Canadian Expert Drug Advisory Committee
Final Recommendation – Plain Language Version

DABIGATRAN ETEXILATE
(Pradax – 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 Pradax, which is also called dabigatran, be listed by Canada's publicly funded drug plans for the prevention of stroke and systemic embolism (blood clots) in patients with atrial fibrillation who meet one of the following criteria:

- Patients in whom warfarin (Coumadin) is indicated but who are not able to get adequate international normalized ratio (INR) control, despite having their warfarin treatment monitored, such as with: regular INR testing, adjustments to warfarin dose based on test results, and patient education. Patients who are not able to get adequate INR control should be referred to an anticoagulation (blood thinning) management service, if available.
  or
- Patients who have had a serious hypersensitivity (reaction) to warfarin.

Reasons for the Recommendation:

1. In one large study (RE-LY) in which patients knew which treatment they were receiving, the annual percentage of patients having a stroke or systemic embolism was statistically lower in the Pradax 150 mg twice daily treatment group (1.11%) compared with the adjusted dose warfarin group (1.71%). The annual percentage of patients having a stroke or systemic embolism with Pradax 110 mg twice daily (1.54%) was similar to adjusted dose warfarin; the small difference between these two treatments may have been due to chance. The improved health benefit with Pradax 150 mg twice daily compared with adjusted dose warfarin was mostly seen in clinics where INR control was not adequate.
2. The daily cost of Pradax ($3.20) is greater than that of warfarin ($0.06 or approximately $1.16 when monitoring costs are included).

Background:

Pradax belongs to a class of drugs called anticoagulant agents (which prevent blood clots from forming). It works by blocking the activity of a protein called thrombin. Pradax is approved by Health Canada to prevent the occurrence of stroke (damage to part of the brain caused by an interruption of its blood supply) and systemic embolism (sudden blocking of a blood vessel by a

blood clot) in people who have a heart condition called atrial fibrillation (irregular heart beat). With atrial fibrillation, part of the heart does not beat the way it should. This can lead to the formation of blood clots, which increases the risk of stroke. Pradax is also prescribed after knee or hip replacement surgery to prevent the formation of blood clots in the leg or lung veins. Pradax is available as 110 mg and 150 mg capsules for the prevention of stroke and systemic embolism in patients who have atrial fibrillation, for which the Health Canada-approved dose is 150 mg twice a day. However, in elderly patients, especially those over the age of 75 with at least one other risk factor for bleeding, Health Canada recommends that a lower dose of 110 mg twice a day may be considered.

Submission History:
Pradax was previously reviewed for the prevention of blood clots in the veins of 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:

To make their decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of Pradax and a review of economic information prepared by the manufacturer of Pradax. Also, CEDAC considered information that patient groups submitted about outcomes and issues important to patients who have the condition for which the drug is indicated, or who might use the drug.

Clinical Trials

The systematic review included one large study, in more than one country, of patients with atrial fibrillation and at least one additional risk factor for stroke (RE-LY). The RE-LY study with 18,113 patients was designed to see if Pradax (both at 110 mg and 150 mg twice a day) was not worse than warfarin (dose adjusted to an INR of 2 to 3, a good range). Patients took part in the study 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 (where the heart does not beat strongly enough), high blood pressure, age, diabetes, and previous stroke or transient ischemic attack (mini stroke). Sixty eight per cent of patients had a $CHADS_2$ score of 2 or greater.

Approximately 96% of patients in all three of the treatment groups completed the study. The average time that the patients were in the study was 24 months.

The accuracy of the results of the RE-LY study may have been affected by patients knowing which treatment they were receiving. In addition, it is uncertain how well the results of the study apply to Canadian patients because INR control was inadequate in a number of the countries that participated in the study.

Outcomes

Outcomes were defined in advance in the CDR systematic review protocol. Of these, the Committee discussed the following: mortality (death), stroke or systemic embolism, bleeding (including major bleeding in the brain and digestive system), stopping participation in the study, and side effects. The main result which was measured in the RE-LY study was the occurrence of stroke or systemic embolism. If study results suggested that the occurrence of stroke or systemic embolism in patients treated with Pradax was not likely to be more than 1.46 times that

seen with adjusted dose warfarin, then Pradax would be considered not worse than adjusted dose warfarin.

Stroke was defined as a sudden onset of a localized nerve or brain problem probably due to a blood clot lasting for 24 or more hours, or causing death. Strokes were categorized as ischemic (lack of blood supply), hemorrhagic (bleeding), or cause unknown, based on computerized tomography or magnetic resonance scanning, or autopsy.

Systemic embolism was defined as sudden blockage of the blood vessels of the arms or legs or any organ (kidneys, mesenteric [digestive system] arteries, spleen, retina [eye], or grafts) as measured by angiography (dye injection of blood vessels), surgery, scintigraphy (tests using radioactive compounds), or autopsy.

Patient groups mentioned that the lowering of risk of stroke and major bleeding episodes was important to them. Other outcomes of importance to patients included work hours lost for patients and/or caregivers, occurrence of drug-food and drug-drug interactions, and other concerns that could affect the quality of life. The amount of drug interactions, lost work hours, and quality of life were not measured as outcomes in the RE-LY study.

