Appendix G -Professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

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

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

Your name: Dr David Bevan FRCP FRCPath

Name of your organisation: Royal College of Pathologists and British Society for Haematology

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? √
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? √
- 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)?
- other? (please specify)

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

The expected place of this technology is as an effective orally-administered treatment option for symptomatic acute pulmonary embolism (with or without DVT, but without haemodynamic instability) that does not require monitoring with regular blood tests, and is therefore capable of reducing hospital admission and attendance.

The critical evidence to support this role is the outcome of the EINSTEIN-PE study (Einstein-PE Investigators: New England Journal of Medicine 2012; 366:2525-2527) which demonstrated non-inferiority of rivaroxaban compared to standard LMWH/VKA treatment for PE in terms of its primary efficacy outcome (symptomatic recurrent venous thromboembolism) and its principal safety outcome (major or clinically relevant non-major bleeding).

How is the condition currently treated in the NHS?

Current NHS treatment of pulmonary embolism (PE) and subsequent prevention of recurrent venous thromboembolism (VTE) is essentially uniform, with little or no geographical variation, according to an international evidence-based consensus.

It consists of initial treatment with heparin (low molecular weight heparin [LMWH] by subcutaneous injection, or unfractionated heparin [UFH] by intravenous infusion) combined with a Vitamin K Antagonist (VKA, usually Warfarin). The two drugs are given together until stable therapeutic anticoagulation due to the VKA effect is demonstrated by laboratory testing of the prothrombin time, expressed as an INR (International Normalised Ratio). Therapeutic anticoagulation is taken to be present if the INR is in the range 2-4, when the heparin is withdrawn.

VKA treatment monitored by INR measurements is then continued, on an individualised basis, from three months' to lifelong duration, after consideration of the provoking and/or long-term risk factors for recurrent VTE operating in the specific patient.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

1. The LMWH / UFH plus VKA therapy currently standard (as above) remains the major alternative. The advantages of this regime are its proven efficacy and the long-term experience and published evidence base of its use accumulated by a wide range of clinicians. In the case of life-threatening bleeding (for example cerebral haemorrhage, which occurs at an approximate rate of 0.7 per 100 patient-years) reversal of VKA anticoagulation can be achieved rapidly by infusion of plasma-derived prothrombin-complex concentrates, and there is wide (if sometimes variable) availability and awareness of this antidote in NHS acute units. In less critical circumstances, the VKA effect can be reversed within 24

hours with Vitamin K to allow surgery or other interventions, and this, as well as other aspects of 'bridging' anticoagulant protection in such cases, is broadly understood by clinicians. Given the constraints discussed below, LMWH/VKA treatment is adaptable to an ambulant treatment model. The disadvantages of this modality include the need for close monitoring with blood INR tests, particularly during the initial phase (which often delays the switch to VKA, thereby prolonging inpatient admissions and increasing costs) but also throughout the duration of therapy, involving multiple attendances at anticoagulant monitoring clinics, primary care facilities, or home attendances. These attendances incur a variety of costs, including transport costs. This need for intensive monitoring is due to VKA manifesting potentially dangerous interactions across a very wide range of commonly co-prescribed drug classes, as well as with diet and alcohol intake, which can exaggerate or reduce the anticoagulant effect, thereby reducing the safety and/or efficacy of the regime in practice.

2. In certain clinical contexts (e.g. cancer-associated thrombosis) LMWH is sustained as single-agent therapy for the whole duration of treatment, often with a step-down in dose after the initial 7-10 days of treatment. The advantage of this regime is that regular blood tests are not usually required. The disadvantages are those of cost and the requirement for daily subcutaneous injections, which may be painful, and may require nurse administration (or training input for carers or patients willing to self-inject). LMWH therapy is not as rapidly reversible as VKA therapy in the case of bleeding: protamine sulphate has a partial effect, but effective reversal may take up to 4 hours.

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?

One key sub-group of patients with pulmonary embolism are those who present with concurrent signs of haemodynamic instability, particularly a falling blood pressure (hypotension). This indicates a massive PE obstructing pulmonary artery flow, a high risk of death, and consequently that systemic fibrinolytic therapy (or surgical thrombectomy) is mandatory. Hypotension may be present at the outset or may develop during the first few hours of observation.

Since rivaroxaban is not indicated in PE treated with fibrinolytic therapy or thrombectomy (such patients were ineligible for EINSTEIN-PE), nearly all EINSTEIN-PE subjects (92%) received standard LMWH for at least 24 hours (some up to 48 hours) before randomisation. Presumably, one reason for this pre-randomisation delay was in order to evaluate blood pressure and other potential signs of right heart obstruction, and thereby exclude all patients who would benefit from fibrinolytic therapy. Accordingly, in the real-world implementation of rivaroxaban therapy for PE, this aspect of EINSTEIN-PE will need to be replicated in clinical protocols, with an initial assessment period on LMWH, to exclude patients who could benefit from fibrinolytic therapy or surgical thrombectomy, before introducing rivaroxaban.

The category of PE patients who remain normotensive but have other evidence indicating right heart strain (on echocardiography) or imaging evidence of high-volume thrombus within the pulmonary arteries (sometimes referred to as sub-massive PE) may also require individualised therapy, although such patients were included in EINSTEIN-PE and had non-inferior outcomes.

The use of rivaroxaban in PE occurring in patients with cancer requires further randomised studies of the agent in that clinical context, although patients with this combination were also entered into EINSTEIN-PE and did not differ in outcome.

It would appear that the technology provides equal or possibly greater benefit for older patients with PE. A sub-group analysis of EINSTEIN-PE subjects >75 years of age showed similar non-inferiority in respect of the efficacy outcome, but a possible superiority in respect of bleeding (Buller, Lensing & Prins New England Journal of Medicine 2012; 366:2525-2527 June 28).

