NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of apixaban within its licensed indication for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism.

Background

Venous thromboembolism is a term used to describe deep vein thrombosis and pulmonary embolism. Deep vein thrombosis is the formation of a thrombus (blood clot) in a deep vein, usually of the lower limbs. When deep vein thrombosis occurs, 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.

Venous thromboembolism has an annual incidence of approximately 2 in 1000 of the general population in the UK. This rate 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.

NICE clinical guideline 144 states that patients with confirmed proximal deep vein thrombosis or pulmonary embolism should be offered a choice of low molecular weight heparin or fondaparinux (started as soon as possible) and a vitamin K antagonist (started within 24 hours). Treatment with low molecular weight heparin or fondaparinux should continue for at least 5 days or until an international normalised ratio of greater than or equal to 2 is reached, and treatment with a vitamin K antagonist should continue for 3 months or beyond depending on the person's risk of recurrent venous thromboembolism and risk of bleeding. 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. Clinical guideline 144 recommends that people with active cancer and a deep-vein thrombosis or

pulmonary embolism should receive low molecular weight heparin for at least 6 months. 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.

NICE Technology Appraisals 261 and 287 recommend rivaroxaban as an option for treatment and prevention of deep vein thrombosis and pulmonary embolism, respectively.

The technology

Apixaban (Eliquis, Bristol-Myers Squibb and Pfizer) is an anticoagulant which affects the blood coagulation cascade by directly inhibiting activated factor X (factor Xa), thereby inhibiting thrombin formation and the development of thrombi. It is administered orally.

Apixaban does not currently hold a UK marketing authorisation for the treatment and secondary prevention of venous thromboembolism. It has been studied in a clinical trial for acute treatment of deep vein thrombosis or pulmonary embolism, compared to enoxaparin plus warfarin. It has also been studied for extended prevention of recurrent venous thromboembolism following 6–12 months of anticoagulant treatment for deep vein thrombosis or pulmonary embolism, compared to placebo.

Apixaban holds a UK marketing authorisation for the prevention of venous thromboembolism in people who have undergone elective hip or knee replacement surgery and for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation.

Intervention(s)	Apixaban
Population(s)	People with deep vein thrombosis and/or pulmonary embolism
Comparators	• Initial treatment with a low molecular weight heparin or fondaparinux and continued vitamin K antagonist • rivaroxaban For people with cancer • low molecular weight heparin • rivaroxaban

Outcomes	The outcome measures to be considered include: • mortality • venous thromboembolism recurrence • complications following deep vein thrombosis or pulmonary embolism, including post thrombotic syndrome, heart failure and chronic thromboembolic pulmonary hypertension • adverse effects of treatment (particularly bleeding, including intracranial and gastrointestinal 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 evidence allows, subgroups will be considered by type of venous thromboembolism (pulmonary embolism or deep vein thrombosis). The analysis should consider both those who require a limited period of anticoagulation (3–6 months) and those who require long-term anticoagulation (usually lifelong). Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No 261, July 2012. “Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism”. Review proposal date May 2015. Technology Appraisal No 287, June 2013. “Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism”. Review proposal date May 2015. Technology Appraisal in preparation, “Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism”.

	Earliest anticipated date of publication October 2014. Medical Technology Guidance in progress, "The geko device for venous thromboembolism prophylaxis". Anticipated date of publication March 2014. 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". Review proposal date February 2016. Clinical guideline No 144, June 2012. "Management of venous thromboembolic diseases". Review proposal date June 2015. Related Interventional Procedures: Interventional Procedure No 349, June 2010. "Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism". Related NICE Pathways: NICE Pathway: Venous thromboembolism, Pathway created: May 2011. Related Quality Standards: Quality Standard No 3, VTE prevention quality standard, June 2010. Quality Standard No 29, Quality standard for diagnosis and management of venous thromboembolic diseases, March 2013.
Related National Policy	NHS England National VTE Prevention Programme. http://www.vteprevention-nhsengland.org.uk/ Commissioning Services that deliver High Quality VTE Prevention, May 2013. http://www.england.nhs.uk/wp-content/uploads/2013/05/vte-prev-guide-may2013.pdf Commissioning for quality and innovation (CQUIN): 2013/14 guidance, February 2013. http://www.vteprevention-nhsengland.org.uk/images/files/cquin-%20draft%20guidance%202013-14.pdf

Questions for consultation

Have all relevant comparators for apixaban been included in the scope? Which treatments are considered to be established clinical practice in the NHS for treatment and secondary prevention of venous thromboembolism?

Have all the relevant clinical outcomes and other potential health related benefits of apixaban been included in the scope? Are there any additional outcomes which may be important when comparing apixaban with currently used treatment options?

Are the subgroups suggested in 'other considerations appropriate? Are there any other 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?

Where do you consider apixaban will fit into the existing NICE pathway for venous thromboembolism?

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 apixaban 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 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 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/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp)