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Single Technology Appraisal (STA)

Deep vein thrombosis, pulmonary embolism (treatment, secondary prevention) – edoxaban tosylate

About you

Your name: [redacted]

Name of your organisation
National Pulmonary Hypertension Service
Hammersmith Hospital, Imperial College Healthcare NHS Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes, but only relating to pulmonary embolism
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? No
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? No
- other? (please specify) Chair of British Thoracic Society Guideline Group on Ambulatory Management of Acute Pulmonary Embolism

What is the expected place of the technology in current practice?

Management of acute deep vein thrombosis (DVT) and pulmonary embolus (PE) as well as secondary prevention has undergone significant changes over the last few years with the advent of direct oral anticoagulant drugs. Up to a few years ago patients with a new diagnosis of venous thromboembolic disease (VTE, the term used to group DVT and PE) were being treated with low molecular weight heparin (LMWH) by subcutaneous injection for immediate anticoagulation followed by oral

anticoagulants, typically the vitamin K antagonist (VKA) drug, warfarin, which takes several days to reach therapeutic levels as measured by the INR blood test (international normalised ratio).

Patients should be treated according to NICE Guidelines (CG144) for 3 months and at this point the decision should be made whether or not to continue on treatment (secondary prevention) if they have a significant risk of recurrence. Prior to this guideline, 6 months of treatment was usually the recommended duration for the primary treatment phase and I am aware that many physicians still use this as a guide. It is also clear from the patients I see in my practice that there is quite wide variation in terms of the use of secondary prevention. These discrepancies are not geographical, but without any strong evidence to support this and mainly from discussion with specialists and colleagues as well as from letters received on patients, in my opinion, Haematologists are more likely to recommend secondary prevention than non-Haematologists treating pulmonary embolus, usually Respiratory Physicians.

In the last few years, new anticoagulants have been developed which do not require INR monitoring with more predictable anticoagulation effects and therefore, fixed dosing. These include Rivaroxaban and Apixaban which are in the same class as Edoxaban (Factor Xa inhibitors) and have been given full and draft NICE approval respectively for treatment and secondary prevention of VTE and Dabigatran which works in a slightly different way (direct thrombin inhibitor) but along the same lines as the others with fixed dosing and is also NICE approved for the same indication. Rivaroxaban was the first of these three drugs to gain approval several years ago and is probably the most widely prescribed for this indication. All these drugs, including Edoxaban, have been shown to be non-inferior to the standard LMWH/VKA regime with some reduction in bleeding risk.

The three drugs Rivaroxaban, Apixaban and Dabigatran are the most obvious drugs to consider as alternatives to Edoxaban. The differences between all four of these drugs are relatively subtle with no clear major differences in efficacy or safety. In terms of trial design, Rivaroxaban was tested in an open-label design whereas all the others were tested in a double-blind double dummy design. The major discriminating difference between these agents is whether they require a LMWH lead-in. Both Edoxaban and Dabigatran require the patient to be treated first with LMWH for at least 5 days and then the patient is given a fixed dose of Edoxaban or Dabigatran. Apixaban and Rivaroxaban can be used up-front as soon as the diagnosis is made without a LMWH lead-in, but have to be given at higher dosage (7 days for Apixaban and 21 days for Rivaroxaban) before switching to the maintenance dose. Having a single dose is an advantage for Edoxaban (and Dabigatran) but the LMWH lead-in is seen as a potential disadvantage. In patients who perhaps have been given at least 5 days of LMWH perhaps for other reasons and then need to transfer on to one of these drugs, then Edoxaban or Dabigatran may provide that advantage, but after 7 days, Apixaban could also be used at maintenance dose. Edoxaban and Rivaroxaban are both once daily drugs unlike Dabigatran and Apixaban. In my opinion, once daily is preferable but there are some who believe twice daily is better in terms of compliance since if a single dose is missed the patient only misses 12 hours of therapy. All drugs have relatively similar half-lives and times to peak effect despite the differences in dosing and in theory this could lead to twice daily drugs

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having less fluctuation in plasma levels and perhaps differences in efficacy or bleeding, but this is not clearly borne out in the studies.

Edoxaban was used at a lower dose (30 mg) in patients with renal impairment (creatinine clearance between 30 and 50 ml/min) or body weight < 60 kg in the trial unlike the other agents which use the same dose for all patients. This means that there is a specific dose which has been licensed for patients with moderate renal impairment.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Patients with cancer have a higher risk of recurrence of VTE. Current recommendations suggest that these patients should be treated with LMWH rather than warfarin. There are not enough data to suggest that the new anticoagulants including Edoxaban than can be used in this subgroup of patients.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? circumstances does this occur?

Edoxaban could and should be used in primary and secondary care settings. When being initiated for the primary treatment of VTE, then this will usually be in the secondary care setting. In the primary care setting, Edoxaban is likely to be initiated when switching from other forms of anticoagulation.

The European Society of Cardiology for the management of pulmonary embolism published in 2014 recommended that all four direct oral anticoagulant drugs be used for the treatment and secondary prevention of VTE. This was based on the evidence from the randomised controlled studies resulting in the licensing of these four agents. The other three new oral anticoagulant drugs, Apixaban, Dabigatran and Rivaroxaban have all been reviewed by NICE and approved (draft in the case of Apixaban) based on very similar evidence.

The advantages and disadvantages of the technology

Compared with the standard of care from a few years ago, namely, LMWH followed by VKA, LMWH followed by Edoxaban provides significant advantages in that no monitoring is required since there is fixed dosing, however compared with the other agents listed above which have recently been approved Edoxaban provides no major advantages. In patients with moderate renal impairment, there is a potential benefit of having a specific dose of drug which has been studied and approved in this group. Having a single dose after 5 days of LWMH compared with the scenario of having to adjust the dose after 21 days in the case of Rivaroxaban or 7 days in the case of Apixaban confers some advantage.

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Compared with VKA, Edoxaban has far fewer drug and food interactions and would be much more straightforward to use, but is similar to the other new agents, Rivaorxaban, Apixaban and Dabigatran.

The data for Edoxaban were generated from studies which reflect UK practice and as such the outcomes seen in the studies would also be seen/gained in UK real world practice.

The major concern over Edoxaban as well as the other new direct oral anticoagulant is bleeding. Any anticoagulant will increase the risk of bleeding, however, across all the trials of the direct oral anticoagulant drugs, including Edoxaban, there was a signal suggesting fewer significant bleeding events compared with VKA, which is reassuring in terms of safety. In practice there is the concern that Edoxaban as well as the other new agents cannot be reversed unlike VKA, such that if patients experienced a major bleed wither as a result of trauma or spontaneously, they may be placed at higher risk of adverse outcomes. This disadvantage has to be weighed against the increased convenience of the drug as well as the overall signal suggesting lower risk of spontaneous bleeding. While antidotes are being developed, these are not yet proven for clinical use.

Equality and Diversity

I cannot think of any possible reason why this treatment could be affected by issues of equality and diversity.

Any additional sources of evidence

There are no other sources of information of which I am aware which could be relevant to this appraisal.

Implementation issues

If Edoxaban were to be approved by NICE, this would have no major implementation issues since it is very similar to other available and approved drug therapies.