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

The technology should initially be used in the acute hospital setting, since this is the only setting in which PE can be diagnosed and assessed. As indicated above, after the acute phase is completed (either in an inpatient or a hospital-delivered ambulant care setting), consideration of the risk factors for VTE operating in the individual patient may lead to prolongation of treatment, which would then be suitable for primary care with intermittent specialist follow-up.

Most acute hospitals have specialised teams for ambulant therapy of acute DVT, and most are extending their remit to the ambulant therapy of appropriate cases of acute PE. Rivaroxaban therapy of acute PE would be suitable for management by these predominantly nurse-led teams.

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

To my knowledge, there are no currently validated UK guidelines on the use of rivaroxaban in the treatment of pulmonary embolism.

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The technology will be easier to use, since it is a single agent given by a single (oral) route. There will be no overlap or switch of two separate drugs during the early phase of therapy governed by the contingent results of laboratory tests (with its capacity for delay and prolongation of inpatient stay). The oral route of the technology will be certain to increase patient acceptability. The total use of blood tests associated with therapy for PE will be much reduced.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

As described above, rules for starting the technology will require an initial pre-treatment phase during which the haemodynamic status of the patient is assessed. This is needed to determine the need for systemic fibrinolytic therapy, since use of the technology is currently contra-indicated if fibrinolytic therapy is given.

Since NICE has already approved the technology as an option in the treatment of acute DVT, and pulmonary emboli (not necessarily symptomatic) are detectable in at least 25% of patients with DVT, non-approval as an option in PE would introduce a problematic and unwelcome requirement for stopping the technology in some circumstances, which would greatly complicate care.

Rules for stopping the technology will depend on assessment of the individual's long-term risk factors for recurrent VTE, as described above. This assessment will be essentially identical to those used to determine length of therapy for the current agent (VKA) used for sustained VTE prophylaxis in such patients.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The EINSTEIN-PE study reflected, as far as possible, the clinical practice of diagnosis and treatment of *de novo* PE, and subject to the reservations indicated

above reflected current UK practice in subgroups of the older patient and the cancer patient with PE. PE is a common complication in acute hospital practice, often occurring in patients with complex co-morbidities, all exclusions from entry into EINSTEIN-PE, and therefore not currently included in the evidence base. Accordingly, the technology should not be used in patients with complex co-morbidities, particularly renal or hepatic compromise, who present with PE. The correct outcomes were measured in the trial and have been validated in many trials of antithrombotic treatment over the years.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The key side effect – or unwanted effect – of all anticoagulants is bleeding, and this equally applies to the technology, which is an anticoagulant. Bleeding was overall identical in both arms of the EINSTEIN-PE study (see above). As described above, a broadly effective NHS strategy exists to reverse the effect of VKA (Warfarin) using a combination of Prothrombin-Complex Concentrate (PCC) and Vitamin K, and empirical evidence to support its capacity to reverse VKA anticoagulation (although there is limited evidence of its effect on *survival* from cerebral or other life-threatening bleeding during VKA therapy, which critically depends on speed of diagnosis and PCC administration).

The reversibility of the anticoagulant effect of the technology in similar circumstances is currently uncertain. Vitamin K is ineffective. Initial *ex vivo* evidence suggests that the coagulation defect in plasma from subjects treated with rivaroxaban can be significantly reversed by PCC. Most units have accordingly adopted this option, but practical examples of PCC use in bleeding associated with the technology remain anecdotal: further evidence is urgently needed.

Any additional sources of evidence

I am not aware of any evidence concerning rivaroxaban treatment in pulmonary embolism, from unpublished studies, registries, or any other potential source, that would not be found by review of the available trial evidence.

Implementation issues

NICE guidance on this technology would be likely to lead to rapid implementation in practice, and a progressive increase in the number of patients with this condition treated with rivaroxaban over a relatively short timescale. Since pulmonary embolism typically presents as a medical emergency, acute receiving medical teams and other hospital clinicians will require extra education and access to detailed in-house guidelines on its use. 24-hour access to rapid and reliable diagnosis with CTPA or

radionuclide lung scanning is already imperative in PE treated with standard heparin/VKA therapy, so this requirement will not change if rivaroxaban treatment is implemented. However, access to rapid PE diagnosis by CTPA or lung scanning is still not optimal in all parts of the NHS, and this will require improvement however the disease is treated.

Implementation of rivaroxaben treatment for PE will require provision of guidance on reversal or amelioration of its anticoagulant effect in the case of bleeding. Because current guidance on this issue is based on very limited evidence, further studies on rivaroxaban reversal are urgently needed.

Although routine monitoring of rivaroxaban therapy, comparable to INR monitoring for VKA, is not required and was not part of EINSTEIN-PE, hospital laboratories will still need to be able to measure the rivaroxaban effect in certain circumstances. This is predictable by analogy with LMWH, which was introduced as never requiring monitoring, whereas anti-Xa assays are now frequently required in complex patients treated with LMWH.

Hospital haemostasis laboratories will therefore need a reliable laboratory method to assess the degree of anti-Xa activity present in the plasma of treated patients, and eventually a specific assay to quantify the plasma level of the active drug.

Each hospital will need to evaluate the performance of their current anti-Xa assay in measuring the rivaroxaban effect if the drug is used to treat PE in complex patients with co-morbidities.

The effect of the drug on frequently-ordered blood tests such as the INR and APTT in the ‘clotting screen’ will need to be established by each laboratory, and staff education carried out so that dangerous degrees of rivaroxaban effect are recognised, and these effects are not attributed to other coagulopathies such as disseminated intravascular coagulation.

Equality
I do not consider that this appraisal, in any way,:

- excludes from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- or 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;
- or could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

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