Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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

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)? ✓
- other? (please specify)

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 UKCPA 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 who require anticoagulation.

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

Edoxaban is the most recent addition to the oral non-vitamin K antagonists that can be prescribed in the management of patients for treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism; the UK product licence is however, still pending.

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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.

Warfarin loading

There are several strategies used for initiating warfarin. Irrespective of the strategy used, it often takes up to six weeks for patients to reach and maintain therapeutic INR levels, during which time frequent monitoring of INR and subsequent dose adjustments are warranted. NOACs can streamline this process by allowing for fixed daily dosing which simplifies both the prescribing and administration of OAC and removes the need for regular coagulation monitoring. Dose adjustments with NOACs may be necessary based on renal/hepatic function or concomitant drug therapy, however compared to the often frequent dose adjustments with warfarin, NOAC dosing is simple.

Advantages of warfarin

- 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
- Should a patient present with a major bleed, the INR can be reduced rapidly following the administration of vitamin K or prothrombin complex concentrate. Important to note that the effects may not be immediately reversed, see disadvantages below.
- There are a number of indications for which the NOACs cannot be prescribed, e.g. for patients with mechanical heart valves or those with valvular heart disease/atrial fibrillation; warfarin is therefore the preferred anticoagulant in such patient groups.

Disadvantages of warfarin

- Managing the patient pathway 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.
- Patient acceptability for INR monitoring can sometimes be an issue.
- Warfarin is subject to a number of drug/drug and drug/food interactions, which can make stabilisation of INR more challenging and necessitate more frequent monitoring.
- Although in the event of a bleed the INR can be reversed rapidly, the effects may persist and the patient may continue to bleed despite reversal.
- 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.
- 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.

Advantages of NOACs

- Edoxaban doesn't necessarily provide any new advantages over the other agents. Edoxaban is the latest NOAC and expected to provide the following advantages like the other agents.
- The introduction of edoxaban 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
- Edoxaban has fewer drug interactions than warfarin and there are currently no reported food interactions, potentially making it easier to manage particularly in patients receiving a number of different medicines.
- Fixed daily dosing is safer and more convenient for patient and prescriber.
- In the event of a bleed, the currently available NOACs do not have an antidote/reversal agent, however, there is emerging evidence to suggest that the effects of edoxaban can be reversed following the administration of prothrombotic complex concentrate. An antidote to rivaroxaban is on the way. Currently unknown whether this is transferable to edoxaban.
- Rapidly absorbed, achieving peak plasma concentrations after 1.5 hours, thereby removing the need for any bridging therapies.

Disadvantages of NOACs

The information below relates to the NOACs in general, edoxaban being no better nor worse than the current NOACs available.

- As indicated by the ESC/EHRA, post-marketing surveillance of the currently available NOACs has uncovered some important information with regards to drug/drug interactions that were previously unknown. Edoxaban, is a relatively new drug and its use in clinical practice is limited; as prescribing of edoxaban increases, so too will the amount of information relating to drug/drug interactions.
- There are instances where coagulation monitoring may be required for patients on edoxaban and it is less accessible than INR monitoring currently.
- Reversal of edoxaban is an area where considerable learning is still taking place. Local and national protocols/guidelines for monitoring and reversal of edoxaban 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.
- Potential issues with the introduction of edoxaban 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 edoxaban 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 edoxaban, 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 edoxaban if the sensitivity of reagents used is known and if there is an appreciation of the effect of edoxaban on these parameters (e.g. curvilinear versus linear relationships). Commercially available edoxaban 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 edoxaban. 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

edoxaban, however this should not preclude the availability of edoxaban in primary care, rather it calls for the introduction of clear pathways and lines of communication to ensure optimal patient care is achieved. For many of the scenarios calling for monitoring of NOACs, the patient would be in a secondary care setting or referred to secondary care. The BCSH advise that non-urgent quantitative tests to determine drug levels of edoxaban 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 edoxaban 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 edoxaban. 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 edoxaban related bleeding. PCC, APCC and recombinant activated Factor 7 should be considered for the reversal of ongoing life threatening bleeding with edoxaban. 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 NOACS are prescribed, it is important that prescribers counsel sufficiently to support their safe use. Because there is no requirement to monitor coagulation frequently with edoxaban 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; prescibers will need to stress the importance of adherence. There is a risk that prescribers may also underestimate the risks. 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.
The reduced need for regular monitoring and subsequent lack of patient contact may make it harder to identify and address non-adherence in a timely manner. It is essential that side effects, cautions, drug interactions and monitoring requirements (baseline anticoagulation and renal function) are communicated effectively because patients will not be reminded at regular anticoagulation clinic appointments.

