NICE advice

Reversal of the anticoagulant effect of dabigatran: idarucizumab

Evidence summary
Published: 24 May 2016

www.nice.org.uk/guidance/esnm73

Key points from the evidence

The content of this evidence summary was up-to-date in May 2016. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

Idarucizumab is the first agent to be licensed in the UK that reverses the anticoagulant effect of a non-vitamin K antagonist oral anticoagulant (NOAC). Its action is specific against the NOAC dabigatran etexilate. In the interim analysis of an ongoing, phase III, uncontrolled, cohort study (RE-VERSE AD; n=90), treatment with a 5 g dose of idarucizumab completely reversed the anticoagulant effect of dabigatran etexilate in adults who had either serious bleeding or required urgent surgery. People may still need other supportive measures, for example blood products, to manage their bleeding and

these should be considered as medically appropriate.

Regulatory status: Idarucizumab (Praxbind, Boehringer Ingelheim Limited) was launched in the UK in December 2015. It is licensed for use in adults treated with dabigatran etexilate (Pradaxa, Boehringer Ingelheim Limited) when rapid reversal of its anticoagulant effects is required for emergency surgery or urgent procedures, or in life-threatening or uncontrolled bleeding.

Effectiveness	Safety
• In an ongoing, uncontrolled, phase III, cohort study (RE-VERSE AD) in adults taking dabigatran etexilate who have either serious bleeding or require urgent surgery, interim results from 90 people found treatment with a 5 g dose of idarucizumab: – reversed the anticoagulant effect of dabigatran etexilate (median maximum reversal 100%) – normalised dilute thrombin time and ecarin clotting time in 88–98% of people (efficacy analysis; n=68 to 81). • Median investigator-reported time to cessation of bleeding was 11.4 hours (n=35; see the evidence review section for more information). • Normal intraoperative haemostasis was seen in 92% of people (n=36).	• Idarucizumab binds specifically to dabigatran and its metabolites and will not reverse the effects of any other anticoagulant. • Reversing the anticoagulant effect of dabigatran etexilate with idarucizumab exposes people to the thrombotic risk of their underlying disease; restarting anticoagulant therapy should be considered as soon as is medically appropriate (idarucizumab summary of product characteristics). • The summary of product characteristics for idarucizumab states that during the ongoing RE-VERSE AD study, 26 out of a total of 123 people died. Each of these deaths could be attributed either as a complication of the index event or associated with comorbidities. • The amount of sorbitol contained in each dose of idarucizumab is very high and the summary of product characteristics includes a warning about use in people with hereditary fructose intolerance. • According to the summary of product characteristics for idarucizumab, no adverse reactions to idarucizumab were identified when safety was evaluated in 224 healthy people as well as 123 people in the ongoing RE-VERSE AD study.

Patient factors	Resource implications
• Idarucizumab is given as an intravenous infusion or bolus injection and is a hospital-only drug. • No dose adjustment of idarucizumab is required based on renal function, age, or weight.	• Idarucizumab costs £2,400 per 5 g (2×2.5 g/50ml) dose excluding VAT (MIMS, April 2016). • In certain clinical situations, administration of a second 5 g dose of idarucizumab may be considered. • People treated with idarucizumab may still need other supportive measures; these should be considered as medically appropriate.

Introduction and current guidance

Anticoagulant therapy is used for preventing and treating thromboembolism across various clinical indications. Licensed oral anticoagulants that are used in the UK include warfarin, and the NOACs apixaban, dabigatran etexilate, edoxaban and rivaroxaban.

The most common adverse effect of anticoagulants is bleeding, ranging from mild events to serious and fatal haemorrhage. Until recently, there were no specific antidotes for NOACs, unlike warfarin. Idarucizumab is the first agent to be licensed to reverse the anticoagulant effect of a NOAC, and it is specific for dabigatran etexilate.

This evidence summary looks at the evidence for the efficacy and safety of idarucizumab for reversing the anticoagulant effect of dabigatran etexilate.

Full text of introduction and current guidance.

Product overview

Idarucizumab (Praxbind, Boehringer Ingelheim Limited) is a humanised monoclonal antibody fragment (Fab) with a very high affinity to dabigatran. It potently and specifically binds to dabigatran and its metabolites, thereby preventing dabigatran from exerting its anticoagulant effect. Its action is specific to dabigatran etexilate and so it will not reverse

the action of other anticoagulants (idarucizumab summary of product characteristics).

Idarucizumab is licensed for use in adults treated with dabigatran etexilate (Pradaxa, Boehringer Ingelheim Limited) when rapid reversal of its anticoagulant effects is required:

- for emergency surgery or urgent procedures
- in life-threatening or uncontrolled bleeding.

The recommended dose of idarucizumab is 5 g given intravenously as 2 consecutive infusions of 2.5 g/50 ml over 5 to 10 minutes each or as 2 consecutive 2.5 g bolus injections. Administration of a second 5 g dose of idarucizumab may be considered in the following clinical situations:

- recurrence of clinically relevant bleeding together with prolonged clotting times **or**
- if potential re-bleeding would be life-threatening and prolonged clotting times are observed **or**
- patients require a second emergency surgery or urgent procedure and have prolonged clotting times.

The cost per 5 g (2×2.5 g/50 ml) dose of idarucizumab is £2,400 excluding VAT (MIMS, April 2016).

Full text of product overview.

Evidence review

- This evidence summary includes the interim analysis of an ongoing, phase III, prospective, cohort study (NCT02104947; RE-VERSE AD) reported by Pollack et al. 2015. This included 90 adults aged 18 years and above who were taking dabigatran etexilate and had either overt, uncontrollable, or life-threatening bleeding (group A, n=51) or required surgery or other invasive procedures that could not be delayed for at least 8 hours and for which normal haemostasis was required (group B, n=39).

- The primary end point of the study is the maximum percentage reversal of the anticoagulant effect of dabigatran etexilate at any point from the end of the first infusion of idarucizumab to 4 hours after the second infusion, based on measurement of the dilute thrombin time or ecarin clotting time. In the interim analysis, 90 people were enrolled and given idarucizumab because they met inclusion criteria for the study. However, 22 people were subsequently found to have normal dilute thrombin times at baseline, and 9 people were found to have normal ecarin clotting times, so they were excluded from the efficacy analysis.

- In 68 people with elevated dilute thrombin time, and 81 people with elevated ecarin clotting time at baseline, the median maximum reversal of the anticoagulant effect of dabigatran etexilate was 100% (95% confidence interval [CI] 100 to 100%). The dilute thrombin time returned to normal in 93–98% of people and the ecarin clotting time returned to normal in 88–89% of people after a 5 g dose of idarucizumab.

- The mortality rate in the interim analysis of the RE-VERSE AD study was 20% with 18/90 people dying. Half of the deaths occurred within 96 hours of treatment with idarucizumab and appeared to be related to the index event. The remaining deaths occurred after 96 hours and appeared to be related to existing comorbidities rather than the index event. Participants in the RE-VERSE AD study include high risk populations such as those with intracranial bleeding in whom the mortality rate is expected to be high.

- Other clinical outcomes reported in the interim analysis of the study were median investigator-reported time to cessation of bleeding in group A (which was 11.4 hours) and intraoperative haemostasis in group B (which was reported to be normal in 92% of people). