NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Proposed Health Technology Appraisal

Rivaroxaban for the treatment and secondary prevention of venous thromboembolism

Draft scope (Pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of rivaroxaban within its licensed indication for the treatment and secondary prevention of venous thromboembolism.

Background

Venous thromboembolism is a term used to describe deep vein thrombosis and pulmonary embolism. Deep vein thrombosis is the formation of a thrombus in a deep vein, usually of the lower limbs. With deep vein thrombosis, dislodged thrombi may travel to the lungs and this is called pulmonary embolism. Pulmonary embolism can cause sudden death and those who survive a pulmonary embolism occasionally require intensive care and recovery can take several weeks or months.

The NICE clinical guideline (CG92) identifies the following risk factors for venous thromboembolism including active cancer or cancer treatment, age over 60 years, critical care admission, dehydration, known thrombophilias, obesity, the presence of comorbidities such as heart disease and metabolic pathologies, family history, use of hormone replacement therapy or oestrogen containing contraceptive therapy and varicose veins with phlebitis. Venous thromboembolism has an annual incidence of approximately 1 in 2000 of the general population. This varies substantially with age, for people under 40 years the annual incidence is 1 in 10,000, for people over 80 years the incidence rises to 1 in 100. People who have had an episode of venous thromboembolism have a risk of recurrence within 8 years of approximately 30%. However, the risk of recurrence decreases substantially with time.

Treatment for venous thromboembolism is usually initiated with anticoagulant drugs such as heparin or low molecular weight heparin such as enoxaparin, bemiparin, dalteparin or tinzaparin. Continued treatment with an oral vitamin K antagonist, most commonly warfarin is usually given but other vitamin K antagonists such as acenocoumarol or phenindione may be considered for the treatment of people with an allergy or resistance to warfarin. For people at high risk of venous thromboembolism (such as patients with cancer), or for people in whom a vitamin K antagonist is unsuitable, unfractioned heparin or low molecular weight heparin may be continued instead of vitamin K antagonist. People with ongoing risk factors may require long term treatment to prevent recurrence. Frequent monitoring and possible adjustment of dose is required with the use of vitamin K antagonists.

The technology

Rivaroxaban (Xarelto, 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 hold a UK marketing authorisation for the treatment and secondary prevention of venous thromboembolism. It has been studied in clinical trials of people with acute symptomatic deep vein thrombosis without pulmonary embolism in comparison with enoxaparin plus a vitamin K antagonist. It has also been studied in a clinical trial of people with acute symptomatic pulmonary embolism in comparison with enoxaparin plus a vitamin K antagonist. Rivaroxaban has also been compared with placebo in a clinical trial of people with symptomatic pulmonary embolism or deep vein thrombosis who have been treated for 6 or 12 months with rivaroxaban or a vitamin K antagonist.

Intervention(s)	Rivaroxaban
Population(s)	People with acute symptomatic venous thromboembolism (deep vein thrombosis or pulmonary embolism)
Comparators	Initial treatment with unfractioned heparin or a low molecular weight heparin (such as enoxaparin) - Continued therapy with a vitamin K antagonist (such as warfarin) - Continued therapy with unfractioned heparin or a low molecular weight heparin for people at high risk of venous thromboembolism or for whom a vitamin K antagonist is unsuitable
Outcomes	The outcome measures to be considered include: • mortality • recurrent venous thromboembolism • complications following deep vein thrombosis, including post thrombotic syndrome • adverse effects of treatment including bleeding events • 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. 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
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal in Preparation, Dabigatran etexilate for the treatment of acute venous thromboembolic events. Earliest anticipated date of publication TBC Related Guidelines: Clinical Guideline No 92, January 2010. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital Clinical guideline in preparation, Management of venous thromboembolic diseases. Expected date of publication June 2012

Questions for consultation

How are treatment and secondary prevention defined and differentiated in clinical practice? Should treatment and secondary prevention be considered separately in an appraisal?

Have the most appropriate comparators for rivaroxaban been included in the scope? Are the comparators listed routinely used in clinical practice? Is rivaroxaban intended to replace treatment with both heparin/low molecular weight heparin and a vitamin K antagonist?

Are there any subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? Should deep vein thrombosis and pulmonary embolism be considered separately? Should the appraisal differentiate between people with reversible risk factors who do not need long term treatment and people with a continuing risk factor?

Are there any issues that require special attention in light of the duty to have due regard to the need to eliminate unlawful discrimination and promote equality?

What do you consider to be the relevant clinical outcomes and other potential health related benefits of rivaroxaban in the treatment and secondary

prevention of venous thromboembolism particularly when compared with currently used treatment options?

Do you consider the technology 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 the technology 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

NICE intends to appraise rivaroxaban for the treatment and secondary prevention of venous thromboembolism through its Single Technology Appraisal (STA) Process.

Should treatment and secondary prevention of venous thromboembolism be considered together as a single STA, separately as two STAs, or as a Multiple Technology Appraisal (MTA)?

Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp