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.

About you

Your name: [redacted]

Name of your organisation: United Kingdom Clinical Pharmacy Association (UKCPA) Haemostasis, Anticoagulation and Thrombosis Group
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)? ✓ Consultant Pharmacist, Anticoagulation
- other? (please specify)

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

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

Patients with pulmonary embolism are generally treated with immediate parenteral anticoagulation most commonly in the form of a low molecular weight heparin (LMWH). In patients with moderate to severe renal impairment unfractionated heparin may be used instead of LMWH due to its shorter half-life. Traditionally, longer term anticoagulation has been provided to patients using oral vitamin K antagonist anticoagulants such as warfarin started often on the same day as LMWH or shortly after. The LMWH is continued for at least five days or until the patient's INR is within the therapeutic range for 24 hours. For patients presenting with PE and haemodynamic instability they may receive thrombolysis (or embolectomy if thrombolysis is contraindicated) prior to receiving warfarin. Currently there is little variation in this clinical practice across the UK, however there may be variation in patient pathways and whether aspects of care (such as INR monitoring and LMWH prescribing) are provided in primary or secondary care.

Advantages of the traditional combined LMWH / warfarin treatment include the requirement for ongoing and regular contact with healthcare professionals particularly for INR monitoring to ensure the patient's treatment is optimal and reinforce key messages pertaining to management such as how to minimise complications of post thrombotic syndrome in patients also presenting with DVT.

Disadvantages of the traditional combined LMWH / warfarin include managing the patient pathway particularly post-discharge from secondary care if there is not an ambulatory fast response service in place or if there is insufficient capacity in local anticoagulation clinics to ensure that patients' INR is followed up in a timely manner. In addition, if it takes the patient some time to be stabilised on warfarin ensuring an uninterrupted supply of LMWH in areas where primary care prescribing / shared care is not in place can at times be challenging, putting the patient at risk of sub-optimal care. Whilst regular INR monitoring can be regarded as an advantage it can also be regarded as a disadvantage of warfarin therapy, often referred to as time-consuming and inconvenient, particularly in localities where there are limited anticoagulation service models available for patients to choose from. In addition, the need to take injections for some patients may be regarded as a disadvantage of LMWH/warfarin treatment. The lack of a fixed dose and the need for dose adjustments according to INR results can limit the willingness for prescribers to use warfarin in certain patients where there is concern for confusion and ability to adhere to frequently altered doses. In many localities and as per NPSA recommendations, warfarin is not dispensed in medicines compliance aids because of the changing doses. However, there are some localities that have put systems in place to support safe dispensing of warfarin into compliance aids. Warfarin is subject to a wide variety of drug interactions and a number of food interactions, which can make stabilisation of the INR more challenging and necessitate more frequent monitoring.

The introduction of rivaroxaban has the potential to simplify the patient pathway, particularly if prescribed in the primary care setting. As routine coagulation

monitoring is not required patients no longer have to attend an anticoagulation clinic regularly for INR monitoring. However it is noted that there are some instances where coagulation monitoring may be required for patients on rivaroxaban (eg. suspected overdose) and access to monitoring and appropriate interpretation might not be readily available in all settings. In addition, reversal of rivaroxaban is an area where considerable learning is still required. Local and national protocols / guidelines for monitoring and reversal of rivaroxaban should be utilised to ensure appropriate management of patients.

The use of just one medication from initiation of treatment rather than two medications overlapping is an improvement to the patient pathway with the introduction of rivaroxaban, particularly with the absence of LMWH injections. The dosing regimen is simple and apart from reducing from 15mg twice daily to 20mg once daily after three weeks no other dose adjustments are required, making it easier for patients to take. Avoiding the transition between LMWH and warfarin and potential issues of arranging anticoagulation clinic follow up in a timely manner should represent a considerable improvement to the patient experience and may also reduce potential harm through incidents particularly related to the transfer of care. However, procedures for follow up for patients on rivaroxaban still need to be in place to avoid suboptimal care (eg. systems to ensure patients are not inadvertently left on the higher twice daily dose). Rivaroxaban can be dispensed in a medicines compliance aid if required. Rivaroxaban has less drug interactions than warfarin and currently no reported food interactions potentially making it easier to manage particularly in patients receiving a number of different medicines.

Given that rivaroxaban therapy does not require routine monitoring or overlap with LMWH, it should be easier to prescribe and its introduction should simplify the patient pathway. Potential issues with the introduction of rivaroxaban include management of adherence in the absence of the requirement for clinic attendance and INR monitoring. In addition there is a need to understand at the local level how to access monitoring and protocols for reversal, particularly in the primary care setting.

Monitoring

The BCSH clearly outline circumstances where urgent assessment of the degree of anticoagulation with rivaroxaban would be required:

- before surgery or invasive procedure when a patient has taken a drug in the previous 24 h (or longer if creatinine clearance <50 ml/min),
- when a patient is bleeding,
- when a patient has taken an overdose,
- when a patient has developed renal failure,
- when a patient has thrombosis on treatment (to assess whether there is failure of therapy or lack of adherence).

Currently, commercial monitoring is not widely available for rivaroxaban, making accurate and rapid quantitative determination of anticoagulation challenging. More readily available coagulation tests such as APTT and PT can be used to determine

the degree of anticoagulation with rivaroxaban if the sensitivity of reagents used is known and if there is an appreciation of the effect of rivaroxaban on these parameters (e.g. curvilinear versus linear relationships). Commercially available rivaroxaban calibrants can be used by laboratories to determine the sensitivity of the reagents they use. The results of such tests give an indication of therapeutic anticoagulation, over-anticoagulation and under-anticoagulation but cannot be used to determine the plasma concentration of rivaroxaban. At present the input of a specialist is likely to be required to accurately interpret laboratory coagulation results in the context of the last dose, half-life and consideration of factors that affect the pharmacokinetics of rivaroxaban. However this should not preclude the availability of rivaroxaban in primary care, rather it calls for the introduction of clear pathways and lines of communication to ensure optimal patient care is delivered.

The BCSH advise that non-urgent quantitative tests to determine drug levels of rivaroxaban may be required in the following instances:

- patients with deteriorating renal function;
- establishing the optimal dose in patients taking other drugs that are known to significantly affect pharmacokinetics;
- establishing the optimal dose in patients at extremes of body weight.

Quantitative assessment of rivaroxaban can be carried out using the anti-factor Xa chromogenic method.

Reversal

Management options for reversal of over-anticoagulation due to VKA anticoagulants are well defined and benefit from the availability of vitamin K and prothrombin concentrate complex (PCC) which act as specific antidotes to warfarin treatment. Currently there is no specific antidote to reverse anticoagulation with rivaroxaban. As it has a relatively short half-life dose omission should suffice in most cases, but prescribers should keep up to date with local and national guidance on the management of over-anticoagulation. Current BCSH guidance on management of antithrombotic induced bleeding recommends that in addition to treatment cessation, general haemostatic measures should be employed to minimise rivaroxaban related bleeding. PCC, Activated PCC and recombinant activated Factor 7 should be considered for the reversal of ongoing life threatening bleeding with rivaroxaban.

Patient understanding and Adherence

Warfarin has long been recognised as a high risk drug and patients on warfarin receive extensive counselling together with an information pack at initiation. When rivaroxaban is prescribed it will be important that prescribers counsel sufficiently to support its safe use. Because there is no requirement to monitor coagulation frequently with rivaroxaban and no need for injections, patients may underestimate the importance of their anticoagulation therapy and give no thought to the risks of under- or over-anticoagulation. Prescribers will need to stress the importance of adherence. Further, given the short half-lives of the newer agents any missed doses

could rapidly result in under-anticoagulation, leaving the patient at increased risk of thrombotic events, particularly soon after an event.

As there is no requirement for regular monitoring it may be harder to identify non-adherence and address concerns promptly. It is essential that side effects, cautions, drug interactions and monitoring requirements (eg. baseline coagulation and renal function) are communicated effectively because patients will not be reminded at regular anticoagulation clinic appointments.

Patient alert cards are available for patients on rivaroxaban to aid identification that the patient is on rivaroxaban in the event of an emergency. Systems need to be in place to ensure that patients on rivaroxaban receive these cards and understand the importance of keeping them on their person as part of risk management.

Other Licences

Rivaroxaban is currently licensed for DVT treatment and secondary prevention; stroke and systemic embolism prevention in patients with non valvular Atrial Fibrillation (AF) and also for venous thromboembolism prevention in patients post hip or knee replacement. The DVT and AF licences are relatively recent therefore the uptake of prescribing for these indications has been variable as have patient pathways for initiation and continuation of treatment. Over time there has been an increase in the use of rivaroxaban for VTE prevention post hip and knee replacement. Some localities have seen an increase in the use of rivaroxaban in unlicensed orthopaedic indications such as hip fracture, hip revision and removal of metal work from hip procedures, these are short-term indications and prescribing occurs in specialist settings and is not passed to primary care.

Evidence Base

In the open label Einstein –PE non-inferiority study rivaroxaban was compared with standard treatment of LMWH and warfarin, therefore in general the results are applicable to current UK practice. There were a number of study exclusions including patients who had received either thrombolysis or embolectomy. Therefore in the context of current UK practice, there is limited data on the efficacy of rivaroxaban in patients presenting with PE and haemodynamic instability who receive thrombolysis or embolectomy as treatment. The standard dose of enoxaparin for VTE treatment in the UK is 1.5mg /kg once daily. Although not a licensed dose for VTE treatment in the UK the 1mg/kg twice daily dose used in the Einstein – PE study is seen in practice most often in specific circumstances e.g. in patients with active cancer or when treating pregnant patients. The specified target INR range for patients in the LMWH/warfarin arm of the study (2.0 – 3.0) is in line with current UK practice and guideline recommendations. Treatment durations of first provoked PE tend to be between 3-6 months, whereas unprovoked PE frequently warrants longer treatment durations if the risk of recurrence is deemed to outweigh the risk of bleeding, therefore treatment durations within Einstein – PE are applicable to current practice. The results of Einstein – PE demonstrated that rivaroxaban was non-inferior to LMWH / warfarin, with no significant difference in the primary efficacy outcome of the rate of VTE recurrence (50 versus 44 events respectively). The

percentage of time patients in the LMWH / warfarin arm of the study were in range throughout the study was 62.7%. Specifically at month 11, the percentage of time patients were in range was 72.7%, this is comparable to levels of control achieved in the UK, bearing in mind the caveat that there is wide variation in the levels of anticoagulation control observed in clinics across the UK. There was no significant difference in the primary safety outcome of rates of major and clinically relevant nonmajor bleeding. There was a significant reduction in the predefined secondary outcome of the rate of major bleeding in the rivaroxaban arm.

In standard UK practice patients who have had a PE within 4 -12 weeks who have a sub-therapeutic INR (e.g. <1.7 - <1.5) after being established on warfarin generally receive bridging therapy with LMWH to minimise the period of sub-optimal anticoagulation and hence the risk of recurrence, which is greatest soon after an event. The trial authors state that 'in the rivaroxaban group, adherence to therapy was above 80% in 94.2% of patients', whether this level of adherence to therapy can be achieved in the real-world setting remains to be seen, but numerous studies on medication adherence, would tend to suggest that particularly for longer durations of treatment, real-world adherence rates are not sufficient for the benefits of treatments observed in clinical trials to be realised. Another important aspect related to adherence is that due to the short half –life of rivaroxaban anticoagulation cover is rapidly depleted with missed doses, leaving patients suboptimally anticoagulated, therefore sustaining patient adherence particularly soon after an event is of critical importance.

There is no clear consensus on the optimal duration of treatment for recurrent provoked and unprovoked PE, however it is accepted that long-term treatment may be required for selected patients. In the Einstein – Ext superiority study extended durations of treatment for patients who had completed an initial index treatment course of 6 – 12 months and where there was uncertainty about the benefit of continued anticoagulation were randomised to receive rivaroxaban or placebo (double blind design). Results demonstrated that there was a significantly lower rate of recurrence in the rivaroxaban arm at the expense of increased major bleeding (4 vs 0; p=0.11) and increased clinically relevant nonmajor bleeding. It is important to state that data for rivaroxaban for acute treatment of PE and secondary prevention is limited to two years. Therefore the benefits of data after two years are uncertain.
In terms of influencing clinical practice, it would have been useful if the comparator for the Einstein-Extension study was warfarin to ascertain whether it was more appropriate to continue therapy with warfarin or with rivaroxaban.

Patients with cancer

Patients with active cancer and VTE have a greater risk of recurrence. In the UK patients requiring treatment for VTE who have active cancer are treated with LMWH for at least six months rather than LMWH/warfarin as LMWH has shown superior efficacy in this patient group. A small number of patients with active cancer were enrolled in the Einstein – PE study, data showed that rivaroxaban was non-inferior to LMWH/warfarin with similar rates of clinically relevant nonmajor and major bleeding in this patient group. However given that cancer patients did not receive the

standard recommended LMWH treatment, the data cannot be easily transferred to the current clinical context within the UK. Further data comparing rivaroxaban to LMWH treatment is required in this patient group before a change in practice can be fully considered.

Outcomes

The most important outcomes for patients with PE are recurrence of VTE, death, major bleeding and post-thrombotic syndrome for patients presenting with associated DVT. VTE recurrence was a primary outcome in the Einstein trials, death and major bleeding were predefined secondary outcomes in the Einstein – PE trial. In the Einstein – Extension trial major bleeding was a primary safety outcome and death was a secondary safety outcome. Post-thrombotic syndrome was not included as a predefined outcome within the Einstein studies.

Other subgroups

There has been some interest in the potential to use rivaroxaban in patients with a greater baseline risk of bleeding. However, the practicalities of clearly categorising bleeding risk in this patient cohort to aid patient selection for subsequent anticoagulation are uncertain.

Implementation issues

Patients receiving rivaroxaban rather than LMWH/warfarin would benefit from not having to attend regular anticoagulation clinic appointments and not having to use LMWH injections and being maintained on a fixed dose regimen. However, regular follow up may be reduced and this might have an impact on patient understanding of their condition, adherence to their medication and benefits of treatment.

There is no routine monitoring requirement and no need for dose adjustment so intensive training should not be required for prescribers. Prescribers will need to have read the available literature and satisfy themselves that they are aware of the baseline and ongoing monitoring requirements (e.g. adherence, renal function), doses, drug interactions, cautions and contra-indications of use. Prescribers may need occasional support from haematologists or other suitable specialists to interpret coagulation monitoring data, and to manage peri-operative anticoagulation. Local pathways and / or good communication links should facilitate access to this level of support. Reversal of rivaroxaban for life threatening bleed will be dealt with in secondary care with support from specialists.

With the introduction of rivaroxaban for PE alongside other indications for new oral anticoagulants the number of patients receiving warfarin is likely to fall, albeit over a protracted period. Given the fixed costs associated with running an anticoagulation clinic, substantial monies are unlikely to be released from this gradual fall, until such time as patient caseloads drop sufficiently to allow either reduced staff count or reduced number of clinic operation days. The incremental cost of rivaroxaban will vary from region to region largely depending on current cost of INR monitoring.

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Equality
There are no equality issues affecting individuals that fall within the defined protected characteristic categories that UKCPA HAT is aware of in relation to this appraisal.