Economic Evaluation of Rivaroxaban (Xarelto®) for the Treatment of Deep Vein Thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.

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1. Rivaroxaban (Xarelto®) is an oral direct factor Xa inhibitor. In November 2011, Bayer Ltd. submitted an economic evaluation on rivaroxaban for the 'Treatment of Deep Vein Thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults'.

2. The cost-effectiveness of rivaroxaban, compared to a Vitamin K antagonist (VKA), was demonstrated using a Markov model. The model is based on the outcomes of the EINSTEIN-DVT trial [1] with longer term (to 40 years) implications of treatment estimated from published literature.

3. EINSTEIN-DVT was an open-label, randomised noninferiority study in patients with acute, confirmed, symptomatic proximal DVT (without symptomatic PE). Oral rivaroxaban (n = 1731) (15 mg twice daily for 3 weeks followed by 20 mg once daily) was compared with enoxaparin followed by a VKA (warfarin or acenocoumarol) (n = 1718). Treatment duration was 3, 6, or 12 months. The incidence rate of the primary efficacy outcome (recurrent VTE - the composite of DVT or non fatal or fatal PE) was 2.1% in the rivaroxaban group and 3.0% in the enoxaparin/VKA group; hazard ratio (HR) = 0.68 (95% CI 0.44, 1.04; p < 0 .001). The test for superiority was not significant. The rates of the primary safety endpoint (clinically relevant bleeding - the composite of major and clinically relevant non-major bleeding) were 8.1% in each group.

4. The Markov model default ('combined across treatments') applies a distribution independent of treatment pertaining to (a) the probability that a venous thromboembolism is a DVT and (b) the probability that a major bleed manifests as an intracranial haemorrhage. The model also includes an option to apply a treatment specific distribution ('single arm') to events for rivaroxaban and VKA arms based on the observed events in each arm of EINSTEIN-DVT. The review team have considered both options.

5. In the primary analysis, six months of rivaroxaban dominates six months of VKA (GMS and DPS prices) when either model-option is considered. This result was robust to single parameter change. Probabilistic analysis (PSA) indicates that the

'single arm' model is associated with greater uncertainty. In the 'combined across treatments' model the probability that rivaroxaban is the most cost-effective strategy is 99.4% and 97.7% with GMS and DPS prices respectively (at a €20,000/QALY threshold). The respective probabilities fall to 78.8% and 69.1% with the 'single arm' model.

6. The secondary analysis indicates that, with GMS prices, 12 months of rivaroxaban dominates 12 months of VKA when either model-option is considered. With DPS prices, ICERs of €2,945/QALY and €16,232/QALY respectively were obtained for the 'combined across treatments' and 'single arm' models. In the 'combined across treatments' model the probabilities that rivaroxaban is the most cost-effective strategy are 96% and 87% with GMS and DPS prices respectively (at a €20,000/QALY threshold). The respective probabilities fall to 70% and 49.6% with the 'single arms' model.

7. In EINSTEIN-DVT, the time in therapeutic range (TTR) was 57.7% in the VKA group. The economic evaluation assumes a TTR of 61.4%. Subgroup analysis to determine the cost-effectiveness of rivaroxaban vs. VKA in patients with good control of INR has not been presented. In a sub-analysis of EINSTEIN-DVT, the treatment effect of rivaroxaban was similar across different INR subgroups.

   The review team note that there is no specific antidote to the pharmacodynamic effect of rivaroxaban. The economic evaluation assumes that bleeds secondary to either rivaroxaban or VKA are associated with the same costs/consequences.

8. The Net Budget Impact (BI) projects a saving to the HSE in the region of €2.85 million over 5 years. The Gross BI, which only includes the annual cost of rivaroxaban, estimates a cost to the HSE of approximately €9.76 million over 5 years.

9. Expected value of Perfect Information (EVPI) analysis combines both the probability of a decision error and the consequence of this error in terms of financial loss. The uncertainty associated with the 'single arm' model is greater than that associated with the 'combined across treatments' model. The EVPI on

the ‘single arm’ model is presented here. The population EVPI analysis estimates that the potential financial loss over 10 years (at €20,000/QALY) is €0.96 million. The estimate for the 12 month comparison model (at €20,000/QALY) is €1.77 million.

10. The NCPE consider that, at the submitted price, rivaroxaban could be deemed cost-effective for the specific indication of ‘Treatment of DVT, and prevention of recurrent DVT and PE following an acute DVT in adults’. However, the cost-effectiveness of rivaroxaban is sensitive to the assumption that the costs associated with INR monitoring will be released from anticoagulant services in substituted patients.