NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Rivaroxaban for preventing major cardiovascular events in people with coronary or peripheral artery disease

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of rivaroxaban within its marketing authorisation for preventing major cardiovascular events in people with coronary or peripheral artery disease.

Background

Coronary heart disease (CHD) also known as coronary artery disease or ischaemic heart disease is narrowing (stenosis) of the coronary arteries as a result of a build-up of fatty material in artery walls to form a plaque (also known as atheroma), which results in an insufficient supply of oxygen to the heart muscle. If the atheroma ruptures, it can cause a blood clot (thrombus), a condition referred to as atherothrombosis, which may block blood flow to heart muscles causing a heart attack (myocardial infarction). Sometimes blood clots may dislodge and travel in the blood stream (embolism) and block blood flow to the brain causing a stroke.

Risk factors for CHD include smoking, a diet high in saturated fat, high levels of low-density lipoprotein cholesterol, high blood pressure, diabetes, being overweight or obese, lack of exercise, age, gender and family history.[1] People who survive a cardiovascular event are at high-risk of reoccurrence or developing further cardiovascular disease. CHD is one of the leading causes of death in England, accounting for over 53,000 deaths each year and over 66,000 in 2016. 1.8 million people in England are living with CHD. Incidence of CHD increases with age and is higher among males than females. Mortality and morbidity rates also vary by socio-economic group, geographic area and ethnicity.[2]

Similarly to CHD, peripheral arterial disease (PAD) is caused by atherosclerosis in which narrowed arteries reduce blood flow to your limbs (usually develops in the legs). Many people with peripheral arterial disease have no symptoms. However, some people develop a painful ache in their legs when they walk, which usually disappears after a few minutes rest. In severe cases some people may develop critical limb ischaemia, which can result in tissue loss, ulceration and gangrene. The process of atherosclerosis that causes peripheral arterial disease can also lead to serious and potentially fatal problems such as heart attacks and stroke.[3]

Risk factors for PAD include smoking, diabetes and high blood pressure or cholesterol. The presence of PAD has been shown to identify people who are at increased risk of cardiac and cerebrovascular morbidity and mortality.[3] Approximately 348,000 people in England are living with PAD. The incidence of PAD increases with age and population studies have found that about 20% of people aged over 60 years have some degree of PAD. Over 9,000 people in England died from diseases of the arteries, arterioles and capiliaries, including PAD, in 2016.[2]

NICE clinical guideline 172 for the secondary prevention of atherothrombotic events for people following a myocardial infarction recommends exercise, dietary changes and help to stop smoking for people who smoke. It also recommends that everyone who has an acute myocardial infarction should be offered treatment with a combination of an angiotensin-converting enzyme inhibitor, dual antiplatelet therapy (aspirin plus a second antiplatelet agent), a beta-blocker and a statin. The guideline recommends that aspirin should be offered indefinitely after a myocardial infarction. NICE technology appraisal guidance 420 also recommends ticagrelor in combination with aspirin for people who had a myocardial infarction and who are at high risk of a further event. Ticagrelor should be offered for a maximum of 3 years. NICE clinical guideline 172 also recommends clopidogrel monotherapy as an alternative for people with aspirin hypersensitivity.

People with lower limb PAD are considered separately in NICE clinical guideline 147. The recommendations align with NICE clinical guideline 172 and additionally recommend clopidogrel as an option to prevent occlusive vascular events, in line with NICE technology appraisal guidance 210.

The technology

Rivaroxaban (Xarleto, Bayer) is an anticoagulant which acts by direct inhibition of activated factor X (Factor Xa). Factor Xa is a key component in the formation of blood clots. It is administered orally.

Rivaroxaban does not currently have a marketing authorisation in the UK for preventing major cardiovascular events in people with coronary or peripheral artery disease. It has been studied in a clinical trial as monotherapy or in combination with aspirin compared with aspirin alone in people with coronary or peripheral artery disease.

