

Dabigatran etexilate (Pradaxa®) for the Prevention of Stroke and Systemic Embolism in Adult Patients with Atrial Fibrillation



August 2011

Summary

An economic evaluation on the cost-effectiveness of dabigatran etexilate (Pradaxa) for the prevention of stroke and systemic embolism in adult patients with atrial fibrillation with one or more specific risk factors was submitted to the National Centre for Pharmacoeconomics (NCPE) by the manufacturer Boehringer Ingelheim Ltd in October 2010. On the 20th December 2010 the NCPE requested clarification on a number of issues. A revised submission was made on the 28th January 2011. After further discussion, a final report was submitted on the 13th May 2011.

Dabigatran etexilate is an oral pro-drug which is rapidly converted to its active form dabigatran which is a reversible direct thrombin inhibitor. Dabigatran is indicated for the prevention of stroke and systemic embolism in adult patients with atrial fibrillation and one or more of the following risk factors (a) previous stroke, transient ischaemic attack or systemic embolism (b) left ventricular ejection fraction < 40% (c) symptomatic heart failure \geq NYHA class 2 (d) age \geq 75 years (e) age \geq 65 years associated with one of the following: diabetes mellitus, coronary artery disease or hypertension.

The cost-effectiveness of dabigatran etexilate was demonstrated using a Markov cohort model. For the primary analysis (dabigatran versus warfarin) principal clinical parameters were derived from re-analysis of the RE-LY study. For the secondary analysis (dabigatran versus aspirin) clinical parameters were derived from a mixed treatment comparison. The model included a stratified use of the two dabigatran doses as follows: patients aged less than 80 years were initiated on dabigatran 150mg twice daily and switched to dabigatran 110 mg twice daily at age 80 years. Patients aged 80 years or over were initiated on dabigatran 110 mg twice daily. The economic model assumed that the relative treatment effects continued beyond the 2 year time horizon of the RE-LY trial. Published literature was used to extrapolate beyond the trial period and the perspective was that of the Health Service Executive (HSE).

In the primary analysis the incremental cost-effectiveness ratio (ICER) for dabigatran versus warfarin was €6,311/QALY in patients under 80 years and €20,654/QALY in patients 80 years or older. In the secondary comparison the ICERs for dabigatran versus aspirin were €2,125/QALY and €3,056/QALY in patients under 80 years and those 80 years or older respectively. One way sensitivity analysis indicated that the model was sensitive to a number of parameter changes including the time horizon, cost of INR monitoring and dabigatran price. Extracranial haemorrhage was an important cost driver (versus warfarin in those 80 years and over) and disability costs were important across all comparisons. The ≥ 80 years model was also sensitive to the relative risk (dabigatran versus warfarin) of modelled clinical events including ischaemic stroke, intra and extra-cranial haemorrhage, haemorrhagic stroke and acute myocardial infarction.

Probabilistic sensitivity analysis indicated that the probability of dabigatran being cost-effective versus warfarin was 94% and 98% at payer thresholds of €20,000/QALY and €30,000/QALY respectively, in patients under 80 years of age. For patients 80 years or older the probability of dabigatran being cost-effective was 52% and 63% at the €20,000/QALY and €30,000/QALY thresholds respectively. For the secondary comparison the probability that dabigatran was cost-effective versus aspirin was 100% at both threshold levels for patients under 80 years. For patients 80 years or older the probability of dabigatran being more cost effective versus aspirin was 86% and 91% at the €20,000/QALY and €30,000/QALY threshold levels respectively.

The pharmacoeconomic evaluation included a budget impact estimate. The gross budget impact, which only included the annual cost of dabigatran was estimated to increase from over €3.0 million in 2011 to approximately €8.6 million in 2015. The net budget impact to the HSE was estimated to be in the region of €1.2 million in 2011 increasing to €3.3 million in 2015. We consider the budget impact an underestimate and suggest net and gross budget impact estimates have the potential to exceed €6.9 and €17.1 million by 2015. At a threshold of €20,000/QALY (assuming a 10 year decision time horizon) we estimate the population expected value of perfect information (EVPI) at approximately €13 million.

The review group expressed a number of concerns regarding the RE-LY study including the relatively short median follow up period of 2 years. The rates of major gastrointestinal (GI) bleeding and GI life-threatening bleeding were significantly higher with dabigatran 150 mg versus warfarin and the rates of any GI bleeding were significantly higher with both dabigatran doses as compared with warfarin. We note with some concern the absence of a specific antidote to the anticoagulant effect of dabigatran. The increased frequency of myocardial infarction in the dabigatran arms of the RE-LY trial was also noted.

There were also concerns in relation to some of the assumptions in the economic model including: the inability for patients to improve their disability level beyond the 1st 3-6 months post event, treatment effects extending beyond the limit of the clinical trial, patients who have an acute myocardial infarction and extracranial haemorrhage have no increased mortality risk beyond the acute event, extracranial haemorrhage resulting in discontinuation of anticoagulant therapy in 50% of patients and the failure to include pulmonary embolism in the model.

Following our assessment of the economic evaluation submitted by the manufacturer (Boehringer Ingelheim Ltd) we believe that dabigatran etexilate could be considered a cost effective treatment for the prevention of stroke and systemic embolism for adult patients with atrial fibrillation and one or more of the specified risk factors. However there are uncertainties associated with some of the clinical input data and the model assumptions in addition to the considerable opportunity cost, in the region of €13 million over 10 years. In view of this and the price/ICER relationship we recommend a reimbursement price significantly below €2.80 per day to ensure value for money for the HSE.