Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Edoxaban tosylate for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation

Thank you for agreeing to make a submission 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 submission, 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:

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 groups represent both Cardiac and 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.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Edoxaban tosylate for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation

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 with non-valvular atrial fibrillation; the UK product licence is however, still pending.
Despite being available to prescribe in the context of stroke prevention since 2010, the uptake of NOACs has not been as high as initially expected and there is a great deal of variability in the choice of oral anticoagulant (VKA vs NOAC) across the UK. However, we anticipate that in view of the trial data to support the use of edoxaban, once a UK product licence is granted, it will be a desirable treatment option to prescribe in patients diagnosed with NVAF.

Currently NOACs are being prescribed in primary care, however use is low. It is important that all prescribers of NOACs whether in primary, secondary or tertiary care understand the implications of prescribing NOACs and undertake to ensure that patients are appropriately educated about the indication for treatment and NOAC therapy. Where appropriate, prescribers may need education on anticoagulation therapy, particularly NOACs to ensure safe and appropriate use.
In some areas, NOAC prescribing clinics have been setup in secondary care for the purpose of initiating anticoagulation therapy, either a NOAC or warfarin, after a diagnosis of NVAF. Options for OAC, are discussed with the patient and the choice of agent is made based on clinical features (cautions, contra-indications, licensed indications all of which should be considered in relation to the patient) and patient preference.

Advantages of warfarin

Advantages of warfarin therapy 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. The NICE guidance on patient self-testing of vitamin K antagonist anticoagulants indicates that for patients with AF self-testing may result in an improvement in anticoagulation control compared to traditional clinic management
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

Disadvantages of warfarin include managing the patient pathway post-discharge from secondary care if there is insufficient capacity in local anticoagulation clinics to ensure that patients' INR is followed up in a timely manner. Whilst regular INR monitoring is useful, it can also be regarded as a disadvantage of warfarin therapy, since the number of follow up appointments to monitor INR and adjust doses is time-consuming and can be a drain on resources, particularly in those localities where there are limited anticoagulation service models available. Patient acceptability for INR monitoring can sometimes be an issue. The use of compliance aids is

increasing, in an attempt to facilitate adherence with prescribed drug therapies; the variable dosing of warfarin would make the use of dosette boxes quite difficult to implement and manage. 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 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.

Warfarin loading

Depending on local policy, clinician preference and patient specific factors (i.e. age, co-morbidities, concomitant drug therapies), the initiation of warfarin in patients with NVAF is somewhat variable.

There are several strategies, which can be implemented when initiating warfarin; slow loading regimes or rapid loading regimes.

Slow loading with warfarin may be preferred since with fast loading there is the risk of paradoxical thrombosis requiring LMWH cover. Some trusts may fully load the patient alongside prophylactic/treatment dose of LMWH whereas others may choose slow loading without LMWH alongside. However, 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 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 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.
- Edoxaban shows non-inferiority to warfarin in terms of reducing stroke, reduction in ICH and reduced CV mortality.
- 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, with data to suggest that it reverses apixaban also. 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.
It is noted that there are instances where coagulation monitoring may be required for patients on edoxaban and it is less accessible than INR monitoring currently. In addition, 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. 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.

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.

Bridging

There is also variation in other aspects of treatment, in particular bridging for invasive procedures where anticoagulation therapy is interrupted. This area of practice is still evolving, especially since there is limited data available on the optimal management of NOACs. The uncertainty is related to the lack of randomised controlled trials. The

time needed for interruption of NOACs is shorter due to their reduced half-life meaning that bridging is potentially unnecessary. There are concerns related to varying pharmacokinetics, limited data in patients with severe renal impairment, variability in routine coagulation tests to demonstrate the presence of therapeutic levels of anticoagulation with NOACs and the absence of specific reversal agents. Therefore some expert bridging groups suggest a longer period of interruption and bridging pre- and post-operatively meaning that the NOACs are potentially not so straight forward to interrupt therapy for an invasive procedure.

National guidance

Monotherapy with aspirin 75mg daily is no longer advocated as a treatment option for stroke prevention in AF. However, in those patients in whom anticoagulation has been refused or is not appropriate, alternative treatment options include the use of dual antiplatelet therapy (aspirin and clopidogrel) or an invasive procedure, left atrial appendage occlusion.

For those patients currently prescribed aspirin 75mg daily for SPAF, primary care teams should be in the process of identifying these patients and are re-calculating their thromboembolic and bleeding risks (CHA_2DS_S-VASc and HAS-BLED) to determine whether anticoagulation is required.

