

rivaroxaban 2.5mg film-coated tablet (Xarelto®)

Bayer Plc Ltd

11 January 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

rivaroxaban (Xarelto®) is accepted for restricted use within NHSScotland.

Indication under review: Co-administered with acetylsalicylic acid for the prevention of atherothrombotic events in adult patients with:

- coronary artery disease, or
 - symptomatic peripheral artery disease
- at high risk of ischaemic events.

SMC restriction: use in patients with stable coronary artery disease that does not require dual antiplatelet therapy.

Addition of rivaroxaban to low-dose aspirin (acetylsalicylic acid) reduced the incidence of a composite outcome that included stroke, cardiovascular death and myocardial infarction, mainly due to reductions in stroke and cardiovascular death. It also increased the incidence of major bleeding.

Chairman
Scottish Medicines Consortium

Indication

Co-administered with acetylsalicylic acid (aspirin) for the prevention of atherothrombotic events in adult patients with:

- coronary artery disease, or
 - symptomatic peripheral artery disease
- at high risk of ischaemic events.¹

Dosing Information

2.5mg rivaroxaban orally twice daily. It should be taken with aspirin 75mg to 100mg orally once daily. Duration of treatment should be determined for each individual patient based on regular evaluations and should consider the risk for thrombotic events versus the bleeding risks.¹

Product availability date

23 August 2018

Summary of evidence on comparative efficacy

Rivaroxaban is a factor Xa inhibitor that inhibits thrombin formation and development of thrombi. It has been licensed for an additional indication: in combination with aspirin, for the prevention of atherothrombotic events in adults at high risk who have coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD).¹ The submitting company has requested that SMC considers rivaroxaban when positioned for use in patients who have CAD that is stable and does not require dual antiplatelet therapy.

A double-blind phase III study (COMPASS) recruited adults with CAD or PAD. Those with CAD aged less than 65 years had atherosclerosis or revascularisation in at least one additional non-coronary vascular beds or at least two additional risk factors: current smoker, diabetes mellitus, renal dysfunction with estimated glomerular filtration rate <60mL/min, heart failure or non-lacunar ischaemic stroke more than one month before randomisation. Patients entering the study 4 to 14 days after a coronary artery bypass graft (CABG) were randomised at that point. Other patients were randomised if they successfully completed a 30-day run-in where they received aspirin 100mg once daily plus placebo. Patients not currently receiving a proton-pump inhibitor (PPI) were randomised equally to pantoprazole 40mg once daily or placebo. The main randomisation was then stratified by centre and PPI use and patients were equally assigned to oral treatment with rivaroxaban 2.5mg twice daily plus aspirin 100mg once daily, rivaroxaban 5mg twice daily or aspirin 100mg once daily. The primary outcome was a composite of myocardial infarction, stroke and cardiovascular death in the intention-to-treat population, which comprised all randomised patients.^{2,3}

On the advice of an independent data and safety monitoring board the anti-thrombotic part of the study was stopped early at the first interim analysis, after mean follow-up of 23 months. At this point the primary outcome had occurred significantly less often in both the rivaroxaban plus aspirin group and rivaroxaban group compared with low-dose aspirin in the total study population and CAD subgroup representative of the positioning. This was mainly due to reductions in stroke and cardiovascular deaths, with rates of myocardial infarction similar across the groups.^{2,3} Results for the licensed regimen, rivaroxaban plus aspirin, are in table 1 below.

