Cost Effectiveness of Apixaban (Eliquis®) for the Prevention of Venous Thromboembolic Events in Adult Patients who have Undergone Elective Total Hip Replacement or Total Knee Replacement

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1. Apixaban (Eliquis®) is an oral, reversible, direct and highly selective active site inhibitor of factor Xa. In January 2012 Bristol-Myers Squibb Pharmaceuticals and Pfizer Healthcare Ireland submitted an economic evaluation on the cost effectiveness of apixaban for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement (THR) or total knee replacement (TKR) surgery.

2. The basecase compared apixaban with enoxaparin using direct head-to-head evidence. In ADVANCE 2 patients undergoing elective unilateral or bilateral TKR were randomised to double-blind treatment with oral apixaban 2.5 mg twice daily (BD) (n=1528) or enoxaparin 40mg once daily (OD) (n=1529) for 10 to 14 days. The primary outcome (composite of asymptomatic and symptomatic deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), and all-cause mortality during treatment) was reported in 15% and 24% of apixaban and enoxaparin patients respectively (Odds Ratio (OR) = 0.55; 95% CI 0.438, 0.691: p<0.00001)). Apixaban was superior for the primary endpoint. For symptomatic VTE or VTE-related death, the frequencies were 0.5% (7/1528) vs. 0.5% (7/1529). There were no statistically significant differences between apixaban and enoxaparin in the incidence of any bleeding events (OR= 0.81; 95% CI 0.62, 1.07: p=0.12). In ADVANCE 3 patients undergoing THR were randomised to receive apixaban 2.5mg BD (n=2699) or enoxaparin 40mg OD (n=2708) for 32 to 38 days. The primary efficacy outcome occurred in 1.4% and 3.9% of the apixaban and enoxaparin groups respectively (OR=0.35; 95% CI 0.224, 0.546: p<0.00001). Apixaban was superior for the primary endpoint. For symptomatic VTE or VTE-related death, the frequencies were 0.1% (4/2708) vs. 0.4% (10/2699) p=0.11. There were no statistically significant differences between apixaban and enoxaparin in the incidence of any bleeding events (OR= 0.93; 95% CI 0.79, 1.09: p=0.38).

3. Apixaban was also compared to dabigatran. In the absence of head-to-head evidence, a Bucher *et al* indirect comparison was used to incorporate data from relevant randomised controlled trials (enoxaparin 40mg OD was the common comparator). ADVANCE 2 and RE-MODEL (dabigatran vs. enoxaparin (both 6 to 10 days) were incorporated into the adjusted indirect comparison for the TKR analysis. ADVANCE 3 and RE-NOVATE (dabigatran vs. enoxaparin (both 28 to 35 days) were included in the indirect comparison for the THR analysis. Dabigatran was significantly less efficacious than apixaban (THR: OR = 2.511; 95% CI 1.497, 4.212: p=0.0005; TKR: OR=1.718; 95% CI 1.221, 2.417: p=0.002) for the prevention of the composite outcome (all VTE and all-cause death). There were no statistically significant differences between apixaban and dabigatran in the incidence of any bleeding events (THR: OR= 1.161; 95% CI 0.861, 1.567: p=0.33; TKR: OR = 1.185; 95% CI 0.8, 1.755: p=0.40).

4. A Cost-Utility and Cost-Effectiveness Analysis (CUA/CEA) was undertaken using a comprehensive two-stage Decision tree/Markov model. Events in the peri-operative (includes the prophylaxis phase (hospital admission to end of prophylaxis) and post-prophylaxis phase (to 90 days)) were modelled within the decision tree. The events covered include VTE events (PE, proximal DVT and distal DVT), intracranial haemorrhage (ICH), other major bleeding, non-major clinically relevant bleeding and minor bleeding. The health status of patients as they exit the decision tree is used to inform the longer term (chronic phase) events within the Markov model (to 35 years).

5. The CUA and CEA predict that apixaban dominates both comparators in either disease state. One-way sensitivity (SA) indicates that the model results are robust. The probabilities that apixaban is the most cost effective option after THR are 99.85% (at €20,000/QALY) and 99.95% (at €45,000/QALY). After TKR there is a 100% probability of cost effectiveness at either threshold. The review team note that a number of parameters are fixed during the PSA. Therefore, it is likely that the PSA underestimates the decision uncertainty.

6. The review team have concerns regarding a number of parameters in the economic model. In particular, the risks of developing a recurrent VTE or post thrombotic

syndrome (PTS) after an asymptomatic VTE are higher than the risks after a symptomatic VTE. Further, patients with no primary VTE are not at risk of idiopathic VTE and idiopathic PTS. The economic model also assumes that all recurrent VTEs are symptomatic. This structural uncertainty has been investigated; alternative parameters were introduced into the model. Apixaban continued to dominate.

7. The submitted net budget impact (which estimates an uptake of about 14% by end of Year 5) indicates that apixaban has the potential to generate 5-year cumulative savings of about €301,408. The 5-year cumulative gross budget impact is estimated to be in the region of €400,700. The NCPE considers that this budget impact may be an underestimate. If the end of Year-5 uptake is increased to 30%, the 5-year cumulative gross impact is estimated to be about €888,559. The net budget impact indicates a potential 5-year cumulative saving of about €959,376. In a further analysis, the NCPE reduced the duration of enoxaparin prophylaxis from 35 days to 12 days in the THR cohort (similar to the TKR cohort). The cost of public nurse administration was also removed. The 5-year cumulative gross and net impacts are estimated to be about € 400,700 and €139,509 respectively.

8. The NCPE performed an EVPI analysis on the submitted economic model under the assumption that the market share for apixaban is 20% in the first two years and increases to 30% thereafter. The Population EVPI estimate is negligible. The low estimate reflects the high probabilities of cost effectiveness in the PSA. As previously indicated it is likely that the PSA underestimates the decision uncertainty.

9. The National Institute for Health and Clinical Excellence (NICE) Final Appraisal Determination (November 2011) recommends apixaban as an option for the prevention of VTE in adults after elective THR or TKR. Likewise the Scottish Medicines Consortium has accepted apixaban for this indication (December 2011).

10. We believe that apixaban may be considered cost effective (compared to enoxaparin and dabigatran) for this indication. We believe that there is associated

uncertainty and that the true uncertainty has not been explored. The cost effectiveness of apixaban relative to rivaroxaban has not been investigated.