A summary of new antidotes to New Oral Anticoagulants (NOAC’s) and antidotes to NOAC’s currently in development, which could impact NOAC use in the future

February 2016

**SUMMARY**

NOACs offer convenient fixed dosing without need for routine coagulation monitoring and they have predictable pharmacokinetics, fewer interactions and quicker onset (and offset) of action than warfarin. Warfarin can be rapidly reversed but, until now, NOACs have no validated reversal strategies which could compromise the clinical outcome. Three specific antidotes to NOACs have recently been developed or are in current development. These are:

<table>
<thead>
<tr>
<th>Product name(s)</th>
<th>Mode of action / license</th>
<th>UK availability</th>
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<tbody>
<tr>
<td>Idarucizumab</td>
<td>• Fully humanised monoclonal antibody (mAb) fragment. Binds with high specificity and affinity to dabigatran to prevent it from inactivating thrombin and neutralises its anticoagulant effect. Licensed for rapid reversal of anticoagulant effects for emergency surgery or in life-threatening or uncontrolled bleeding.</td>
<td>Launched December 2015 Priced at £2,400 per dose (2 x 50g vials) – shelf life 24 months.</td>
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<tr>
<td>Boehringer Ingelheim</td>
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<td>Andexanet alpha</td>
<td>• Recombinant modified factor Xa decoy protein. Binds and sequesters factor Xa inhibitors (rivaroxaban, apixaban) within vascular space, restoring endogenous factor Xa activity.</td>
<td>Estimated for launch in 2017</td>
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<td>Portola (USA)</td>
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<td>Aripazine (PER977)</td>
<td>• Small, synthetic, water-soluble, cationic molecule. Binds anticoagulants through non covalent hydrogen bonding. Being developed as a universal antidote to NOACs as well as to oral factor Xa inhibitors, fondaparinux, LMWH’s and unfractionated heparins.</td>
<td>Not known</td>
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<tr>
<td>Perosphere (USA)</td>
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Idarucizumab is supported by an ongoing phase 3, prospective, open-label, uncontrolled cohort study (REVERSE-AD) which will complete in July 2017. Published interim results (n=123) show that the median maximum percentage reversal of anticoagulation with dabigatran within 4 hours after intravenous (IV) idarucizumab was 100% in patients with elevated dilute thrombin time and elevated ecarin clotting time at baseline (primary endpoint) in patients with serious bleeding or required and urgent procedure.

Andexanet alfa is supported by two published, parallel, randomised, double-blind, placebo-controlled phase 3 studies (n=145) of IV andexanet used to reverse anticoagulation with apixaban (ANNEXA-A) or rivaroxaban (ANNEXA-R) in healthy older volunteers. Anti–factor Xa activity was rapidly reduced (<2 to 5 minutes) with andexanet compared to placebo in ANNEXA-A (mean reduction, 94% vs. 21%; P<0.001) and in ANNEXA-R (92% vs. 18%. P<0.001). ANNEXA-4 (a phase 4, open-label, single-arm study) was initiated to evaluate the haemostatic efficacy and safety of andexanet alfa in patients with acute bleeding. Completion of this study is expected in 2022.

The pharmacokinetic and pharmacodynamic effects of Aripazine (PER977) were evaluated in a phase 2, double-blind, placebo-controlled dose escalation study aripazine in 80 healthy volunteers who were either untreated or pretreated with 60mg of edoxaban. Aripazine reduced whole-blood clotting time (WBCT) 3 hours after the administration of edoxaban, to within 10% above baseline in <10 minutes compared to 12 to 15 hours with placebo.

In the above studies, NOAC antidotes were well tolerated and data did not suggest any prothrombotic effects or significant immunogenic potential. The above studies may be criticised for several reasons; not being randomised controlled trials (RCTs), use of non-standardised surrogate outcome measures or because the population studied is not reflective of the patient population. A US based Think Tank (sponsored by the FDA) acknowledged the difficulties and time consuming nature of conducting robust RCT’s in relevant populations given the emergency situations in which NOAC antidotes would be used. On consensus, they agreed that NOAC antidotes could be approved for use in life-threatening situations if their pharmacodynamic and pharmacokinetic nature were well characterised and safe in humans and if efforts are made to acquire a body of evidence to demonstrate real-world clinical outcomes.