Table 1: Primary, secondary and some tertiary outcomes of COMPASS study.²⁻⁴

Total Study Population			Coronary Artery Disease (CAD) Subgroup		
Rivaroxaban Aspirin	Aspirin	Hazard Ratio (95% CI)	Rivaroxaban Aspirin	Aspirin	Hazard Ratio (95% CI)
N=9152	N=9126		N=8313	N=8261	
Primary outcome: MI, stroke or cardiovascular death					
379 (4.1%)	496 (5.4%)	0.76 (0.66, 0.86)	347 (4.2%)	460 (5.6%)	0.74 (0.65, 0.86)
Secondary outcome: MI, ischaemic stroke, coronary heart disease death or ALI					
329 (3.6%)	450 (4.9%)	0.72 (0.63, 0.83)	299 (4.0%)	411 (5.0%)	0.72 (0.62, 0.83)
Secondary outcome: MI, ischaemic stroke, cardiovascular death or ALI					
389 (4.3%)	516 (5.7%)	0.74 (0.65, 0.85)	349 (4.2%)	470 (5.7%)	0.73 (0.64, 0.84)
Secondary outcome: All-cause mortality					
313 (3.4%)	378 (4.1%)	0.82 (0.71, 0.96)	262 (3.2%)	339 (4.1%)	0.77 (0.65, 0.90)
Non-cardiovascular death					
153 (1.7%)	175 (1.9%)	0.87 (0.70, 1.08)	123 (1.5%)	155 (1.9%)	0.79 (0.62, 1.00)
Cardiovascular death					
160 (1.7%)	203 (2.2%)	0.78 (0.64, 0.96)	139 (1.7%)	184 (2.2%)	0.75 (0.60, 0.93)
Stroke					
83 (0.9%)	142 (1.6%)	0.58 (0.44, 0.76)	74 (0.9%)	130 (1.6%)	0.56 (0.42, 0.75)
Myocardial Infarction					
178 (1.9%)	205 (2.2%)	0.86 (0.70, 1.05)	169 (2.0%)	195 (2.4%)	0.86 (0.70, 1.05)
Main safety outcome: major bleeding					
288 (3.1%)	170 (1.9%)	1.70 (1.40, 2.05)	263 (3.2%)	158 (1.9%)	1.66 (1.37, 2.03)
Fatal bleeding					
15 (0.2%)	10 (0.1%)	1.49 (0.67, 3.33)	14 (0.2%)	9 (0.1%)	1.55 (0.67, 3.58)
Non-fatal symptomatic intracranial haemorrhage					
21 (0.2%)	19 (0.2%)	1.10 (0.59, 2.04)	19 (0.2%)	19 (0.2%)	0.99 (0.52, 1.87)
Non-fatal, non-intracranial haemorrhage, symptomatic bleed into critical organ					
42 (0.5%)	29 (0.3%)	1.43 (0.89, 2.29)	36 (0.4%)	25 (0.3%)	1.42 (0.85, 2.36)
Other major bleeding					
210 (2.3%)	112 (1.2%)	1.88 (1.49, 2.36)	194 (2.3%)	105 (1.3%)	1.85 (1.46, 2.34)
Minor bleeding					
838 (9.2%)	503 (5.5%)	1.70 (1.52, 1.90)	775 (9.3%)	454 (5.5%)	1.74 (1.55, 1.95)
Net clinical benefit: MI, stroke, CV death, fatal or symptomatic bleed into critical organ					
431 (4.7%)	534 (5.9%)	0.80 (0.70, 0.91)	392 (4.7%)	494 (6.0%)	0.78 (0.69, 0.90)

MI = myocardial infarction; ALI = acute limb ischaemia; CI = confidence interval

Key secondary outcomes were assessed in the following order: (1) a composite of coronary heart disease death, myocardial infarction, ischaemic stroke or acute limb ischaemia; (2) a composite of cardiovascular death, myocardial infarction, ischaemic stroke or acute limb ischaemia and (3) all-cause mortality. All were reduced in the rivaroxaban plus aspirin group versus low-dose aspirin alone. The reduction in all-cause mortality (0.7% in total population and 1.0% in CAD subgroup) was due to reductions in both cardiovascular (0.5% and 0.6%, respectively) and non-cardiovascular (0.2% and 0.4%, respectively) deaths. In the total study population the reduction in non-cardiovascular deaths was mainly due to a reduced rate of malignancy.²⁻⁴

