NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Rivaroxaban for the treatment of pulmonary embolism and the prevention of recurrent venous thromboembolism

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of rivaroxaban within its licensed indication for the treatment of acute symptomatic pulmonary embolism with or without symptomatic deep vein thrombosis and the prevention of recurrent venous thromboembolism.

Background

Venous thromboembolism is a term used to describe how blood clots (thrombi) form in a vein and can break off (embolise) into the vascular system; it includes deep vein thrombosis (DVT) and pulmonary embolism. Deep vein thrombosis is the formation of a thrombus in a deep vein, usually of the lower limbs. 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. Pulmonary embolism can be either provoked for example, following trauma or from a transient risk factor such as surgery, or unprovoked for example, when there is no known cause or it occurs spontaneously, and this impacts the risk of recurrence. Unprovoked pulmonary embolisms have a higher risk of recurrence than provoked pulmonary embolisms. 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.

The annual incidence of venous thromboembolism is approximately 2 in 1000 of the general population and the annual incidence of diagnosed pulmonary embolism in the UK has been reported as 7–8 per 10,000 people. The risk 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.

The NICE clinical guideline (CG144, venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing) identifies the following as some of the risk factors for venous thromboembolism; thrombophilia, history of deep vein thrombosis, age over 60 years, surgery, obesity, prolonged travel, acute medical illness,

cancer, immobility and pregnancy. Treatment for venous thromboembolism is usually initiated with anticoagulant drugs such as heparin or low molecular weight heparin such as enoxaparin, 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. People who have had cancer or a pregnancy associated thrombosis are usually treated with heparin. 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 the treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.

Rivaroxaban does not hold a UK marketing authorisation for the treatment of pulmonary embolism and the secondary prevention of venous thromboembolism. Rivaroxaban has received a CHMP positive opinion for the treatment of DVT and pulmonary embolism and the prevention of recurrent DVT and pulmonary embolism; this is an extension of a previous license that was considered in TA261. Treatment of pulmonary embolism with rivaroxaban has been studied in two clinical trials of people with acute symptomatic pulmonary embolism with or without deep vein thrombosis that compared rivaroxaban to enoxaparin plus vitamin K antagonist, unfractioned heparin, and warfarin. 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 rivaroxoban or vitamin K antagonist.

Intervention(s)	Rivaroxaban
Population(s)	People with pulmonary embolism.
Comparators	Initial treatment with a low molecular weight heparin (such as enoxaparin, tinzaparin and dalteparin) or fondaparinux with continued therapy as follows: ○ vitamin K antagonist (such as warfarin, acenocoumarol and phenindione). ○ low molecular weight heparin for people for whom a vitamin K antagonist is not considered an appropriate treatment.

Outcomes	The outcome measures to be considered include: • mortality. • venous thromboembolism recurrence. • complications of pulmonary embolism such as pulmonary hypertension and heart failure. • complications following deep vein thrombosis, including post thrombotic syndrome. • adverse effects of treatment (including clinically relevant bleeding). • 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 the subgroups according to: • Underlying risk of bleeding. • Provoked or unprovoked venous thromboembolism. • Presence of active cancer. If evidence allows, consideration will be given to a comparison of rivaroxaban with unfractionated heparin for: • Patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m2) • For patients with an increased risk of bleeding • For patients with PE and haemodynamic instability. Guidance will only be issued in accordance with the marketing authorisation.

Related NICE recommendations	Related Technology Appraisals: Technology appraisal No 170, April 2009. Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults Technology appraisal No. 261, July 2012. Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism Technology appraisal No. 157, Sept 2008. Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults Technology appraisal No. 254, January 2012. Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults Technology appraisal in development. Apixaban for the prevention of venous thromboembolism in acute medical illness 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 No. 144, issued June 2012. Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing Related pathways: August 2012. Venous thromboembolism Quality standards: Quality standard No. 3, June 2010. Venous thromboembolism prevention quality standard