Discussion

The Committee reviewed an application from Bayer New Zealand Ltd for the listing of rivaroxaban (Xarelto) on the Pharmaceutical Schedule for venous thromboembolism prophylaxis after major orthopaedic surgery.

The Committee noted the RECORD 1 (Study Number 11354 report, Eriksson et al. 2007: Eriksson et al. 2008: NEJM: 358 (26). pp. 2765-2775), RECORD 2 (Study Number 11357 report, Kakkar et al. 2007), RECORD 3 (Study Number 11356 report, Lassen et al 2007: Lassen et al. 2008: NEJM: 358 (26). pp. 2776-2786), and RECORD 4 (Study Number 11355 report, Turpie et al. 2008 report) trials which compared rivaroxaban with enoxaparin for the prevention of venous thromboembolism after total hip replacement or total knee replacement using various treatment regimes. The Committee considered that the quality of the trials was very good and that they indicated that rivaroxaban was perhaps slightly more efficacious than enoxaparin in preventing venous thromboembolism following total hip replacement and total knee replacement, but that it also had a slightly larger increase in the risk of major bleeding.

The Committee noted the conclusions and recommendations of NICE (April 2009), the Scottish Medicines Consortium (November 2008), CEDAC (November 2008) and NPS RADAR (August 2009).

The Committee considered that the most appropriate comparator to rivaroxaban, that is currently subsidised, is low molecular weight heparin as this was the comparator used in the clinical trials; however, the Committee noted that aspirin and warfarin might be used in clinical practice in New Zealand.

The Committee considered that rivaroxaban had the same or similar clinical effect as enoxaparin and dabigatran and that these three products could be listed in the same therapeutic subgroup for the purposes of reference pricing.

The Committee considered that PHARMAC staff should seek the opinion of orthopaedic surgeons to determine current practice, and the place in therapy, if any, they considered rivaroxaban would occupy.

The Committee considered that if rivaroxaban was listed then it should be restricted via Special Authority to a daily dose of 10 mg for the prophylaxis of venous thromboembolism following total hip replacement (up to five weeks) or total knee replacement (up to two weeks). The Committee considered that if this restriction were not applied it would be likely that rivaroxaban would be used for acute coronary syndrome and atrial fibrillation as an alternative to warfarin, even though it is not registered for these indications.

The Committee noted that the supplier's estimates of the rate of Post Thrombotic Syndrome and the cost and proportion of home visits to administer enoxaparin were reasonable.

The Committee noted that the entry of generic enoxaparin would reduce the cost-effectiveness of rivaroxaban.

The Committee considered that, for patient convenience and to improve compliance, it would be appropriate for patients to receive a full course when they are discharged from hospital.

November 2010 PTAC minutes

Dabigatran (Pradaxa) for stroke, systemic embolism, atrial fibrillation

Application

The Committee considered an Application from Boehringer Ingelheim NZ Limited to fund dabigatran for prevention of stroke, systemic embolism and reduction of vascular mortality in patients in atrial fibrillation.

Recommendation

The Committee **recommended** that dabigatran be funded with low priority for prevention of stroke, systemic embolism and reduction of vascular mortality in atrial fibrillation.

The Decision Criteria particularly relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (ii) *The particular health needs of Māori and Pacific peoples;* (iii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* (iv) *The clinical benefits and risks of pharmaceuticals;* (v) *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services;* (vi) *The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

The Committee noted that dabigatran is registered in New Zealand, and was previously reviewed by PTAC in November 2008 for the prevention of venous thromboembolism (VTE) following total hip and knee replacement, but is not currently registered for use in atrial fibrillation. The Committee noted that dabigatran was recently reviewed by the Cardiovascular Subcommittee for this indication, but the minutes were not yet available.

The Committee noted the pivotal study for dabigatran in atrial fibrillation, the RE-LY study (Connolly et al NEJM 2009; 361: 1139-1151), which was a randomised trial comparing two fixed doses of dabigatran, 110mg or 150mg twice daily administered in a blinded manner, and open label warfarin in patients with atrial fibrillation. The Committee noted that in the warfarin group, the mean percentage of the study period during which the International Normalised Ratio (INR) was within the therapeutic range was 64%. The Committee noted the rates of stroke or systemic embolism, which was the primary outcome, were 1.69% per year in the warfarin group compared with 1.53% per year in the 110mg dabigatran group and 1.11% per year in the 150mg dabigatran group. Both doses of dabigatran were non-inferior to warfarin ($p < 0.001$), and the 150mg dose of dabigatran was superior to warfarin with an absolute risk reduction (ARR) of 0.58% and number-needed-to-treat (NNT) of 172.

