Economic Evaluation on the Cost Effectiveness of Dabigatran Etexilate (Pradaxa®) for the Primary Prevention of Venous Thromboembolic Events in Adult Patients who have undergone Total Hip Replacement or Total Knee Replacement Surgery

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Summary

1. Dabigatran etexilate (Pradaxa®) is an oral, direct thrombin inhibitor which is licensed for the primary prevention of venous thromboembolic events (VTE) in adults who have undergone total hip replacement (THR) or total knee replacement (TKR). There will be two licensed doses of dabigatran etexilate, a standard dose of 220mg once daily (110mg on day 1) and a reduced dose of 150mg once daily (75mg on day 1) reserved for special patient populations (moderate renal impairment, elderly aged over 75 years and concomitant use of amiodarone). Treatment should be initiated within 1- 4 hours of completed surgery, provided that haemostasis has been established and should be continued for 28-35 days post THR and for 10 days post TKR.

2. In July 2008, Boehringer Ingelheim Limited submitted an economic evaluation on the cost effectiveness of dabigatran etexilate for this indication to the National Centre for Pharmacoeconomics, to support its application for reimbursement. An amendment to the cost effectiveness report was submitted on the 20th August 2008. The economic evaluation is conducted from the perspective of the Irish Health Services Executive.

3. The cost effectiveness of dabigatran etexilate was demonstrated using economic modelling. A distinct two-stage approach was adopted using a combination of a decision tree and a Markov model. The duration of the acute phase considered in the decision tree was 10 weeks, which mirrors the maximum duration of follow up in the pivotal dabigatran etexilate clinical trials. Patients surviving the first 10 weeks enter the Markov Model chronic phase. The timeframe of the analysis was designed to encompass the lifetime of the patient. The base case analysis assumes that the minimum age at operation is 40 years. The model timeframe is 60 years from surgery.

   The evaluation considers the two forms of surgery, THR and TKR, separately.

4. The acute phase of the economic submission was supported by two phase-III trials. The treatment duration in the Re-Novate THR study was 28 to 35 days, followed by venographic assessment with follow up for 12-14 weeks. In the Re-Model TKR study the treatment duration was 6-10 days, followed by venographic assessment with follow-up for 12-14 weeks. Both trials had a double blind, double dummy design and compared both doses of dabigatran etexilate, 220mg and 150mg once daily, started 1 to 4 hours post-operatively with a half dose on day one, to enoxaparin 40mg once daily started the evening of the day before surgery. The primary efficacy outcome was the composite of total VTE (venographic or symptomatic deep vein thrombosis or symptomatic pulmonary embolism) and all cause mortality.

   In the acute phase decision tree, the probabilities of the primary efficacy

endpoint, major bleed and minor bleed were derived from the pivotal trials. Other probabilities used in the acute and chronic phase models were derived from literature sources and in the absence of a value from the literature, by a secondary analysis of available data, or assumed.

The economic evaluation assumes that all LMWHs are bioequivalent.

5. The economic evaluation reported both the mean expected life years and the mean total expected Quality Adjusted Life Years (QALYs) per patient. The model focuses on the impact of VTE events, bleed events, heparin induced thrombocytopenia (HIT) and death.

6. Data was presented on the incremental cost effectiveness ratio (ICER).

   Total Hip Replacement:
   The economic model predicts that THR patients will accrue less healthcare costs and slightly better health outcomes over the course of their lifetime with dabigatran etexilate 220mg compared to LMWH. Whilst medication costs are similar, the education of patients in self-administration of LMWH drives the difference between the treatments. Costs incurred for VTE and adverse events are similar for both treatments. The model predicts that there is a 72% probability that a 28 to 35 day course of standard 220mg dose will be cost effective at a cost effectiveness threshold of €45,000 when compared to a 28 to 35 day course of LMWH.

   Dabigatran etexilate 150mg and LMWH are effectively cost neutral, with dabigatran etexilate 150mg associated with slightly less lifetime health benefits. The model predicts that there is a 12% probability that a 28 to 35 day course of the reduced dose of 150mg will be cost effective at a cost effectiveness threshold of €45,000 when compared to a 28 to 35 day course of LMWH.

   Total Knee Replacement:
   The economic model predicts that TKR patients receiving dabigatran etexilate 220mg will accrue less healthcare costs and slightly better health outcomes over the course of their lifetime compared to LMWH, due to costs associated with VTE events. Costs incurred for adverse events are similar for both treatments. The model predicts that there is a 63% probability that a 6 to 10 day course of standard 220mg dose will be cost effective at the cost effectiveness threshold of €45,000 when compared to a 6 to10 day course of LMWH.

   For dabigatran etexilate 150mg, patients accrue higher lifetime costs with lower lifetime health outcomes. The model predicts that there is a 19% probability that a 6 to 10 day course of the reduced dose of 150mg will be cost effective at a cost effectiveness threshold of €45,000 when compared to a 6 to 10 day course of LMWH.

   These results are based on the assumption that health outcomes derived from a 28-35 day thromboprophylaxis course in THR patients and a 6-10 day

thromboprophylaxis course in TKR patients will extend for a further 60 years.

The 150mg dose is to be reserved under the license for special patient populations as detailed above. There was no subgroup analysis in these populations to determine the cost effectiveness of this dose in appropriate cohorts.

7. In the amended base case, an indirect comparison in the sensitivity analysis was performed to provide a comparison of extended dabigatran etexilate (33 days) with standard LMWH (7.6 days) in THR. The analysis showed that the additional cost of medication was offset by the benefits associated with the prevented VTE events, with no additional administration costs.

8. A budget impact analysis was presented using the modified base case assumptions. In the analysis, the durations of therapy considered were dabigatran etexilate 30 days in THR and 10 days in TKR and LMWH 28 days in THR and 10 days in TKR.

   The analysis estimates that the introduction of dabigatran etexilate will lead to saving of €12.44 per THR patient and €2.71 per TKR patient. The submission states that this will lead to an overall saving to the HSE of €19,538 in 2012, based on a projected up-take proportion of 37%. It is worth noting however, that extended duration of LMWH in THR is currently not standard practice in Ireland and hence these cost savings are likely to be overestimated.

9. The results of this economic evaluation indicated that dabigatran etexilate therapy for the primary prevention of venous thromboembolic events in adult patients undergoing total hip replacement or total knee replacement was dominant when compared to enoxaparin. We believe that dabigatran etexilate can be considered cost effective for this particular indication in the Irish healthcare setting.