NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE
Single Technology Appraisal

Edoxaban tosylate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism [ID662]

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of edoxaban tosylate 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 consequence of pulmonary embolism.

Venous thromboembolism has an annual incidence of approximately 1 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 about 0.2 in 1000, whereas for people aged 70–79 years the incidence rises to about 2.4 in 1000. Compared with the general population, people who have experienced one episode of venous thromboembolism have a higher risk of another episode. The risk of recurrence can be reduced using anticoagulation therapy. Approximately 8% of people who have had symptomatic venous thromboembolism and 3 months of anticoagulation treatment with a vitamin K antagonist will experience a recurrence within 12 months of stopping treatment.

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 appraisal guidance 261 and 287 also recommend rivaroxaban as an option for treating deep vein thrombosis and pulmonary embolism, respectively. The final appraisal determination for the appraisal of dabigatran etexilate recommends the treatment as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults.

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

Edoxaban tosylate (brand name unknown, Daiichi Sankyo) is an anticoagulant that acts by direct inhibition of activated factor X (factor Xa). Factor Xa is a key component in the formation of blood clots. Edoxaban tosylate is administered orally.

Edoxaban tosylate does not currently have a marketing authorisation in the UK for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. It has been studied in a clinical trial compared with warfarin in adults with acute symptomatic proximal deep vein thrombosis and/or symptomatic pulmonary embolism. All patients in the clinical trial also received initial treatment with low molecular weight or unfractionated heparin.

Intervention(s)	Edoxaban tosylate
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 • Dabigatran For people for whom a vitamin K antagonist is unsuitable: • Low molecular weight heparin or fondaparinux alone • Rivaroxaban • Dabigatran

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	Related Technology Appraisals Technology Appraisal No. 261, Jul 2012. Rivaroxaban

and NICE Pathways	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, Jun 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 Dec 2014. Technology Appraisal in preparation, Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism. Earliest anticipated date of publication Jun 2015. Medical Technology Guidance No 19, Jun 2014. The geko device for reducing the risk of venous thromboembolism. Related Guidelines: Clinical Guideline No. 92, Jan 2010. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. An update of this guideline will be scheduled into the work programme. Details of the update will be available on the guidelines in development webpage in due course. Clinical guideline No. 144, Jun 2012. Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. Review proposal date June 2015. Related Quality Standards: Quality Standard No. 3, Jun 2010, VTE prevention. Quality Standard No. 29, Mar 2013, Diagnosis and management of venous thromboembolic diseases. Related NICE Pathway: NICE Pathway: Venous thromboembolism, Pathway created May 2011.
Related National Policy	NHS England National VTE Prevention Programme. NHS England Guidance for Commissioners: Commissioning Services that deliver high quality VTE prevention, May 2013.

	Commissioning for quality and innovation (CQUIN): 2013/14 guidance, February 2013 (section 8).