NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal

Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism

Final scope

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. Other complications of deep vein thrombosis include post-thrombotic syndrome, a chronic disorder that may include symptoms such as pain, heaviness, swelling, cramps, itching or tingling, increased skin pigmentation and ulceration in the affected limb. In addition, chronic thromboembolic pulmonary hypertension is a rare but potentially treatable cause of pulmonary hypertension.

The NICE clinical guideline (CG92, Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital) 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 of thromboembolic disease, use of hormone replacement therapy or oestrogen containing contraceptive therapy and varicose veins with phlebitis. Other risk factors include recent surgery, trauma and immobilisation. The annual incidence is approximately 48-182 per 100,000 of the general population for deep vein thrombosis and approximately 1 in 2000 of the general population for venous thromboembolism. This varies substantially with age - for people under 40 years the annual incidence of venous thromboembolism is 1 in 10,000, whereas 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 and may vary according to the treatment received.

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. Treatment is continued orally with the vitamin K antagonist warfarin or, rarely, with either acenocoumerol or phenindione. For people in whom a vitamin K antagonist is not considered an appropriate treatment, unfractionated heparin or low molecular weight heparin may be continued instead of a vitamin K antagonist. Some people 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 holds a UK marketing authorisation for prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery. However, it does not hold a UK marketing authorisation for the treatment of symptomatic deep vein thrombosis and the prevention of recurrent deep vein thrombosis and pulmonary embolism. 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 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 confirmed symptomatic deep vein thrombosis
Comparators	Initial treatment with unfractionated heparin or a low molecular weight heparin (such as enoxaparin) with continued therapy as follows: - vitamin K antagonist (such as warfarin) - unfractionated heparin or a low molecular weight heparin for people for whom a vitamin K antagonist is not considered an appropriate treatment. - No preventative therapy

Outcomes	The outcome measures to be considered include: • mortality • recurrent venous thromboembolism • complications following deep vein thrombosis, including post thrombotic syndrome and chronic thromboembolic pulmonary hypertension • 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	If the evidence allows, consideration will be given to subgroups according to: • underlying risk of recurrent thromoboembolism including the presence of active cancer. • underlying risk of bleeding (for example people over 60 years of age) 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