Cost-effectiveness of rivaroxaban + aspirin for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral arterial disease (PAD) at high risk of ischaemic events

The NCPE has issued a recommendation regarding the cost-effectiveness of rivaroxaban + aspirin. Following assessment of the applicant's submission, the NCPE recommends that rivaroxaban + aspirin not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Bayer Ireland Ltd) economic dossier on the cost effectiveness of rivaroxaban + aspirin for the prevention of atherothrombotic events in adult patients with CAD or symptomatic PAD at high risk of ischaemic events. The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE.

About the National Centre for Pharmacoeconomics
The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics   **June 2019**

Summary

On the 14th January 2019 Bayer Ireland Ltd submitted an economic dossier on the cost-effectiveness of rivaroxaban + aspirin for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral arterial disease (PAD) at high risk of ischaemic events. Marketing authorisation for rivaroxaban 2.5 mg twice daily, for this indication was granted by the EMA on the 23rd August 2018. Rivaroxaban is a direct acting oral anticoagulant that inhibits clotting factor Xa and aspirin is an antiplatelet agent that inhibits the cyclo-oxygenase enzyme.

The development of atherosclerosis leading to CAD and PAD is attributable to several risk factors including smoking, hypertension, hyperlipidaemia, diabetes mellitus, obesity, alcohol, physical inactivity in addition to genetic pre-disposition and socio-economic status. Despite the use of effective secondary prevention strategies such as antihypertensive agents or lipid lowering drugs 5% to 10% of patients with cardiovascular disease have recurrent events each year. Inhibition of platelet aggregation and the coagulation cascade in patients with stable atherosclerotic vascular disease with rivaroxaban 2.5mg twice daily plus aspirin 75mg daily represents another secondary prevention strategy. The cost-effectiveness of such an approach is the subject of this submission.

1. Comparative effectiveness

The main clinical evidence came from the pivotal clinical trial i.e. the COMPASS study which was a double-blind trial where 27,395 patients with stable atherosclerotic vascular disease were randomised to receive rivaroxaban 2.5mg twice daily + aspirin 100mg once daily (n=9152), rivaroxaban 5mg twice daily (n=9117) or aspirin 100mg once daily (n=9126). The mean age of participants was just over 68 years and approximately 22% were female. Over 90% of patients had a history of CAD and over 27% had a history of PAD. Baseline risk factors included hypertension ~ 75%, smoking ~ 21% and diabetes mellitus ~ 37%. Over 89% were being treated with a lipid lowering drug, ~ 71% were treated with an angiotensin-converting enzyme inhibitor (ACE) or angiotensin II receptor blocker (ARB) and approximately 70% were treated with a β blocker at baseline. The patient population could

be considered representative of the population that are likely eligible for treatment in the Irish healthcare setting.

The primary outcome (measured in the intent-to-treat population) was a composite of cardiovascular death, stroke or myocardial infarction. The study was discontinued after a mean follow-up of 23 months due to superiority of the rivaroxaban + aspirin group. The primary outcome occurred in 379 patients (4.1%) in the rivaroxaban + aspirin group versus 496 patients (5.4%) in the aspirin group, hazard ratio (HR) 0.76; 95% confidence interval (CI), 0.66 - 0.86; P < 0.001. Rivaroxaban alone did not result in better cardiovascular outcomes than aspirin alone and resulted in more major bleeding events. There were 313 deaths (3.4%) in the rivaroxaban + aspirin group as compared with 378 (4.1%) in the aspirin group HR 0.82; 95% CI 0.71 – 0.96; P = 0.01; threshold for significance, 0.0025. The number of patients needed to treat (NNT) with combination therapy over a 23 month period was approximately 77 for the primary endpoint and 139 for death.

COMPASS – CAD reported for the subgroup of patients in the COMPASS trial with coronary heart disease. The combination of rivaroxaban + aspirin was superior to aspirin in reducing the number of patients experiencing the primary endpoint from 460 (6%) to 347 (4%) HR 0.74; 95% CI 0.65 – 0.86; P < 0.0001. Treatment with rivaroxaban alone did not significantly improve the primary outcome measure when compared with aspirin monotherapy.

COMPASS – PAD reported for the subgroup of patients in the COMPASS trial with stable peripheral or carotid artery disease. The combination of rivaroxaban + aspirin reduced the composite endpoint of cardiovascular death, myocardial infarction or stroke from 174 patients (7%) with aspirin alone to 126 patients (5%) HR 0.72; 95% CI 0.57 – 0.90; P=0.0047. Similarly, for major adverse limb events including major amputation with 32 (1%) in the rivaroxaban + aspirin group compared with 60 (2%) in the aspirin group HR 0.54; 95% CI 0.35 – 0.82; P=0.0037. However, major and minor amputations were not significantly reduced by rivaroxaban + aspirin. Rivaroxaban compared to aspirin did not significantly reduce the composite endpoint but did reduce major adverse limb events including major amputation.

2. Safety

The main clinical safety information was derived from the intent-to-treat population from the COMPASS trial where major bleeding events occurred in 288 patients (3.1%) in the rivaroxaban + aspirin group as compared with 170 patients (1.9%) in the aspirin monotherapy group HR = 1.70; 95% CI, 1.45 - 2.05; P < 0.001. This difference was mainly due to bleeding events that led to presentation at an acute care facility or hospitalization. Major bleeding events occurred in more patients in the rivaroxaban group as compared with aspirin alone (255 patients (2.8%) versus 170 patients (1.9%) HR = 1.51; 95% CI, 1.25 - 1.84; P<0.001.