Net clinical benefit, defined as myocardial infarction, stroke, cardiovascular death, fatal or symptomatic bleed into a critical organ, indicated a benefit with the addition of rivaroxaban to low-dose aspirin in the total study population (difference 1.2%) and CAD subgroup (difference 1.3%).²⁻⁴

Summary of evidence on comparative safety

The European Medicines Agency (EMA) review noted that no new safety concerns were identified and the main concern with rivaroxaban was bleeding. It concluded that rivaroxaban's safety profile in the COMPASS study did not differ markedly from previous studies of rivaroxaban.²

The main safety outcome of the COMPASS study was major bleeding, defined by a modification of the International Society on Thrombosis and Haemostasis (ISTH) criteria. It included fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring re-operation and bleeding that led to hospitalisation, including presentation to acute care facility without overnight stay. It occurred at a higher rate with rivaroxaban plus aspirin compared with aspirin alone in the total study population and in CAD subgroup (differences 1.2% and 1.3% in respective populations) and was mainly due to increased bleeding that led to hospitalisation. In the total population rates of hospital admission for bleeding were 1.7% with rivaroxaban plus aspirin and 0.8% with aspirin alone. These were mainly for gastro-intestinal bleeding, 1.2% versus 0.5%, respectively. Results for the main safety outcome and component parts are presented in table 1 above.²

The population for other safety analyses included all patients who had received at least one dose of study treatment. Events of bleeding, which were reported as outcomes, were not included as adverse events. In the rivaroxaban plus aspirin group compared with the aspirin alone group, treatment-emergent adverse events were reported by 13% (1219/9134) and 12% (1140/9107), with 4.6% and 3.1% treatment-related, 7.0% and 6.4% serious and 0.6% and 0.2% treatment-related serious adverse events in the respective groups. Study drug was discontinued due to adverse events in 3.4% and 2.6% of patients, respectively. Adverse events were mainly gastrointestinal events and blood or lymphatic disorders. In the CAD subgroup (excluding Japanese patients) treatment-emergent adverse events were reported by 8.8%, and 8.1% in the respective groups and were serious in 5.5% and 5.3%.²

Summary of clinical effectiveness issues

Rivaroxaban is the first anticoagulant licensed for the prevention of atherothrombotic events in patients with PAD or CAD at high risk of these events.¹ The company proposed that it be positioned for use in patients with CAD which is stable and does not require dual antiplatelet therapy.

CAD is characterised by atherosclerosis of the coronary arteries, leading to an increased risk of atherothrombotic events, such as myocardial infarction.² To reduce this risk, patients are given low-dose aspirin 75mg daily or if they are not able to receive this, clopidogrel may be an alternative option.⁵ After acute coronary events (for example, unstable angina, non-ST segment elevation myocardial infarction or ST segment elevation myocardial infarction) patients may receive dual antiplatelet therapy with aspirin plus a P2Y₁₂ adenosine diphosphate (ADP) antagonist antiplatelet (clopidogrel, prasugrel or ticagrelor), with duration of treatment dependent upon risk-benefit balance for each individual patient and usually at least six months. After dual antiplatelet therapy low-dose aspirin would be continued for the majority of patients.⁶ This population with stable CAD after dual antiplatelet therapy is included in the positioning for rivaroxaban. One antiplatelet agent, ticagrelor, is also licensed for use in combination with low-dose aspirin in these patients. It is licensed for prevention of atherothrombotic events in patients who have suffered a myocardial infarction over a year ago and who are at high risk of atherothrombotic events.⁷ SMC has issued advice (number 1224/17) in April 2017 that ticagrelor is not recommended for use within NHSScotland in this indication. No other antiplatelet or anticoagulant medicines are licensed for use in combination with low-dose aspirin for prevention of atherothrombotic events in patients with stable CAD.