As for warfarin, patients should be advised to carry an oral anticoagulation alert card to indicate to other healthcare professionals that they are prescribed an anticoagulant. Systems need to be in place to ensure that patients on edoxaban receive these cards and understand the importance of keeping them on their person.

Other Licences

The licensing for edoxaban is currently pending for for VTE 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.

Evidence base

In the double-blind Hokusai-VTE non-inferiority study edoxaban was compared with warfarin. For both arms, patients rececived initial treatment with heparin for 5 days. A well-documented limitation of the Hokusai-VTE study is that in practice it would be preferable that patients are treated with edoxaban immediately without any heparin lead-in. Because of this limitation, the methods of the Hokusai-VTE study are not comparable with planned implementation of NOACs in UK practice. Or the methods used in this study where patients are given a heparin lead-in is unlikely to be adopted in UK practice.

There were a number of study exclusions including patients with contraindications to heparin or warfarin, had received treatment for more than 48 hours with therapeutic doses of heparin, had received more than one dose of vitamin K antagonist, had cancer for which long term treatment with low-molecular weight heparin was anticipated, had another indication for warfarin therapy, continued to receive treatment with aspirin at a dose of more than 100mg daily or dual antiplatelet therapy or had creatinine clearance of less than 30ml per minute.

The specified target INR range for patients in the heparin/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 Hokusai-VTE are applicable to current practice. The results of Hokusai-VTE demonstrated that heparin/edoxaban was non-inferior to heparin/warfarin and no significant difference in the primary efficacy outcome of the rate of VTE recurrence (130 versus 146 events respectively). In the patients given the lower dose of edoxaban (30mg for patients with creatinine clearance of 30-50ml per minute or a body weight below 60kg) recurrent VTE occurred in 22 receiving edoxaban versus 30 receiving warfarin. The percentage of time patients in the LMWH/warfarin arm of the study were in therapeutic INR range throughout the study was 63.5%. 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.

Clinically relevant bleeding (major or nonmajor) occurred in 349 patients in the edoxaban group and in 423 in the warfarin group. In the 30mg edoxaban group, clinically relevant bleeding occurred in 58 in edoxaban group versus 92 in the warfarin group. Major bleeding occurred in 11 patients in the edoxaban group versus 22 patients in the warfarin group.

The trial authors state that "in the edoxaban group, adherence to therapy was above 80% or more in 99% 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 edoxaban 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.

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 Hokusai-VTE..

Implementation issues

There is expected to be considerable variation in the uptake of edoxaban 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 edoxaban 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 NOACs (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. Options for OAC should be discussed with the patient and the choice of agent made based on clinical features (cautions, contra-indications, licensed indications all of which should be considered in relation to the patient) and patient preference.

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.

Without a direct comparison of edoxaban (without heparin lead-in) versus LMWH/warfarin, clinicians will not have the evidence-base for prescribing edoxaban in favour of other therapy with direct comparison. Since all NOACs are comparatively priced, the decision to prescribe one agent over another will be based on the strength of clinical evidence, the prescribers' interpretation of that evidence and individual prescriber and patient preference. Because differences between the available NOACs are modest, it may be challenging to provide patients with an indepth understanding of the differences between the NOACs to enable selection of one over another. Discussions to aid patients in making a choice between warfarin versus NOAC is much easier as there are some clear differences that can be discussed in some detail.

Patients receiving edoxaban rather than warfarin would benefit from not having to attend regular anticoagulation clinic appointments and being maintained on a fixed dose regimen. However, regular follow up is likely to be reduced and this might have an impact on patient understanding of their condition and adherence to their medication.

There is no routine coagulation monitoring requirement and no need for regular dose adjustment, nevertheless it is critical that prescribers ensure 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 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 edoxaban for life threatening bleed will be dealt with in secondary care with support from specialists.

With the introduction of edoxaban 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 edoxaban 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 and quality of oral anticoagulation across the UK. Individual patients may not be offered the choice of NOAC due to financial rather than clinical constraints on organisations.