There is scope for rationalising which NOAC antidotes would need to be stocked in hospitals as this would be based on choice of NOAC used in primary and secondary care (or vice versa). Whilst the manufacturer of idarucizumab estimates that around 1% of patients using NOACs would require antidotes, it is not actually clear how frequently NOAC antidotes would actually be needed. Regardless, their immediate need in acute situations may mean that most hospitals need to carry a stock of them. NOAC antidotes will be expensive and it may be prudent to restrict their use for urgent procedures/life-threatening situations, as per the license for idarucizumab.
Background
The New Oral Anticoagulants (NOACs) are classified into two groups: direct thrombin inhibitor (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban and edoxaban). Factor Xa catalyses the activation of prothrombin into thrombin so all NOACs exert an anti-thrombin effect and prevent activation of fibrinogen into fibrin. (1) Warfarin inhibits the formation of active clotting factors II, VII, IX and X. (2) A meta-analysis compared the safety and efficacy of the four NOACs to warfarin in patients with atrial fibrillation (AF). Whilst NOACs were found to be equally effective in the prevention of stroke, the incidence of intracranial haemorrhage was reduced by almost 50% and there was a significant reduction in all-cause mortality compared to warfarin. (3,4) NOACs have more predictable pharmacokinetics, fewer food and drug interactions, shorter half-lives, and quicker onset of action than warfarin. With the net benefit of the NOACs established and the convenience of fixed dosing without routine coagulation monitoring, NOACs are replacing warfarin as anticoagulants of choice in many patients.

This briefing aims to provide an update on products, including the evidence base underpinning their use, which may be licensed as antidotes to NOACs now or in the relatively near future. (1,3)

Bleeding risk with NOACs
It has been estimated that 1-4% of patients treated with NOACs may experience major bleeding and around 1% may require emergency surgery or rapid reversal of the anticoagulant effect for other reasons. (2) The manufacturer of idarucizumab (a recently licensed antidote to dabigatran) estimates that between 0.3% to 2.87% of patients using dabigatran will experience a major bleed and around 1.2% of patients using dabigatran would be eligible for therapy with idarucizumab. (5) However it is not yet clear how frequently NOAC antidotes will actually be required to manage bleeding emergencies in patients taking NOACs.

The anticoagulant effect of warfarin can be effectively and rapidly reversed by giving phytomenadione (vitamin K) or in severe cases by using prothrombin complexes or fresh frozen plasma to manage bleeding. (6) The NOACs (until now) have no clear and validated mechanism of reversal. (7) Currently, in the event of life-threatening haemorrhage in patients taking NOACs, off-label use of prothrombin complex concentrate, activated prothrombin complex concentrate or recombinant-activated factor VIIa may be considered. However, their effectiveness is not demonstrated in clinical trials and conflicting data mean that no consensus is available for treatment protocols. It is feared that an inability to rapidly reverse the anticoagulant effects of NOACs with validated reversal strategies may seriously compromise the clinical outcome and even render the situation unsalvageable. (1-4,8)

Development of specific antidotes designed to reverse the anticoagulant activity of NOACs may provide an important treatment option for patients who experience a major bleeding event or require emergency surgery. The availability of antidotes to NOACs may help provide clinicians and patients with reassurance about the safety of using NOACs, in case an emergency were to occur. (2)

Antidotes to NOACs
Specific antidotes to NOACs have recently been developed or are in current development. Three products of potential interest were identified. (1,3,4)

- **Idarucizumab** is currently available to reverse the anticoagulant effects of dabigatran.
- **Andexanet alpha** is being developed (for potential launch in 2017) to reverse the anticoagulant effects of rivaroxaban, apixaban and potentially edoxaban.
- **Aripazine (PER977)** is being developed (currently in phase 2 studies) as a universal antidote to reverse the anticoagulant effect of NOACs, oral factor Xa inhibitors, fondaparinux, LMWH’s and unfractionated heparins.

Idarucizumab
Idarucizumab (Praxbind®) is a fully humanised monoclonal antibody (mAb) fragment which binds specifically to dabigatran with high affinity, preventing dabigatran from inactivating thrombin and neutralising its anticoagulant effect. It will not reverse the effects of other anticoagulants. It was launched in December 2015 by Boehringer Ingelheim who also manufactures dabigatran and is indicated in adults treated with dabigatran when rapid reversal of its anticoagulant effects is required for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding. It is restricted to hospital use only. (1,2,8,9)

Clinical trials supporting the use of idarucizumab
An ongoing phase 3, prospective, open-label, non-randomised, uncontrolled cohort study (REVERSE-AD, NCT0210494) is evaluating reversal of the anticoagulant effects of dabigatran 110mg BD by 5g of IV idarucizumab in patients with serious bleeding or requiring an urgent procedure. This trial is expected to complete in July 2017. (5,8-10)