Intervention(s)	Rivaroxaban in combination with aspirin
Population(s)	Adults with coronary or peripheral artery disease

Comparators	In people with stable coronary artery disease: • aspirin • aspirin in combination with ticagrelor In people with peripheral arterial disease: • aspirin • aspirin in combination with ticagrelor • clopidogrel
Outcomes	The outcome measures to be considered include: • non-fatal myocardial infarction (STEMI and NSTEMI) • non-fatal stroke • urgent coronary revascularisation • bleeding events • limb ischemia • mortality • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. The use and costs of reversal agents for Factor Xa inhibitors should be considered in the modelling. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE	**Related Technology Appraisals:**

recommendations and NICE Pathways	Ticagrelor for preventing atherothrombotic events after myocardial infarction (2016) NICE technology appraisal guidance 420 Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (2010) NICE technology appraisal guidance 210 Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease (2012) NICE technology appraisal guidance 223 **Related Guidelines:** Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease (2013) NICE guideline CG172 Peripheral arterial disease: diagnosis and management (2012) NICE guideline CG147 Stable angina: management (2011) NICE guideline CG126 Cardiovascular disease prevention (2010) NICE guideline PH25 Chest pain of recent onset: assessment and diagnosis (2010) NICE guideline CG95 Cardiovascular disease: identifying and supporting people most at risk of dying early (2008) NICE guideline PH15 **Related Quality Standards:** Cardiovascular risk assessment and lipid modification (2015) NICE quality standard 100 Secondary prevention after a myocardial infarction (2015) NICE quality standard 99 Peripheral arterial disease (2014) NICE quality standard 52 Stable angina (2012) NICE quality standard 21 **Related NICE Pathways:**

	Lower limb peripheral arterial disease (2018) NICE pathway Cardiovascular disease: identifying and supporting people most at risk of dying early (2017) NICE pathway Cardiovascular disease prevention (2017) NICE pathway Chest pain (2017) NICE pathway Myocardial infarction: rehabilitation and preventing further cardiovascular disease (2017) NICE pathway
Related National Policy	NHS England (2017) Manual for Prescribed Specialised Services 2017/18. see: 7. Adult specialist cardiac services (pp31-35) Department of Health and Social Care, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1–5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

What is the treatment pathway for patients with CAD? What other therapies would they be on at this stage? Would they continue on these as well as rivaroxaban?

What is the treatment pathway for patients with PAD? What other therapies would they be on at this stage? Would they continue on these as well as rivaroxaban?

Have all relevant comparators for rivaroxaban been included in the scope? Which treatments are considered to be established clinical practice in the NHS for preventing major cardiovascular events in people with coronary or peripheral artery disease?
Is aspirin in combination with warfarin a comparator for people with CAD and PAD?
Are treatments specifically for intermittent claudication (e.g. naftidrofuryl oxalate) a comparator for people with PAD?

Are the outcomes listed appropriate?

Are there subgroups of people in whom rivaroxaban is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider rivaroxaban will fit into the existing NICE pathways

- Lower limb peripheral arterial disease (2018) NICE pathway,
- Cardiovascular disease prevention (2017) NICE pathway,
- Myocardial infarction: rehabilitation and preventing further cardiovascular disease (2017) NICE pathway?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which rivaroxaban will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider rivaroxaban to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of rivaroxaban can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1. NHS Choices (2016) Cardiovascular disease. Accessed March 2018. Available at: http://www.nhs.uk/conditions/Cardiovascular-disease/Pages/Introduction.aspx
2. British Heart Foundation (2018) Cardiovascular disease statistics 2018. Accessed March 2018. Available at: https://www.bhf.org.uk/research/heart-statistics/heart-statistics-publications/cardiovascular-disease-statistics-2018
3. NHS Choices (2016) Peripheral arterial disease. Accessed March 2018. Available at: https://www.nhs.uk/conditions/peripheral-arterial-disease-pad/