CDEC FINAL RECOMMENDATION

DABIGATRAN ETEXILATE
(Pradaxa — Boehringer Ingelheim [Canada] Ltd.)
Indication: Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation

This recommendation supersedes the Canadian Expert Drug Advisory Committee (CEDAC) recommendation for this drug and indication dated June 22, 2011.

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that dabigatran be listed for the prevention of stroke and systemic embolism in patients with atrial fibrillation who meet all of the following clinical criteria:

Clinical Criteria:
1. Patients with a $CHADS_2$ score ≥ 1.
2. Patients who are unable to readily achieve adequate anticoagulation with warfarin.

Reasons 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 international normalized ratio (INR) control.

2. At recommended doses, the daily cost of dabigatran (110 mg or 150 mg twice daily; $3.20) is equal to the cost of apixaban (2.5 mg or 5 mg twice daily; $3.20), but is greater than the cost of warfarin (2 mg to 10 mg daily; $0.07), ASA (80 mg to 325 mg daily; $0.01), and rivaroxaban (15 mg or 20 mg daily; $2.84).

Background:
This submission for dabigatran is for the 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 dose recommended in the product monograph is 150 mg twice daily, but in geriatric patients, especially those older than 75 years who have at least one other risk factor for bleeding, a reduced dose of 110 mg twice a day may be considered.

Submission History:
In June 2011, CEDAC recommended 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 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.

As part of a Canadian Agency for Drugs and Technologies in Health (CADTH) Therapeutic Review *(Antithrombotic Therapy for Patients with Atrial Fibrillation)*, CDEC issued recommendations to address the optimal use of antithrombotic therapy for patients with atrial fibrillation. These recommendations stated that new oral anticoagulants should be considered for the prevention of stroke for patients with non-valvular atrial fibrillation who have a $CHADS_2$ score ≥ 1 and are unable to readily achieve adequate anticoagulation with warfarin.

The Common Drug Review (CDR) participating drug plans submitted a request for advice to ask CDEC for additional clarity on the following: Should the CDR recommendation for dabigatran (Pradaxa) be updated to align with the recommendations from the Therapeutic Review of *Antithrombotic Therapy for Patients with Atrial Fibrillation*?

Summary of CDEC Considerations:
CDEC considered the following information from the 2011 CDR review of dabigatran:

- A systematic review of RCTs
- A critique of the manufacturer's pharmacoeconomic evaluation
- Patient group-submitted information about outcomes and issues important to patients.

CDEC considered the following to address the request for advice:

- Materials included in the CEDAC brief for the 2011 CDR review of dabigatran.
- The 2011 CEDAC recommendation for dabigatran (June 22, 2011).
- The 2012 CDEC recommendations from the Therapeutic Review of *Antithrombotic Therapy for Patients with Atrial Fibrillation*.
- The CDR Request for Advice Brief, which included an updated literature search from the Therapeutic Review.

Patient Input Information:
The following is a summary of information provided by three patient groups who responded to the CDR call for patient input in the 2011 CDR review of dabigatran:

- 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 the elimination of the need for frequent blood monitoring, reduction in drug-food and drug-alcohol interactions, and reduction in major bleeding events.

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 $CHADS_2$ 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 $CHADS_2$ 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 end point comprising 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). 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

- 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 end point 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 end point by the mean time in therapeutic range achieved at individual study centres indicated the following: 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, 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%).
- 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.

At recommended doses, the daily cost of dabigatran (110 mg or 150 mg twice daily; $3.20) is equal to the cost of apixaban (2.5 mg or 5 mg twice daily; $3.20), but is greater than the cost of warfarin (2 mg to 10 mg daily; $0.07), ASA (80 mg to 325 mg daily; $0.01), and rivaroxaban (15 mg or 20 mg daily; $2.84).

Other Discussion Points:
The Committee noted the following:

- 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.
- Dabigatran is contraindicated in patients with creatinine clearance < 30 mL/min. The Committee considered that the older target patient population may have declining and/or unpredictable renal function. The product monograph recommends precautionary measures such as dosage reduction for patients 80 years and older.
- 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.
- There is no reversal agent for dabigatran.

CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

June 19, 2013 Meeting

Regrets:
None

Conflicts of Interest:
None

About This Document:
CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

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

The CDEC recommendation or record of advice 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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