In the COMPASS study there was a significantly lower rate of the primary outcome, a composite of myocardial infarction, stroke and cardiovascular death with addition of rivaroxaban to low-dose aspirin both in the total study population (absolute difference 1.3%) and CAD subgroup (absolute difference 1.4%), which comprised 90% of the total study population and is representative of the positioning. The differences were mainly due to reductions in stroke (0.7%) and cardiovascular death (0.5%), with similar rates of myocardial infarction across the treatment groups.^{2,3}

Subgroup analysis of the primary outcome in the total study population by demographic and disease characteristics (age, sex, geographic region, race, weight, renal function, previous tobacco use, history of diabetes, hypertension, dyslipidaemia and PAD) suggest that treatment effects were consistent with the primary analysis, with no significant p-values for interaction.^{2,3} The hazard ratio (HR) was 0.68 (95% confidence interval [CI]: 0.58 to 0.80) in those with no previous CABG (71% of study population), 0.69 (95% CI: 0.33 to 1.47) in the small group (5.3% of study population) with CABG at study baseline and 1.00 (95% CI: 0.77 to 1.28) in the remaining 24% with other prior CABG.²

The EMA review noted that subgroup analysis indicated that magnitude of treatment effect for the primary outcome was less pronounced in the elderly (aged at least 75 years) and not significant in this small group (21% of study population), which was limited by sample size, with a HR of 0.89 (95% CI: 0.69 to 1.14). The HR in the subgroup aged less than 65 years (24% of study population) was 0.63 (95% CI: 0.48 to 0.84) and in the subgroup aged 65 to 74 years (55% of study population) was 0.74 (95% CI: 0.61 to 0.90).^{2,3} However, treatment effect on stroke reduction was considered clinically relevant in these elderly patients. It was also noted that available data suggest that the risk of bleeding increases with age. Therefore, it was advised that the ongoing benefit-risk balance of treatment with rivaroxaban for individual patients should be regularly assessed.²

The anti-thrombotic part of the study was stopped early. This may over-estimate treatment effect, reduce power to detect rarer adverse events, such as severe bleeding, and limit any subgroup analyses. A key issue was multiplicity and interpretation of secondary ordered outcomes, as the multiplicity strategy as planned was no longer valid when the study stopped early and there was no pre-planned strategy to analyse key secondary endpoints at this point. The EMA review noted that, being strict, no formally valid claims can be made for secondary endpoints.^{2,3}

The first two secondary outcomes were composites of atherothrombotic events and supported the primary outcome. The EMA review noted that evidence for the third secondary outcome, all-cause mortality, was less clear and a claim in respect of this could not be supported. It was noted that there was overlap of 95% CI around death rates per 100-patient years and mortality was increased or unchanged in some subgroups.²

Addition of rivaroxaban to low-dose aspirin was associated with an increased incidence of major bleeding, with an absolute difference of 1.2% in total study population and 1.3% in CAD subgroup. This was mainly due to an increased rate of hospital admissions for non-fatal gastro-intestinal bleeding. About a third of the patients were receiving a PPI at baseline and half of the remaining patients were randomised to have a PPI. Therefore, about two thirds of the study population had a gastro-protective medicine.^{2,3} This may limit the application of safety data to clinical practice that does not include the routine use of PPI. Concern about the potentially increased rate of bleeding in practice compared with rate in the study population are compounded by early study termination, which has limited detection of rarer serious bleeding events, including fatal bleeding, intracranial haemorrhage and bleeding into other critical organs.

Net clinical benefit was defined as myocardial infarction, stroke, cardiovascular death, fatal or symptomatic bleed into a critical organ, that is the primary outcome and main safety outcome, excluding bleeding that led to presentation at hospital, admission or re-operation post-surgery. It indicated a benefit with addition of rivaroxaban to low-dose aspirin in the total study population (difference 1.2%) and CAD subgroup (difference 1.3%). However, if the other components of the main safety outcome (that is bleeding leading to hospitalisation, which accounted for much of the difference in bleeding rates) were included in a definition of net clinical benefit, there may be no difference between the groups.^{2,3}

Patients requiring dual antiplatelet therapy were excluded from the COMPASS study. This reflects the proposed positioning. Patients with CAD who were aged less than 65 years of age and did not have evidence of atherosclerosis in a non-coronary vascular bed or two additional risk factor (smoking, diabetes, renal impairment [GFR <60mL/min], heart failure or non-lacunar ischaemic stroke) were excluded.² This may limit application of study results to younger patients who have no or limited concomitant risk factors.