The published interim analysis of REVERSE-AD included data for 123 patients (median age 77): 66 patients with serious bleeding (Group A) and 57 requiring an urgent procedure (Group B). (8-10) The median maximum percentage reversal of anticoagulation within 4 hours after administration of IV idarucizumab was 100% in patients with elevated dilute thrombin time and an elevated ecarin clotting time at baseline (primary endpoint).
Haemostasis was reported in 92% of patients who required surgery or invasive procedures (key secondary endpoint). In an interim analysis for 39 patients with elevated baseline anticoagulation levels, idarucizumab 5g IV infusion led to initiation of emergency surgery as early as 1.7 hours post administration of the drug. (8,10-12)

In the REVERSE-AD study, there were no serious adverse effects or deaths attributable to idarucizumab. It showed no prothrombotic effect and was considered to have a low immunogenic potential. Mild symptoms of potential hypersensitivity (pyrexia, bronchospasm, hyperventilation, rash or pruritus) were reported but no causal relationship to idarucizumab could be established. Other adverse events with >5% frequency were hypokalaemia (9/123; 7%), delirium (9/123; 7%), constipation (8/123; 7%), pyrexia (7/123; 6%) and pneumonia (7/123; 6%). (9)

Andexanet alfa
Andexanet alfa is a recombinant modified human factor Xa decoy protein which binds and sequesters factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) within the vascular space, thereby restoring the activity of endogenous factor Xa. It is currently being developed by Portola (USA) as an antidote for patients taking either rivaroxaban or apixaban. Portola aim to launch it in the USA during 2016 and in Europe during 2017. (1,2,12,13)

Clinical trials supporting the use of andexanet alfa
Two published, parallel, randomised, double-blind, placebo-controlled studies demonstrated the ability of andexanet to reverse anticoagulation with apixaban (ANNEXA-A, NCT02207725) or rivaroxaban ANXEXA-R, NCT02217025) in 145 healthy volunteers aged 50-75. The primary outcome measure was the mean percent change in anti–factor Xa activity. Subjects were randomly assigned in a 3:1 (ANNEXA-A) or 2:1 ratio (ANNEXA-R) to receive andexanet or matching placebo in two consecutive parts. Part 1 evaluated andexanet as an IV bolus and part 2 evaluated andexanet as an IV bolus followed by a continuous IV infusion. In ANNEXA-A, subjects received apixaban 5mg BD for 3.5 days and then andexanet as a 400mg IV bolus (30 mg per minute), 3 hours after the last apixaban dose in part 1. In part 2, andexanet was administered as a 400mg IV bolus followed by a continuous infusion of 4mg/minute for 120 minutes (480mg in total). In ANNEXA-R, subjects received 20mg of rivaroxaban OD for 4 days. Four hours after the last dose of rivaroxaban, andexanet was administered as an 800mg IV bolus (30 mg/minute) in part 1. In part 2, andexanet was administered as 800mg IV bolus followed by a continuous infusion of 8mg/minute for 120 minutes (960mg in total). The dose of andexanet required to reverse the effects of 20mg of rivaroxaban OD is higher than that required to reverse the effects of 5 mg of apixaban BD because of the higher initial plasma concentration of rivaroxaban and its larger volume of distribution. (13)

Among the apixaban-treated subjects in the modified intention-to-treat population, anti–factor Xa activity was rapidly reduced (<2 to 5 minutes) with andexanet compared to placebo in ANNEXA-A (mean reduction, 94% vs. 21%; P<0.001) and in ANNEXA-R (92% vs. 18%. P<0.001). After administration of the andexanet bolus, reversal of anti–factor Xa activity persisted for 2 hours, which is consistent with the half-life of andexanet (approximately 1 hour). The effects were sustained when andexanet was administered as a bolus plus an infusion. (13)

In both ANNEXA-A and ANNEXA-R studies, andexanet showed no lasting prothrombotic effect and was considered to have a low immunogenic potential. In a subgroup of subjects, transient increases in levels of d-dimer and prothrombin fragments 1 and 2 were observed, which resolved within 24 to 72 hours. No serious adverse events were reported. Non-serious drug related adverse events were mild (e.g. taste disturbance, flushing and rash). (13)