Most of the excess major bleeding with rivaroxaban + aspirin versus aspirin alone was gastrointestinal with no significant difference in the rate of fatal bleeding, intracranial bleeding or symptomatic bleeding into a critical organ. Subgroup analysis indicated that major bleeding was more likely in older patients particularly in those aged 75 years or over. The total number of serious adverse events were higher in the rivaroxaban + aspirin group i.e. 949 (10.4%) as compared to patients treated with aspirin alone at 820 (9.0%). Adverse events classified as blood and lymphatic system, eye, renal and urinary disorders were 2 to 3 times more likely in the rivaroxaban + aspirin group versus the aspirin group.

3. Cost effectiveness

The population in the economic model reflected the therapeutic indication i.e. patients with a diagnosis of stable CAD or PAD at high risk of ischaemic events. A de novo state transition Markov model was created in Microsoft Excel to assess cost-effectiveness following a systematic literature review conducted to identify all relevant cost-effectiveness models applied to a CAD and/or PAD population. The time horizon of the model was 33 years as the model began with patients aged 68 years (78% male). The cycle length was 3 months and a half cycle correction applied. Adverse events were included in the model. Neither treatment discontinuation nor treatment interruption was applied in the model.

The model comprised of six mutually exclusive health states. The outcome was the occurrence of thrombotic events in a high-risk CAD or PAD population, where "main events" were defined as myocardial infarction, ischaemic stroke or intracranial haemorrhage. There were six health states including i) event-free, ii) acute first event, iii) post-acute first event, iv) acute second event, v) post-acute second event and vi) death. Main events were modelled using "acute" or "post-acute" and were differentiated for each health state. The model did not consider the possibility of a third event, as the number of patients experiencing a third event in the COMPASS trial was low.

Patients may experience 'health events', defined as clinical outcomes (not main events), within any health state. The assumption is made that the health events do not affect the subsequent risk of main events or survival. The health events included in the model are major non-fatal extracranial bleed, acute limb ischaemia, major amputation, minor amputation, and venous thromboembolism. The perspective was that of the Health Service Executive (HSE) and only direct healthcare costs were taken into consideration. A discount rate of 5% was used for both costs and outcomes in the model.

Treatment effectiveness applied in the model was derived from the intent-to-treat population from the COMPASS trial where aspirin 100mg daily was a comparator. In Ireland the comparator is aspirin 75mg daily and the applicant assumed equal efficacy. Transition probabilities were calculated from the trial data directly and applied as a constant risk for the first 4 years. The probabilities for the rivaroxaban + aspirin arm were calculated by applying the hazard ratios from the trial to the aspirin transitions. The NCPE review group considered the proportional hazards assumption to be appropriate for the first 4 years of the model. The background mortality data was obtained from the Central Statistics Office and was adjusted to remove the proportion of deaths attributable to CV disease by age and gender in Ireland. The transition probabilities for the first four years were extrapolated over a lifetime horizon in the model using the REACH registry data. The NCPE review group considered that treatment efficacy waning beyond the trial duration would be a more realistic and conservative approach and incorporated this into the NCPE basecase where the treatment effect at 75 years of age reverted to that of aspirin alone.

Utility values were sourced from the COMPASS trial and the values for health states and utility decrements for health events were assumed to be the same for both treatment groups. Costs included in the economic model included drug acquisition costs, drug administration, monitoring costs, health state and health event costs and costs associated with mortality events. The NCPE review group considered the utility and cost data acceptable.

The total annual cost of rivaroxaban + aspirin (inclusive of mark-up, rebate and dispensing fee) was estimated at € 962 per patient. The NCPE review group basecase incremental cost-effectiveness ratio (ICER) was estimated at €54,513/QALY (Incremental Costs: €8,303, Incremental QALYS; 0.152) which was considerably higher than the manufacturers ICER of €28,256/QALY (Incremental Costs: €7,849, Incremental QALYS; 0.28). The review group attempted to run a sensitivity analysis around the ICER but the model functionality did not permit this, rendering it impossible to quantify the uncertainty around the ICER value. According to the applicant's sensitivity analysis the main factors impacting the ICER was patient age (greater the age the less cost-effective) followed by the hazard ratios for mortality from sudden cardiac death and other cardiovascular death.

4. Budget impact

The number of patients treated with rivaroxaban + aspirin per annum was estimated to increase from 2,060 in year one to 20,696 by year five. The gross budget impact was predicted to increase from €1,953,591 in year 1 to €19,629,570 in year 5. The cumulative 5 year gross budget impact was estimated at €46,245,150 with a net 5 year budget impact predicted to be in the region of €42,151,984.

5. Conclusion

The COMPASS trial indicated that treatment of patients with stable atherosclerotic vascular disease with rivaroxaban 2.5mg twice daily plus aspirin 100mg daily resulted in better cardiovascular outcomes but more major bleeding events as compared with aspirin alone. When considering the benefits or otherwise of rivaroxaban + aspirin for secondary prevention of CVD it is important to determine whether other risk factors have been

adequately treated prior to using this expensive treatment option which costs €962 per patient per year. The manufacturer was unable to address the NCPE review group concerns in relation to this.

The review group believes this therapeutic strategy is not cost effective and due to the significant patient numbers the estimated gross budget impact exceeds € 46 million over 5 years. The NCPE recommends that rivaroxaban + aspirin should not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.