The majority of patients in the COMPASS study were taking lipid-lowering medication (90%), angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor antagonists (71%) and beta-blockers (70%), with concomitant medication including a diuretic in 30% and a calcium-channel blocker in 26%. About three quarters of patients had hypertension and 22% had heart failure. 38% of patients had diabetes and the EMA review noted that information was lacking on their glycaemic control.^{2,3} It is not possible to estimate differences between the study population and the Scottish population in use of concomitant medications that may affect risk of cardiovascular events.

Clinical experts consulted by SMC noted that rivaroxaban in this indication may have limited use in clinical practice in a small number of patients who have a particularly high risk of atherothrombotic events and low risk of bleeding.

*Other data were also assessed but remain confidential.**

Summary of comparative health economic evidence

The company submitted a cost-utility analysis using a lifetime Markov model to evaluate rivaroxaban co-administered with aspirin versus aspirin alone for prevention of atherothrombotic events in adult patients with CAD.

In the analysis, patients received rivaroxaban 2.5mg twice per day plus aspirin 75mg once per day, or aspirin (at 75mg once per day) alone. Clinical data were taken from the COMPASS study for the first four years. It should be noted that the aspirin dose in the COMPASS study was 100mg once daily but the submitting company had considered the possible difference in effect of the 75mg once daily dose, used in clinical practice in Scotland, to be minimal. Patients started off in the model in the “event free” state, and could remain in that state or experience either an acute myocardial infarction (MI), ischaemic stroke (IS) or intracranial haemorrhage (ICH), before moving to a post-acute phase, or experiencing a 2nd event of the same nature of the first. In addition, second events of any kind (MI, IS or ICH) could also occur whilst the patient was in the post-acute phase. Patients could experience death or adverse events as a result of experiencing the cardiovascular MI, IS or ICH events, namely non-fatal major bleeding, venous thromboembolism, acute limb ischaemia, minor amputations or major amputations.

Extrapolation beyond the four year COMPASS study timeframe used a published study based on the REACH registry data that had specified a regression model for predicting long-term cardiovascular events and deaths based on patient age.⁹

Utility data were taken from the COMPASS study which had administered the EQ-5D-3L at various time points. From these data, a repeated measure mixed model that considered the difference in time between two assessments was used in the base case to estimate disutilities from baseline (event free state) as experienced by patients completing the EQ-5D-3L once they are no longer event-free and have experienced other model health states. Scenario analysis explored alternative approaches including those used in the NICE submission for ticagrelor (TA420). However, the range of inputted utility values was narrow.

Cost data included medicines costs, the cost of inpatient, day case and outpatient visits and rehabilitation costs in both acute and post-acute states, as well as for treating the adverse health events and the cost of cardiovascular death. Sources predominantly used to inform costs in the base case were NHS Reference Costs (price year 2017) and a published study.¹⁰

Table 2: The base case results.

	Costs (£)	Life years gained	QALYs gained	Incremental costs (£)	Incremental life years	Incremental QALYs	ICER (£)
Rivaroxaban + Aspirin	9,866	11.57	9.33	3,626	0.257	0.222	16,311
Aspirin	6,240	11.31	9.11	-	-	-	

These data were tested in deterministic and probabilistic sensitivity analyses; scenario analyses were also undertaken. The deterministic analysis identified that uncertainty in parameters of patient age, and hazard ratios for sudden cardiac death, other cardiovascular death and for fatal bleeding, along with those for acute MI events and acute IS events, caused most variation to the ICER. The probabilistic sensitivity analysis estimated the probability of the treatment being cost-effective at £20,000 per QALY gained is 69.21%. At a willingness-to-pay threshold of £30,000 per QALY the likelihood is 93.70%.

