

## CEDAC FINAL RECOMMENDATION

### DABIGATRAN ETEXILATE

[Pradox – Boehringer Ingelheim (Canada) Ltd.]

#### New Indication: Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation

##### Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that dabigatran be listed for the prevention of stroke and systemic embolism in patients with atrial fibrillation meeting one of the following criteria:

- Patients in whom warfarin is indicated but who fail to achieve adequate international normalized ratio (INR) control, despite monitored warfarin treatment, such as with: regular INR testing, dosage adjustment according to a validated nomogram, and patient education. Patients who fail to achieve adequate INR control should be referred to an anticoagulation management service, if available.
- or
- Patients who have a history of a serious hypersensitivity reaction to warfarin.

##### Reason for the Recommendation:

1. In one large open-label randomized controlled trial (RCT) (RE-LY) the annual incidence of stroke or systemic embolism was statistically significantly less with dabigatran 150 mg twice daily (1.11%) compared with adjusted dose warfarin (1.71%); however the annual incidence with dabigatran 110 mg twice daily (1.54%) was not statistically significantly different compared with adjusted dose warfarin. In a pre-planned subgroup analysis the benefit of dabigatran 150 mg twice daily, compared with adjusted dose warfarin, was primarily observed in centres that failed to achieve adequate INR control.
2. The daily cost of dabigatran (\$3.20) is greater than warfarin (\$0.06 or approximately \$1.16 when monitoring costs are included).

##### Background:

This submission for dabigatran (administered as dabigatran etexilate) is for the new Health Canada indication of prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate. The anticoagulant activity of dabigatran is through direct inhibition of thrombin. It is available as 110 mg and 150 mg capsules for this indication. The Health Canada-recommended dose is 150 mg twice a day, but in geriatric

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patients, especially those older than 75 years who have at least one other risk factor for bleeding, Health Canada recommends that a reduced dose of 110 mg twice a day may be considered.

## **Submission History:**

Dabigatran was previously reviewed for the prevention of venous thromboembolic events in patients who have undergone total hip replacement or total knee replacement surgery, and received a recommendation of “do not list” (see Notice of CEDAC Final Recommendation, January 28, 2009).

## **Summary of CEDAC Considerations:**

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs, a critique of the manufacturer’s pharmaco-economic evaluation, and patient group-submitted information about outcomes and issues important to patients.

## **Clinical Trials**

The systematic review included one large open-label multinational RCT of patients with atrial fibrillation and at least one additional risk factor for stroke (RE-LY). The RE-LY study (N=18,113) was designed to test the non-inferiority of dabigatran (at both 110 mg and 150 mg twice a day) compared with warfarin (dose adjusted to an INR of 2 to 3 [therapeutic range]). Study participation was to be for a minimum of one year and a maximum of three years.

Patients in the RE-LY study were 71.5 years of age on average and most (64%) were male. Patients’ risk of stroke was assessed through use of the CHADS<sub>2</sub> score, named for the five risk factors assessed: congestive heart failure, hypertension, age, diabetes, and previous stroke or transient ischemic attack. Of the total patient population, 68% had a CHADS<sub>2</sub> score of 2 or greater.

Approximately 96% of randomized patients in all three treatment groups completed the study. The median follow-up time was 24 months. Limitations of the RE-LY study include the open-label design and the uncertain generalizability of results due to the inadequate INR control observed in a number of the participating countries.

## **Outcomes**

Outcomes were defined a priori in the CDR systematic review protocol. Of these the Committee discussed the following: mortality, stroke and systemic embolism, bleeding (including major intracranial and gastrointestinal bleeds), study withdrawals and adverse events. The primary outcome in the RE-LY study was the incidence of a composite endpoint comprised of stroke or systemic embolism. RE-LY was designed to accept the non-inferiority of either dose of dabigatran compared with warfarin for the primary outcome if the upper limit of the 95% confidence interval (CI) of the hazard ratio (HR) did not exceed 1.46.

Stroke was defined as an acute onset of a focal neurological deficit of presumed vascular origin lasting for 24 or more hours, or resulting in death. Strokes were classified as ischemic, hemorrhagic, or cause unknown (based on computerized tomography or magnetic resonance scanning, or autopsy).

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Systemic embolism was defined as an acute vascular occlusion of the extremities or any organ (kidneys, mesenteric arteries, spleen, retina, or grafts) documented by angiography, surgery, scintigraphy, or autopsy.

Information submitted by patient groups indicated that outcomes of importance to patients include a reduction in the incidence of stroke and major bleeds; the RE-LY trial reported on both of these outcomes. Other outcomes of importance submitted included: work hours lost for patients and/or caregivers, frequency of drug-food and drug-drug interactions, and other general concerns that would be expected to affect quality of life. The frequency of drug interactions, lost work hours, and quality of life were not included as outcomes in the RE-LY study.

