Economic Evaluation of Rivaroxaban (Xarelto®) for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age >75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

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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 'prevention of stroke and systemic embolism (SE) in adult patients with non-valvular atrial fibrillation (AF) with one or more risk factors, such as congestive heart failure, hypertension, age >75 years, diabetes mellitus, prior stroke or transient ischaemic attack'.

2. The basecase analysis compared rivaroxaban 20mg OD (followed by aspirin once discontinued) to warfarin (followed by aspirin once discontinued). Cost-effectiveness was demonstrated using a comprehensive Markov model. Clinical data inputs were mainly obtained from the ROCKET AF trial. Published literature was used to extrapolate beyond the trial period to life (30 years).

3. Rocket AF is a phase III, multicentre, randomised, double-blind, double-dummy trial which involved over 14,000 patients with nonvalvular AF who were at increased risk for stroke. Patients were randomised to receive either rivaroxaban, 20 mg OD (15 mg OD in moderate renal impairment), or dose-adjusted warfarin with target INR of 2.5 (range 2-3) using point-of-care INR devices to receive true or sham INR values depending on drug allocation. Mean and median $CHADS_2$ scores were 3.5 and 3.0 respectively.

   The primary hypothesis was that rivaroxaban would be non-inferior to warfarin for the primary outcome in the per-protocol population. Testing for noninferiority and superiority was also performed in the intention-to-treat (ITT) population. The primary outcome was stroke (ischemic and haemorrhagic) or SE.

   After a median follow-up of 707 days, 23.7% and 22.2% of participants had discontinued rivaroxaban and warfarin respectively.

   In the per-protocol population, stroke or SE occurred in 188 of 6958 patients

(1.7% per year) in the rivaroxaban group and in 241 of 7004 in the warfarin group (2.2% per year) (HR=0.79; 95%CI 0.66, 0.96; p<0.001 for noninferiority). In the ITT analysis, the primary endpoint occurred in 269 of 7081 patients (2.1% per year) and in 306 of 7090 patients (2.4% per year) in the rivaroxaban and warfarin groups respectively (HR= 0.88; 95%CI 0.74, 1.03; p<0.001 for noninferiority; p = 0.12 for superiority).

No significant difference was found in the rates of major and non-major clinically relevant bleeding with rivaroxaban (14.9% per year) vs. warfarin (14.5% per year) (HR=1.03; 95%CI 0.96, 1.11; p=0.44). There were significant reductions in intracranial hemorrhage (0.5% vs. 0.7%; p =0.02) and fatal bleeding (0.2% vs. 0.5%; p = 0.003) in the rivaroxaban group.

It is noted that the INR, in the warfarin cohort, was in the therapeutic range only 55% of the time.

4. The economic model can be switched to use data from the safety on treatment (SoT) or the ITT populations in ROCKET AF. The review team considers the ITT population to be the most appropriate.

   In the primary analysis (ITT population/GMS prices), the incremental cost-effectiveness ratio (ICER) for rivaroxaban vs. warfarin is €22,663/QALY. This ICER is sensitive to a number of single parameter changes. There is a 40% to 64% probability that rivaroxaban is cost-effective at the threshold range of €20,000 to €30,000/QALY. With DPS prices the ICER increases to €39,330/QALY.

   The ICERs for the SoT population are €15,990/QALY (GMS prices) and €28,989/QALY (DPS prices). There is a 40% to 64% probability that rivaroxaban is cost-effective at the threshold range of €20,000 to €30,000/QALY when the SoT population is analysed.

5. 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 warfarin are associated with the same costs/consequences.

The model assumes that the costs associated with INR monitoring will be released from anticoagulant services in substituted patients.
The model indicates that rivaroxaban is not cost-effective when compared to warfarin in patients who have a good INR control.

6. The company Budget Impact model predicts cumulative 5 year net and gross budget impacts of about €27.8 million and €42.3 million respectively.

7. At a threshold of €20,000/QALY, the 10 year Population Expected Value of Information (PEVPI) is estimated to be in the region of €34.9 million. The impact of changing the threshold was investigated; the PEVPI estimates ranges from about €104.3 million (at €0/QALY) to about €11.6 million (at €100,000/QALY).

8. At the submitted price, the National Centre for Pharmacoeconomics do not believe that rivaroxaban is cost-effective for the prevention of stroke and SE in adult patients with non-valvular AF and one or more risk factors.