Recent data indicates that only 50% of patients who should receive OAC for stroke prevention are prescribed warfarin. Under use of warfarin is greatest in elderly patients who are at the highest risk of stroke. Given the change in guidelines, it is likely that number of anticoagulated patients will increase and a significant proportion of those patients currently managed with aspirin may receive a NOAC.

Monitoring of edoxaban

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

- 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 as a qualitative measurement for the avoidance of any doubt. 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) anticoagulation can be monitored as a quantitative measurement. 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 quantitive 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 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. Since edoxaban 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. In addition, the guidance states that 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, howeverthe 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.

Licenses

Not currently licensed

Evidence base

In the double blind double dummy ENGAGE-AF-TIMI trial, two once daily regimens of edoxaban were compared with warfarin in 20000 patients with moderate to high risk atrial fibrillation with a mean $CHADS_2$ score of 2.8. Patients were randomised to either warfarin, edoxaban 30mg daily or edoxaban 60mg daily. In general the study design and recruitment is reflective of UK practice, although a significant number of patients with NVAF will be elderly with potential renal dysfunction and on concurrent antiplatelet therapy for other cardiac related comorbidities and these patients were excluded. There were a number of study exclusions including atrial fibrillation due to a reversible disorder, an estimated creatinine clearance of less than 30ml per minute, a high risk of bleeding, use of dual antiplatelet therapy, moderate-to-severe mitral

stenosis, other indications for anticoagulation therapy, acute coronary syndromes, coronary revascularisation or stroke within 30 days before randomisation.
The primary efficacy end point was stroke or systemic embolism. Each edoxaban regimen was tested for noninferiority to warfarin during the treatment period.
Principal safety end point was major bleeding.
During the treatment period, a stroke or systemic embolic event occurred in 232 patients in the warfarin group (representing a rate of 1.5% per year) as compared with 182 patients in the high dose edoxaban group (a rate of 1.18% per year) and 253 patients in the low dose edoxaban group (1.61% per year).
Annualised rate of hemorrhagic stroke was 0.47% with warfarin compared with 0.26% with high dose edoxaban and 0.16% with low dose edoxaban.
The rate of ischaemic stroke was 1.25% with warfarin as compared with 1.25% with high dose edoxaban and 1.77% with low dose edoxaban.
The annualised rate of major bleeding was 3.43% with warfarin versus 2.75% with high-dose edoxaban and 1.61% with low-dose edoxaban. The corresponding annualised rates of death from cardiovascular causes were 3.17% versus 2.74% and 2.71% and the corresponding rates of the key secondary end point (a composite of stroke, systemic embolism, or death from cardiovascular causes) were 4.43% versus 3.85% and 4.23%.
The study indicates that both once daily regimens of edoxaban were noninferior to warfarin for the prevention of stroke or systemic embolism. Edoxaban was associated with significantly lower rates of major bleeding and death from cardiovascular causes.

Stringent and rigorous controls are in place during clinical trials to ensure compliance/adherence to therapy. It is unknown whether similar levels of adherence will be replicated in real life clinical settings. 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 sub-optimally anticoagulated, therefore ensuring patient adherence particularly soon after an event is of critical importance.

In the warfarin group, the percentage of time in the therapeutic range was 68.4% of the treatment period. Only 40% of patients prescribed warfarin attain a TTR of 60% in UK clinical practice despite regular INR monitoring and adherence to prescribed dosing regimes. Presenting another reason why NOACs may be a useful alternative in patients who are difficult to manage and do not achieve therapeutic INR levels on warfarin therapy.

There may be subtle differences among the new anticoagulant agents with respect to prevention of ischaemic stroke, MI, bleeding or death. Direct comparative studies to determine whether these are real differences in clinical efficacy and safety or whether they reflect differences in the pharmacologic properties, the doses used, patient populations, quality of warfarin management or other aspects of the trial designs are unrealistic. Direct studies would need high patient numbers to be powered to show the difference.

Implementation

Our experience of NOACs to date indicates that there will be considerable variation in the uptake of edoxaban for AF. Although NOACs have been shown to be cost effective, the impact of NOACs on budget will be bigger because NOACs cost more. Warfarin has a lower acquisition cost and in some areas depending on the monitoring costs the combined acquisition and monitoring cost for warfarin is less than for NOACs, therefore this may affect uptake of NOACs.

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 NOACs for PE and NVAF the number of patients receiving warfarin is likely to fall, albeit over a protracted period. In view of recent changes to national guidance regarding the place of aspirin therapy in SPAF, an increasing number of patients will require OAC. Currently,in many CCGs/secondary care clinics, the first line treatment option continues to be warfarin despite most recent NICE guidance.

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.