The Committee noted that the primary safety outcome of major bleeding in the RE-LY trial was lower with both dosages of dabigatran and was statistically significant for the 110mg dose (2.71% versus 3.36% per year, $p=0.003$, ARR 0.65%, NNT 154). The Committee noted that the rate of gastrointestinal bleeding was significantly higher with the 150mg dabigatran dose than warfarin (1.51% versus 1.02% per year, ARR 0.49%, NNT 204), but intracranial haemorrhage was significantly lower with both dosages of dabigatran. The incidence of haemorrhagic stroke was significantly lower for both dosages of dabigatran when compared with warfarin, but the incidence of myocardial infarction was higher in the dabigatran groups ($p=0.048$). The Committee noted that the mortality rate from any cause was not statistically different between the three treatment arms. The Committee noted that the net clinical benefit outcome, which was a composite measure of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death or major bleeding, was better with both dosages of dabigatran but that this was only statistically significant for the 150mg dabigatran dose ($p=0.04$). The Committee noted that unlike ximelagatran, which was withdrawn from the market because of hepatotoxicity, no signal of hepatotoxicity was detected with dabigatran. The Committee considered that dyspepsia was however more common with dabigatran when compared with warfarin ($p<0.001$).

The Committee considered that based on the RE-LY trial, the absolute risk reduction with dabigatran when compared with warfarin, although statistically significant, was very small (ARR 0.58%). Therefore, the Committee considered that dabigatran should be considered therapeutically equivalent to warfarin. The Committee also considered that the evidence for increased safety of the 110mg twice daily dose of dabigatran for patients aged >75 years of age, or with creatinine clearance 30-50ml/min, with concomitant p-glycoprotein inhibitors or previous gastrointestinal haemorrhage, is inadequate.

The Committee also considered that the inability to monitor dabigatran therapy could mean that the first sign of over anticoagulation could be a major haemorrhage, especially in the elderly and those with renal impairment. There is also currently no antidote for dabigatran in the event of haemorrhage. The Committee noted that patients with a creatinine clearance of <30 ml/min were excluded from the RE-LY trial. The Committee also considered that there are potentially significant drug interactions between dabigatran and p-glycoprotein inhibitors, with a risk of severe bleeding, and that possible interacting drugs are likely to include more than just verapamil, amiodarone and quinidine.

The Committee considered that although one of the advantages of dabigatran is its ease of use, it is noteworthy that the rates of discontinuation in the RE-LY trial were about 5% higher with dabigatran when compared with warfarin. Dyspeptic symptoms may also be a significant issue in real life practice. The Committee also considered that, due to its short half-life (unlike warfarin), missing a dose of dabigatran could be associated with an increased risk of stroke.

The Committee noted that there was no direct head-to-head trial comparing dabigatran with aspirin. The Committee noted the meta-analysis by Hart et al (Ann Intern Med 1999; 134:492-501) and the BAFTA study (Mant et al Lancet 2007; 370:493-503), which compared the efficacy of warfarin versus aspirin in atrial fibrillation. The BAFTA study indicated that warfarin resulted in an absolute risk reduction of 2.0% when compared with aspirin. The Committee was however concerned about making an indirect comparison and considered that evidence for dabigatran was currently lacking in patients who currently use aspirin because warfarin is contraindicated or maintaining INRs within the therapeutic range is difficult. This patient group was not included in the

RE-LY trial. The Committee considered that although clinical evidence is currently lacking, this patient group would possibly benefit most from dabigatran.

The Committee noted that dabigatran was significantly more expensive than warfarin even after taking into account the cost of warfarin monitoring. The Committee considered that on average, patients stable on warfarin are tested every four to six weeks.

The Committee noted the supplier's recommendation to limit dabigatran to patients with CHADS₂ score ≥ 2 and who were contraindicated to warfarin or had trialed warfarin but INR levels failed to be maintained within the therapeutic range. The Committee considered that it would be difficult to restrict dabigatran use to certain subgroups of patients with atrial fibrillation without a significant risk of other patients with atrial fibrillation gaining access.

The Committee noted that although there are potential advantages of an oral anticoagulant like dabigatran that does not require regular monitoring, the main issue with dabigatran is its high cost and the risk of it being used in other patient groups beyond the funded indications. The Committee also considered that home INR testing of warfarin is currently being trialed and could reduce some of the burden of warfarin monitoring. The Committee noted that there are a number of other similar oral anticoagulants, namely rivaroxaban and apixaban, which may present for funding, and resulting competition may result in price reductions.