The scenario analysis found reducing the time horizon to 15 years caused the biggest increase in the ICER from £16,311 to £22,238. No other scenario raises the ICER above £20,000 per QALY gained.

The main limitations with the analysis were:

- The potential underestimation of the risks (and application of disutilities and costs) associated with bleeding events and more generally many of the costs used may have been underestimated. In the study, if a participant had more than one bleed, only the most serious event was included. However, increasing the cost associated with major bleeding would not have a large impact on the ICER.

- The failure to vary utilities through an appropriate range (and the subsequent potential underestimation of disutilities used in the model) in the sensitivity analysis. Responses received from the submitting company indicated that the results were robust to larger variations in the utility values.
- Uncertainty about the appropriateness of cardiovascular death estimates in the model and ranges used in the sensitivity analysis, and how age impacts results over the longer term. However, the submitting company provided analysis where age hazard ratios for cardiovascular death were reduced arbitrarily by 10% and 20%, this was shown to proportionately raise the ICER by 15% and 30%. Although the number of events informing the hazard ratio for cardiovascular deaths is small, it is also expected that the longer-term use of the regression model involving the REACH registry data means that the model is likely to be estimating the cardiovascular mortality risk conservatively.

Despite the uncertainties described above, the economic case has been demonstrated.

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from: Chest Heart & Stroke Scotland, Thrombosis UK, Anticoagulation UK, and Diabetes Scotland. Chest Heart & Stroke Scotland, Thrombosis UK and Anticoagulation UK are registered charities and Diabetes Scotland is a Scottish Charitable Incorporated Organisation (SCIO).
- Thrombosis UK has received 9.86% pharmaceutical company funding in the past two years, including from the submitting company. Anticoagulation UK has received 25% pharmaceutical company funding in the past two years, including from the submitting company. Both Chest Heart & Stroke Scotland and Diabetes Scotland have not received any pharmaceutical company funding in the past two years.
- Patients with CAD are at increased risk of cardiovascular disease including heart attack and stroke. Patients in this group often have poor quality of life, caused by pain, immobility, restricted life-style, restricted access to work and everyday life and often suffer financial burdens as a result. Worry and anxiety about the risk of having further illness/attacks, particularly a stroke or heart attack, affects patients, family, friends and carers. Coping with diabetes is difficult, dealing with a dual diagnosis of diabetes and CAD magnifies the difficulties.
- Antiplatelet medication is prescribed, but alone, may have limited effectiveness in reducing risk factors in this group. Other medication is prescribed to help manage related risk areas e.g. hypertension/diabetes, but these may have limited effectiveness on reducing further CVD events such as an ischemic stroke without the addition of anticoagulation.

- The addition of rivaroxaban to aspirin might be expected to improve a patient's outcomes including risk of death, stroke and further CVD events. Whilst this may not directly improve a patient's current quality of life, reassurance of the increased protection would be welcomed by patients and their families. There was some anxiety expressed about the increased bleeding risk, particularly for diabetics whose injuries can take longer to heal and are at increased risk of infection. The patient group representing diabetics also mentioned the importance that any additional medicine doesn't negatively impact on glycaemic control and suggested there needs to be further research in this area.

Additional information: guidelines and protocols

In June 2017 the Scottish Intercollegiate Guidelines Network (SIGN) issued publication number 149, *risk estimation and the prevention of cardiovascular disease*. This notes that the favourable benefit to risk profile of aspirin for patients with established cardiovascular disease is well recognised. The guideline recommends that individuals with established atherosclerotic disease should be offered treatment with aspirin 75mg daily. Clopidogrel should be considered in those with symptomatic cardiovascular disease who have aspirin hypersensitivity or intolerance or in whom aspirin causes unacceptable side effects. It also recommends that individuals with a history of stroke or transient ischaemic attack and who are in sinus rhythm should be considered for treatment with clopidogrel 75mg daily or a combination of low dose aspirin (75mg to 300mg daily) and dipyridamole (200mg twice daily) to prevent stroke recurrence and other vascular events.⁵