## Results

### **Efficacy or Effectiveness**

- Annual all-cause mortality did not differ statistically for either dabigatran 110 mg (3.75%) or dabigatran 150 mg (3.64%) compared with warfarin (4.13%). Vascular deaths were statistically significantly less frequent for dabigatran 150 mg (2.28%) compared with warfarin (2.69%); relative risk (RR) (95% CI): 0.85 (0.72 to 0.99). The incidence of vascular deaths did not differ statistically between warfarin and dabigatran 110 mg (2.43%).
- The annual incidence of the primary composite endpoint was lower for both dabigatran 110 mg (1.54%) and dabigatran 150 mg (1.11%) compared with warfarin (1.71%). Based on these data, dabigatran 110 mg was determined to be non-inferior to warfarin (HR [95% CI]: 0.90 [0.74 to 1.10]), and dabigatran 150 mg was determined to be superior to warfarin (HR [95%CI]: 0.65, [0.52 to 0.81]).
- A pre-planned subgroup analysis of the primary composite endpoint by the mean time in therapeutic range achieved at individual study centres, indicated that dabigatran 150 mg and warfarin produced similar outcomes in centres that achieved adequate INR control; HR (95% CI): 0.69 (0.44 to 1.09) and 0.95 (0.61 to 1.48) for centres with mean time in therapeutic range of 65.5% to 72.6%, and >72.6% respectively. Dabigatran 150 mg provided greater benefit compared with warfarin in centres that failed to achieve adequate INR control; HR (95% CI): 0.57 (0.37 to 0.88) and 0.50 (0.33 to 0.77) for centres with mean time in therapeutic range of <57.1%, and 57.1% to 65.5% respectively.
- Quality of life, while a key component of the submitted economic analyses, was not assessed in RE-LY.

### **Harms (Safety and Tolerability)**

- The annual incidence of major bleeding was similar between warfarin (3.57%) and dabigatran 150 mg (3.32%), but statistically significantly greater for warfarin compared with dabigatran 110 mg (2.87%). Among major bleeds, the annual incidence of intracranial hemorrhage was greater for warfarin (0.76%) compared with both dabigatran 110 mg (0.23%) and dabigatran 150 mg (0.32%). In contrast, the annual incidence of major gastrointestinal bleeds was greater for both dabigatran 110 mg (1.14%) and dabigatran 150 mg (1.57%), compared with warfarin (1.07%).

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- Treatment discontinuation due to adverse events was statistically significantly greater for both dabigatran 110 mg (19.0%) and 150 mg (20.5%) compared with warfarin (15.7%). Further, treatment discontinuation due to gastrointestinal disorders occurred more frequently for both doses of dabigatran compared with warfarin.
- The proportions of patients who experienced an adverse event were statistically significantly greater for both doses of dabigatran compared with warfarin.

## **Cost and Cost-Effectiveness**

The manufacturer submitted a cost-utility analysis comparing dabigatran (150 mg or 110 mg twice daily) with adjusted-dose warfarin in patients with atrial fibrillation and at least one risk factor for stroke. The economic evaluation was based closely on the RE-LY study, for patient baseline characteristics and treatment effects. The long-term impact on health-related quality of life and medical costs associated with the disability from events was estimated from the literature. A lifetime time horizon (30 years) was considered for this analysis. When compared with warfarin, the manufacturer reported cost per quality-adjusted life-year (QALY) estimates of \$9,041 (dabigatran 150 mg twice daily) and \$29,994 (dabigatran 110 mg twice daily). The cost per QALY results were largely driven by the reduction in mortality and lower incidence of clinical outcomes such as stroke and intracranial hemorrhage with dabigatran. The manufacturer did not provide cost-effectiveness estimates stratified by INR control.

The daily cost of dabigatran (\$3.20) is greater than warfarin (\$0.06, or approximately \$1.16 when monitoring costs are included).

## **Patient Input Information:**

The following is a summary of information provided by three patient groups who responded to the CDR Call for Patient Input:

- Prevention of stroke is an important outcome for patients.
- Patient groups consider warfarin treatment to be inconvenient because of the frequent blood monitoring that is required and the potential drug-food and drug-alcohol interactions. Frequent blood monitoring may be a burden to both patients and caregivers, resulting in lost work time. Patients consider that the inconvenience of warfarin treatment and fears of major bleeding events may result in patients choosing less efficacious alternatives, resulting in an increased risk of stroke.
- Information from one patient group indicated that patients expect dabigatran to provide similar or improved efficacy compared with warfarin in terms of stroke risk reduction, but to improve quality of life through elimination of the need for frequent blood monitoring, reduction in drug-food and drug-alcohol interactions, and reduction in major bleeding events.

## **Other Discussion Points:**

- The Committee noted that, for the primary outcome, the absolute risk reduction for dabigatran 150 mg compared with warfarin was 0.6%; indicating that 167 patients would need to be treated for one year with dabigatran 150 mg twice daily, rather than adjusted dose warfarin, to prevent one stroke or systemic embolism.
- The Committee noted that dabigatran is contraindicated in patients with creatinine clearance < 30 mL/min. The Committee considered that the older target patient population may have

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declining and/or unpredictable renal function. The product monograph recommends precautionary measures such as dosage reduction for patients 80 years and older.

- The Committee noted that, contrary to patient-group expectations, dabigatran 150 mg twice daily did not result in a statistically significant reduction in the incidence of major bleeding compared with warfarin.
- The Committee noted there is no reversal agent for dabigatran.

## **CEDAC Members:**

Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, Dr. James Silvius.

## **March 23, 2011 Meeting**

### **Regrets:**

None.

### **Conflicts of Interest:**

One CEDAC member did not participate due to considerations of conflict of interest.

## **June 15, 2011 Meeting**

### **Regrets:**

One CEDAC member did not attend.

### **Conflicts of Interest:**

Three CEDAC members did not participate due to considerations of conflict of interest.

## **About this Document:**

CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer.

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