February 2011 PTAC minutes

PTAC noted the recommendation by the Cardiovascular Subcommittee for dabigatran to be listed with medium priority for patients with atrial fibrillation. PTAC also noted that PHARMAC staff had received a commercial proposal for dabigatran to be listed without restriction on the Pharmaceutical Schedule [REDACTED]. PTAC considered that it was appropriate to list dabigatran without restriction due to the more cost-effective price. PTAC also considered that educational support should be provided to clinicians when dabigatran is listed. PTAC considered that if dabigatran is listed without restriction, a large proportion of patients on warfarin for atrial fibrillation would switch and it would also be used off-indication for conditions like prosthetic heart valves.

May 2011 PTAC minutes

(PHARMAC staff note that this minute had not been approved at the time of writing of this Board paper)

Boehringer Ingelheim's response to PTAC's recommendation for dabigatran for the prevention of stroke, systemic embolism and reduction of vascular mortality in atrial fibrillation (AF)

The Committee noted Boehringer Ingelheim's response to its recommendations in November 2010 for dabigatran for the prevention of stroke, systemic embolism and reduction of vascular mortality in atrial fibrillation (AF).

The Committee considered that it was appropriate to maintain its previous recommendations following review of the supplier's response.

The Committee noted that PHARMAC had recently consulted on a proposal to fund dabigatran without Special Authority restriction. The Committee considered that listing dabigatran without restriction was appropriate considering the proposal resulted in a more cost-effective price for the medicine.

The Committee recommended that PHARMAC consider delaying the listing of dabigatran by a few months. This is to allow for educational programmes to be implemented for prescribers prior to drug listing as dabigatran is part of a new class of treatment and there is very little clinical experience with the product.

The Committee also recommended that dabigatran be included on the Intensive Medicines Monitoring Programme (IMMP) to enable safety monitoring and collection of data given it is a new treatment in New Zealand and worldwide.

October 2010 Cardiovascular Subcommittee minutes Dabigatran for atrial fibrillation

The Subcommittee reviewed an application from Boehringer Ingelheim for the listing of dabigatran etexilate (Pradaxa) on the Pharmaceutical Schedule for the prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation (AF). The Subcommittee noted that dabigatran is currently registered in New Zealand for venous thromboembolism (VTE) prophylaxis post-orthopaedic surgery and registration for the use in AF is expected by the end of 2010.

The Subcommittee noted that the pivotal trial in the application was the RELY trial (Connolly SJ, et al. N Engl J Med 2009; 361: 1139-51) which was a large multi-centre, multi-national, randomised non-inferiority trial comparing open label warfarin and two doses of dabigatran (220 or 300mg/day in 2 divided doses) in 18,113 patients with AF. The median duration of follow-up was 2 years and the primary outcome was stroke or systemic embolism. The Subcommittee considered that the trial showed that both doses of dabigatran were non-inferior to warfarin for the primary outcome with little difference in major bleeding. The Subcommittee noted that although the trial was a non-inferiority trial, the 300mg dabigatran dose was superior to warfarin for the primary outcome with an ARR of 0.58% (relative risk 0.66; NNT 172; 95% CI 0.53-0.82; $p < 0.001$). The Subcommittee noted that there was no difference in hepatic adverse events between any of the three treatment arms but dabigatran was associated with a higher rate of dyspepsia. The Subcommittee considered that this trial was of good quality and grade 1+ level on the SIGN (Scottish Intercollegiate Guidelines Network) rating scheme.

The Subcommittee noted that there were no comparative studies between dabigatran and aspirin currently available. The Subcommittee noted that a meta-analysis (Hart RG, et al. Ann Intern Med 1999; 134: 492-501) showed that warfarin reduced the absolute risk of stroke by 0.7% compared to aspirin. However, the Subcommittee considered that the results of the BAFTA trial (Mant J, et al. Lancet 2007; 370: 493-503) involving 973 patients which showed an ARR of 2% for warfarin versus aspirin, was more accurate as it was a head-to-head trial directly comparing warfarin and aspirin. From the RELY and BAFTA trials, the Subcommittee considered that dabigatran would probably result in an ARR of 2% for stroke when compared to aspirin. When compared to aspirin, dabigatran would likely be associated with an increased risk of bleeding with an absolute risk increase of 0.9% per year based on the difference in the warfarin arm and aspirin only arm in the ACTIVE-W and ACTIVE-A trials.