In April 2018 SIGN issued publication number 151, *management of stable angina*. It recommends that all patients with stable angina due to atherosclerotic disease should receive long-term standard aspirin therapy.¹¹

In April 2016 SIGN issued publication number 148, *acute coronary syndrome*. It recommends that following acute coronary syndrome, all patients should be maintained on long-term aspirin at a dose of 75mg daily and notes that combination therapy with aspirin and a P2Y₁₂-receptor antagonist improves clinical outcomes, recurrent myocardial infarction and death. However, improvements in death and myocardial infarction may be offset by increased rates of major bleeding. The choice of P2Y₁₂ antagonist will vary for different subgroups of patients and will depend on clinical presentation. The guideline recommends that patients should receive dual antiplatelet therapy for six months. Longer durations may be used where risks of atherothrombotic events outweigh the risk of bleeding. Shorter durations may be used where the risks of bleeding outweigh the risk of atherothrombotic events.⁶

In August 2016 the National Institute for Health and Care Excellence (NICE) updated clinical guideline number 126, *stable angina: management*. It recommends that aspirin 75mg daily should be considered for secondary prevention of cardiovascular disease in people with stable angina, taking into account the risk of bleeding and comorbidities.¹²

In July 2013 NICE published clinical guideline number 172, myocardial infarction: *cardiac rehabilitation and prevention of further cardiovascular disease*. It recommends that aspirin should be offered to all people after a myocardial infarction and continued indefinitely, unless they are aspirin intolerant or have an indication for anticoagulation. For patients with aspirin hypersensitivity, clopidogrel monotherapy should be considered as an alternative treatment.¹³

Additional information: comparators

aspirin 75mg daily.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Rivaroxaban	2.5mg orally twice daily	665
Aspirin	75mg orally once daily	
Aspirin	75mg orally once daily	10

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 3 October 2018.

Additional information: budget impact

The number of patients assumed to be eligible to receive rivaroxaban plus aspirin was 110,014 in year 1, rising to 144,743 in year 5. Based on a market share of 0.2% in year 1 to 4.1% in year 5, this results in an estimated 182 patients being treated in year 1, rising to 3,901 in year 5. The estimated budget impact to Scotland is £119k in year 1, rising to £2.6m in year 5.

References

1. Bayer Plc Ltd. Summary of product characteristics for rivaroxaban (Xarelto), last updated 29 August 2018.
2. European Medicines Agency. European public assessment report for rivaroxaban (Xarelto), Committee for Medicinal Products for Human Use (CHMP) assessment report EMA/556022/2018, 26 July 2018.
3. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *New England Journal of Medicine* 2017; 377(14): 1319-30.
4. Connolly SJ, Eikelboom JW, Bosch J, et al. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2018; 391: 205-18.
5. Scottish Intercollegiate Guidelines Network (SIGN). Publication number 149, risk estimation and the prevention of cardiovascular disease, In June 2017.
6. Scottish Intercollegiate Guidelines Network (SIGN). Publication number 148, acute coronary syndrome, April 2016.
7. AstraZeneca UK Ltd. Summary of product characteristics for ticagrelor (Brilique), last updated 6 August 2018.
8. *Commercial in Confidence**
9. Wilson PW, D'Agostino R, Bhatt DL, et al. An international model to predict recurrent cardiovascular disease. *American journal of medicine* 2012; 125(7): 695-703.
10. Walker S, Asaria M, Manca A, et al. Long-term healthcare use and costs in patients with stable coronary artery disease: a population-based cohort using linked health records (CALIBER). *Eur Heart J Qual Care Clin Outcomes* 2016; 2(2): 125-40.
11. Scottish Intercollegiate Guidelines Network (SIGN). Publication number 151, management of stable angina, April 2018.
12. National Institute for Health and Care Excellence (NICE). Clinical guideline number 126, stable angina: management, updated August 2016.
13. National Institute for Health and Care Excellence (NICE). Clinical guideline number 172, myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease, July 2013.

This assessment is based on data submitted by the applicant company up to and including 14 December 2018.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.