In January 2015, Portola initiated ANNEXA-4, a phase 4, open-label, single-arm study (NCT0239327) to evaluate the haemostatic efficacy and safety of andexanet alfa in patients with acute bleeding. The study aims to recruit 270 patients from several sites in North America and Europe who are receiving apixaban, rivaroxaban or enoxaparin and who present with acute major bleeding. Patients will receive an IV bolus of andexanet followed by an infusion. The primary outcome measure will be the proportion of patients with excellent or good haemostasis. Safety endpoints are thrombotic activity and antibody development assessed over 45 days. The study aims to complete in 2022 and will be used to support the approval of andexanet alfa by the US FDA under an accelerated approval pathway. (2,12,14)

The phase ANNEXA-E study will evaluate the effect of andexanet on reversal of edoxaban activity. It was due to begin in 2015 but no further details are available in the public domain about this study. (11)

Aripazine (PER977)
Aripazine is a small, synthetic, water-soluble, cationic molecule being developed by Perosphere (USA) to bind NOACs, unfractionated heparin and LMWH through non covalent hydrogen bonding. The estimated date of launch is not yet clear. (1,2,15)

Clinical trials supporting the use of andexanet alfa
In preclinical testing and during testing with edoxaban in healthy male volunteers, it rapidly reversed the effect of multiple anticoagulants. (8) The pharmacokinetic and pharmacodynamic effects of Aripazine (PER977) were evaluated in a phase 2, double-blind, placebo-controlled dose escalation study (NCT01826266) of IV aripazine (100-300mg) in 80 healthy volunteers who were either untreated or pre-treated with 60 mg of edoxaban. Aripazine reduced whole-blood clotting time (WBCT) three hours after the administration of edoxaban, to within 10% above
baseline in <10 minutes compared to 12 to 15 hours with placebo. The WBCT remained within 10% above or below the baseline value for 24 hours after the administration of a single dose of PER977. (2,3,15) There was no evidence of prothrombotic effect and aripazine. Potentially related adverse events were transient mild parietal and facial flushing and dysgeusia; one person reported a moderate headache. (15) Details for subsequent phase 2 and 3 studies are not available in the public domain. (8)

Critical evaluation of studies underpinning the clinical use of NOAC antidotes

The above studies (REVERSE-AD, ANNEXA-A, ANNEXA-R and the phase 2 study designed to characterise the pharmacodynamic and pharmacokinetic activity of aripazine) may be criticised for several reasons; not being RCTs, using non-standardised surrogate outcome measures or studying a cohort of patients or subjects not reflective of a relevant patient population. Meaningful clinical efficacy data in patients who require urgent reversal in emergency situations are desirable but the studies required to obtain such data are technologically challenging.(13) RCTs are difficult to perform in emergency situations as enrolment, consent, randomisation and drug administration is not feasible in many acutely ill patients. The generation of such robust data could take several years because NOAC reversal agents will be infrequently used at any single institution, making patient recruitment problematic. Ethical issues could also make design of randomised controlled trials difficult. The potential issue with using surrogate endpoints is that measured reversal of the drug may, or may not, equate to reduction in bleeding. (2,7,8,13)

Though the quality of the evidence for NOAC antidotes is limited, the above issues were acknowledged by an Anticoagulant-Induced Bleeding and Reversal Agents Think Tank co-sponsored by the US Cardiac Safety Research Consortium and the US FDA. It was noted that, despite the need for reversal of any anticoagulant being relatively rare, NOAC antidotes would be beneficial to manage patients who require urgent surgery and to treat those with life-threatening bleeds. Availability of NOAC antidotes would improve the confidence of clinicians and patients in using NOACs. There was a consensus that, because it is not feasible to do definitive outcomes studies demonstrating a reversal agent's clinical benefits, NOAC antidotes could be approved for use in life-threatening situations if their pharmacodynamic and pharmacokinetic nature were well characterised and safe in humans and if efforts are made to acquire a body of evidence to demonstrate real-world clinical outcomes. (7,8)

Implications

There is scope for rationalisation which NOAC antidotes would need to be stocked in hospitals as this would be based on choice of NOAC used in primary and secondary care (or vice versa). (2) Whilst the manufacturer of idarucizumab estimates that around 1% of patients using NOACs would require antidotes, it is not actually clear how frequently NOAC antidotes would actually be needed. Regardless, NOAC antidotes are likely to be expensive (idarucizumab costs £2,400 per dose of 2 x 2.5g/50mL vials and andexanet alfa and aripazine may be similarly priced). It may be prudent to restrict their use for urgent procedures or in life-threatening or uncontrolled bleeding, as per the license for idarucizumab. (1,5,9)

References

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Date of Issue: March 2014
Review Date: February 2016
Version Number: 1
This version written by: Alexandra Denby

(Signed)