The Subcommittee noted the ACTIVE-W trial (The Active Writing Group. Lancet 2006; 367:1903-12) which was a large multicentre parallel groups study of clopidogrel plus aspirin versus oral anticoagulation for AF. The primary outcome was the first occurrence of stroke, systemic embolism, myocardial infarction or vascular death. The Subcommittee noted that the median follow up was 1.28 years and the study was discontinued because interim analysis showed superiority of anti-coagulation. The Subcommittee considered that the conclusions from this trial are that the combination of clopidogrel plus aspirin is inferior to oral anticoagulation and possibly results in increased bleeding. The Subcommittee also considered the ACTIVE-A trial (The Active Investigators. N Engl J Med 2009; 360: 2066-78) which was a large multicentre parallel groups study of clopidogrel plus aspirin versus aspirin alone. The primary outcome variable was time to first stroke, myocardial infarction, vascular death or non-CNS metabolism with a median follow up of 3.6 years. The Subcommittee considered that combination clopidogrel and aspirin was superior to aspirin alone with an ARR of 0.8% (NNT 125; 95% CI 0.81-0.98; p=0.01) but with an increased risk of major bleeding (absolute risk increase 0.7%; NNH 142; 95% CI 1.29-1.92; p<0.001). Based on both ACTIVE trials, the Subcommittee considered that clopidogrel in combination with aspirin was inferior to anticoagulation and although evidence suggests it is better than aspirin alone, it is associated with an increased risk of bleeding.

The Subcommittee concluded that the most appropriate comparators to dabigatran were warfarin and aspirin monotherapies. While the Subcommittee also considered that there would be a group of patients on neither warfarin nor aspirin it concluded that these patients would be unlikely candidates for dabigatran and this patient group was not included in the clinical trials.

The Subcommittee considered that there is no publication with robust NZ data to estimate the prevalence of AF or the use of warfarin or aspirin as a treatment. The Subcommittee considered that the NZ Guidelines Group estimate that there are approximately 30,000 to 100,000 New Zealanders living with AF (New Zealand Guidelines Group 2005. The management of people with atrial fibrillation and flutter; xxxi-xxxii). The Subcommittee noted the supplier estimate of 65,000 patients based on a general practice database HealthStat. The Subcommittee considered that there was a higher prevalence of AF among the older population and Maori, as well as Pacific peoples. The Subcommittee considered that approximately 25-40% of patients with AF are using warfarin and most of the remaining patients are using aspirin (30-60%) based on several trials (Burgess C, et al. Ther Clin Risk Manag. 2007 Jun; 3(3): 491-8 and Somerfield J, et al. Stroke 2006; 37: 1217-20). The Subcommittee considered that 10-20% of AF patients may not be on any anti-thrombotic therapy. The Subcommittee considered that it is likely that <1% of AF patients are using dipyridamole or clopidogrel with or without aspirin and likely only in special circumstances.

The Subcommittee noted the suppliers proposed Special Authority criteria to limit dabigatran to patients with a CHADS2 score of ≥ 2 and who have trialed warfarin but INR levels failed to be maintained within the therapeutic range or who are contraindicated to warfarin therapy. The Subcommittee considered that the New Zealand Guidelines Group risk assessment tool based on the Framingham study was more commonly used here. Although it was appropriate to limit patients through risk stratification, the Subcommittee considered that it would be very difficult to restrict its use via Special Authority without a significant risk of slippage.

The Subcommittee noted that while most guidelines do not recommend warfarin for those at very low risk of stroke, the majority of people with AF fall within the intermediate or high risk category and would be candidates for dabigatran. The Subcommittee considered that it is very likely that all patients using warfarin would

switch to dabigatran except those with severe renal impairment (GFR <30ml/min) and those allergic or intolerant of it. The Subcommittee also considered that dabigatran would replace aspirin in patients who are taking aspirin because they have a higher risk of an adverse event with warfarin i.e. those intolerant or allergic to warfarin, those with dementia, the very elderly and those on multiple medications. The Subcommittee considered that approximately 30-60% of AF patients currently on aspirin would switch to dabigatran.

The Subcommittee considered that dabigatran would remove the need for regular venepunctures and the difficulty with drug as well as food interactions with warfarin. The Subcommittee considered that the ease of use of dabigatran would increase the use of anticoagulation and probably reduce the burden of stroke to the health system in those poorly controlled on warfarin or on aspirin. However, the Subcommittee noted that there are risks with dabigatran therapy including a lack of long term outcome and adverse effect data, and no antidote for bleeding from dabigatran, unlike Vitamin K for warfarin. The Subcommittee considered that there would need to be some guidance provided to clinicians to mitigate and manage the bleeding risk if dabigatran is listed.

The Subcommittee considered that while dabigatran and warfarin were clinically equivalent dabigatran would make management of patients easier and would be an advantage for patients contraindicated or difficult to control with warfarin and are therefore on aspirin. The Subcommittee however noted that it had a much higher cost.

The Subcommittee recommended that dabigatran be listed on the Pharmaceutical Schedule with a medium priority. The Subcommittee considered that listing both strengths of dabigatran would be appropriate to allow for dose-adjustment in certain patient groups including those with renal impairment.

The Decision Criteria particularly relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (iv) The clinical benefits and risks of pharmaceuticals and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule