Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism [ID726]

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: Elizabeth Hardy

Name of your organisation:United Kingdom Clinical Pharmacy Association (UKCPA) Haemostasis, Anticoagulation and Thrombosis Group

Is the group (tick all that apply):

- specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ✓
- employees 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? ✓ see below

The United Kingdom Clinical Pharmacy Association was established in 1981 with the aim of supporting and encouraging the emergence of clinical pharmacy. It brings together like-minded pharmacists from different practice areas to share knowledge, research and experiences. We provide a forum for pharmacists and technicians in all settings, notably community and hospital, to discuss and resolve current Clinical issues.

The Association's mission statement is – 'The UKCPA promotes expert practice in medicines management for the benefit of patients, the public and members by establishing standards, workforce development and advancing innovation in all health care settings. The UKCPA encourages Excellence, Leadership and Partnership'.

The HAT group represents Haemostasis, Anticoagulation and Thrombosis specialist and consultant pharmacists. We are experts in the above areas as well as generalists providing acute and long term care to patients on NOACs.

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What is the expected place of the technology in current practice?
Patients with deep vein thrombosis and/or 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 a fair degree of variability in the clinical practice across the UK. Rivaroxaban is now available and being used to simplify pathways/support ambulatory management. A number of institutions are using rivaroxaban for ambulatory management of DVT, thereby decreasing the need for a hospital admission. There is also variation in patient pathways and whether aspects of care (such as INR monitoring and LMWH prescribing) are provided in primary or secondary care. GP practices initiate treatment for "simple" DVTs and then send patients for an outpatient scan thereby reducing the need for A&E attendances. 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 the complications of post thrombotic syndrome in patients also presenting with DVT. Self-monitoring using point of care tests enable patients to monitor their anticoagulation more frequently thereby allowing more accurate dose adjustments and potential improvement in health outcomes. Other benefits include time and cost savings of attending clinics. Of note is that self-monitoring is not advocated for VTE and only AF and valves.

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 it in certain patients where 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 INR more challenging and necessitate more frequent monitoring.

The introduction of apixaban 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 instances where coagulation monitoring may be required for patients on apixaban and it is less accessible than INR monitoring currently. In addition, reversal of apixaban is an area where considerable learning is still taking place. Local and national protocols/guidelines for monitoring and reversal of apixaban should be utilised to ensure appropriate management of patients. In addition, the use of NOACs for VTE does not negate the need for adequate patient investigation and follow up, for example cancer investigations. Also, there is a need to ensure that the appropriate dose change at one week for apixaban is adequately explained and takes place appropriately.

There is expected to be considerable variation in the uptake of apixaban for VTE. This is because of the lack of real-world experience of using this drug particularly for life-long prevention of PE/DVT. Although apixaban is shown to be affordable, many health economies will shy away from this option because warfarin remains the most cost effective prophylactic treatment.

Difficulty in choosing between rivaroxaban and apixaban (on the clinical evidence) for VTE is another confounding factor that will impede uptake of the newer market entrant. Because the difference between the available NOACs is so difficult to articulate to patients it is unreasonable or impossible to offer patients an informed choice of NOAC. Choice between LMWH plus warfarin versus NOAC is much easier to offer patients.

There is an understandable perception that patients would probably choose NOAC over LMWH plus warfarin. And that if patients are on a NOAC they are unlikely to want to change to warfarin. This perception may well be a disincentive to full implementation of the NICE TA as the consequence of this is an increase in the number of patients on higher cost treatment at no clinical benefit.

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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 apixaban, particularly with the absence of LMWH injections. The dosing regimen is simple and apart from reducing from 10mg twice daily to 5mg twice daily after 7 days no other dose adjustments are required making it easier for patients to take. The dose for prevention of recurrent DVT and/or PE is 2.5mg twice daily which was shown to have equivalent efficacy to the 5mg twice daily dose in the extension trial with a more favourable bleeding profile.

In addition, if required, apixaban can be dispensed in a medicines compliance aid. Apixaban 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 apixaban 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 apixaban 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 apixaban would be required:

- Before surgery or invasive procedure when a patient has taken a drug in the previous 24 hours (or longer if creatinine clearance <50ml/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 apixaban, making accurate and rapid quantitative determination of anticoagulation challenging. More readily available coagulation tests such as APPT and PT can be used to determine the degree of anticoagulation with apixaban if the sensitivity of reagents used is known and if there is an appreciation of the effect of apixaban on these parameters (e.g. curvilinear versus linear relationships). Commercially available apixaban 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 apixaban. 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 apixaban, however this should not preclude the availability of apixaban 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 apixaban 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 apixaban 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 prothrombin concentrate complex (PCC) and activated PCC (APCC) which act as specific antidotes to warfarin treatment. Currently there is no specific antidote to reverse anticoagulation with apixaban. 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 apixaban related bleeding. PCC, APCC and recombinant activated Factor 7 should be considered for the reversal of ongoing life threatening bleeding with apixaban. EHRA guidance suggests that the plasma abundance of the drug may block newly administered coagulation factors, however. The EHRA guidance also suggests that pending more data on the clinical effectiveness of use of PCC, the choice may depend on their availability and experience of the treatment centre.

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 new oral anticoagulants are prescribed it will be important that prescribers counsel sufficiently to support their safe use. Because there is no requirement to monitor coagulation frequently with apixaban 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 apixaban to aid identification that the patient is on apixaban. Systems need to be in place to ensure that patients on apixaban receive these cards and understand the importance of keeping them on their person as part of risk management.

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Other Licences
Apixaban 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.

Evidence base
In the double-blind Amplify non-inferiority study apixaban was compared with standard treatment of LMWH and warfarin, therefore in general the results are applicable to UK practice. There were a number of study exclusions including patients with active bleeding, a high risk of bleeding or other contraindications to treatment with enoxaparin and warfarin; if they had cancer and long-term treatment with low molecular weight heparin was planned; if their DVT or PE was provoked in the absence of a persistent risk factor for recurrence; if less than 6 months of anticoagulant treatment was planned; or if they had another indication for long-term anticoagulation therapy, dual antiplatelet therapy, treatment with aspirin at a dose of more than 165mg daily or treatment with potent inhibitors of CYP 3A4.

The standard dose of enoxaparin for VTE treatment in the UK is 1.5mg/kg once daily, however although not a licensed dose for VTE treatment in the UK the 1mg/kg twice daily dose in the Amplify 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 with Amplify are applicable to current practice. The results of Amplify demonstrated that apixaban was non-inferior to LMWH/warfarin and no significant difference in the primary efficacy outcome of the rate of VTE recurrence (59 versus 71 events respectively). The percentage of time patients in the LMWH/warfarin arm of the study were in range throughout the study was 61%. 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.

The Amplify study showed that a fixed-dose regimen of oral apixaban alone was as effective as conventional treatment consisting of enoxaparin followed by warfarin and was associated with a clinically relevant reduction of 69% in major bleeding.

The trial authors state that “in the apixaban group, adherence to therapy was above 80% or more in 96% 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 apixaban anticoagulation cover is rapidly depleted with missed doses, leaving patients suboptimally anticoagulated, therefore sustaining patient adherence particularly soon after an even 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 Amplify-Ext 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 apixaban or placebo (double blind design). Results demonstrated that there was a significantly lower rate of recurrence in the apixaban arm at the expense of increased clinically relevant nonmajor bleeding, but at reduced major bleeding. In terms of influencing clinical practice, it would have been useful if the comparator for the Amplify-Ext study was warfarin to ascertain whether it was more appropriate to continue therapy with warfarin or with apixaban.

Patients with cancer

Patients with 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. Patients with cancer were excluded from Amplify.

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 or death related to VTE were primary outcomes in the Amplify trials. The principal safety outcomes were major bleeding alone and major bleeding plus clinically relevant nonmajor bleeding.

Implementation issues

Patients receiving apixaban 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 (after the dose reduction following the initial seven days of treatment). However, regular follow up may be reduced and this might have an impact on patient understanding of their condition and adherence to their medication.

There is no routine monitoring requirement and no need for regular 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 apixaban for life threatening bleed will be dealt with in secondary care with support from specialists.

With the introduction of apixaban 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 case load drops sufficiently so as to allow either reduced staff count or reduced number of clinic operation days. The incremental cost of apixaban will vary from region to region largely depending on current cost of warfarin and associated INR monitoring.

Equality

There are considerable equality issues as already demonstrated by the uptake of NOACs for SPAF. Individual patients may not be offered the choice of NOAC due to financial rather than clinical constraints on organisations.