Results

Efficacy or Effectiveness

- Annually, the percentage of deaths, from any cause, were similar for Pradax 110 mg (3.75%), Pradax 150 mg (3.64%), and warfarin (4.13%), with differences between the treatments possibly due to chance. Annually, deaths due to blood vessel complications were statistically less frequent for Pradax 150 mg (2.28%) compared with warfarin (2.69%), but similar and possibly due to chance between warfarin and Pradax 110 mg (2.43%).
- Annually, the percentage of patients who had a stroke or systemic embolism was lower for both Pradax 110 mg (1.54%) and Pradax 150 mg (1.11%) compared with warfarin (1.71%). Based on these results, Pradax 110 mg was found to be not worse than warfarin, and Pradax 150 mg was found to be better than warfarin.
- The manufacturer also planned to look at patients' results, based on how well INRs were controlled at the study clinic they attended. For centres that had patient INRs in a good range for 65.5% to 72.6%, or more than 72.6% of the time, the benefit of Pradax 150 mg and warfarin was similar. However, Pradax 150 mg provided greater benefit than warfarin in centres where patient INRs were in a good range for only 57.1% to 65.5%, or less than 57.1% of the time.
- Quality of life, which is very important to patients and was a key part of the economic analyses, was not assessed in RE-LY.

Harms (Safety and Tolerability)

- Annually, the percentage of patients having major bleeding was similar between warfarin (3.57%) and Pradax 150 mg (3.32%), but statistically greater for warfarin compared with Pradax 110 mg (2.87%). The annual percentage of patients having bleeding in the brain was greater for warfarin (0.76%) compared with both Pradax 110 mg (0.23%) and Pradax 150 mg (0.32%). However, the annual percentage of patients having major digestive system bleeding was greater for both Pradax 110 mg (1.14%) and Pradax 150 mg (1.57%), compared with warfarin (1.07%).
- The percentage of patients who stopped treatment due to side effects was statistically greater for both Pradax 110 mg (19.0%) and Pradax 150 mg (20.5%) compared with

warfarin (15.7%). As well, stopping treatment due to digestive system side effects was more common for patients treated with Pradax (both doses) than with warfarin.

- A higher percentage of patients treated with Pradax (either dose) reported side effects, compared with warfarin.

Cost and Cost-Effectiveness

The manufacturer submitted economic information to compare Pradax (150 mg or 110 mg twice daily) versus warfarin to evaluate the health benefits in patients with atrial fibrillation and at least one risk factor for stroke.

The economic evaluation was based closely on the RE–LY study, such as the types of patients starting the study and effects of the treatments on these patients. The long-term effects on the quality of life and medical costs associated with the disability from related health problems were estimated from the literature. The analysis was based on a projection 30 years into the future after starting treatment. Based on the manufacturer's economic assessment, both Pradax 150 mg and Pradax 110 mg were considered cost-effective, mostly due to the lower frequency of death, stroke, and bleeding into the brain observed with Pradax as compared with warfarin. The manufacturer did not provide an economic evaluation that took into account the results based on the level of INR control.

The daily cost of Pradax ($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 feel that warfarin treatment is not very convenient, as frequent blood monitoring is required and there are possible drug-food and drug-alcohol interactions. Frequent blood monitoring may be a burden to both patients and caregivers, and results in lost work time. The combination of the inconvenience of warfarin treatment and the fear of major bleeding may cause patients to choose less effective therapies, which may increase their risk of stroke.
- One patient group said that patients expect Pradax to be similar to, or better than, warfarin in the lowering of stroke risk. They also expect Pradax may improve their quality of life by removing the need for frequent blood monitoring, and through reductions in drug-food and drug-alcohol interactions and major bleeding events.

Other Discussion Points:

- The Committee noted that, based on the results of the RE-LY study, 167 patients would need to be treated for one year with Pradax 150 mg twice daily, rather than adjusted dose warfarin, to prevent one stroke or systemic embolism.
- The Committee noted that Pradax should not be used in patients who have a creatinine clearance of less than 30 mL/min (it indicates poor kidney function). The Committee considered that many of the patients with atrial fibrillation are older and may have kidney function that is worsening and changing unpredictably. The Pradax product monograph recommends precautions such as a lower dose for patients 80 years and older.
- The Committee noted that, while a patient group suggested patients expect Pradax to cause less major bleeding compared with warfarin, there was no notable difference in the occurrence of major bleeding between Pradax 150 mg and warfarin.

- The Committee noted that there is no medication which can reverse the effects of Pradax.

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, and Dr. James Silvius.

March 23, 2011 Meeting

Regrets:
None

Conflicts of Interest:
Once 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:
The information contained within this plain language version of the Canadian Expert Drug Advisory Committee (CEDAC) Recommendation about this drug is based on the information found within the corresponding technical version of the CEDAC Recommendation.
In making its recommendation, CEDAC considered the best clinical and pharmacoeconomic evidence available, up to that time. Health care professionals and those requiring more detailed information are advised to refer to the technical version available in the CDR Drug Database on the CADTH website (www.cadth.ca).

Background on CEDAC
CEDAC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). The committee is made up of drug evaluation experts and public members. CEDAC provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans; however, the individual drug plans make their own decision about whether or not to cover a drug.

In making its recommendations, CEDAC decides if the drug under review ought to be covered by the participating public drug plans based on an evidence-informed review of the medication's effectiveness and safety, and based on an assessment of its cost-effectiveness in comparison with other available treatments. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

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The manufacturer has reviewed this document and has not requested the deletion of any confidential information.