Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

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

Final scope

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 cause a 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 consequence of pulmonary embolism.

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 is 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; in particular, people with active cancer should receive low molecular weight heparin (for at least

6 months). NICE Technology Appraisals 261 and 287 also recommend rivaroxaban as an option for treating deep vein thrombosis and pulmonary embolism, respectively.

Some people may require long-term treatment to prevent recurrence of venous thromboembolism. Treatment options used in clinical practice for the long-term secondary prevention of venous thromboembolism include vitamin K antagonists, rivaroxaban and aspirin. Frequent monitoring and possible adjustment of dose is required with the use of vitamin K antagonists.

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.

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion recommending a variation to the terms of the marketing authorisation for apixaban to include "treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults."

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 for whom a vitamin K antagonist is unsuitable: • Low molecular weight heparin or fondaparinux alone • 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 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). If evidence allows, the analysis should also consider people for whom the need for long-term anticoagulation is uncertain and aspirin or no preventative treatment might be considered. If the evidence allows, the analysis should consider separately people with active cancer and include any effect on the person's cancer or cancer treatment. 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 in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.

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 January 2015. Proposed Technology Appraisal, Edoxaban tosylate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. Publication TBC. Medical Technology Guidance No 19, June 2014. “The geko device for reducing the risk of venous thromboembolism”. 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. http://pathways.nice.org.uk/pathways/venous-thromboembolism 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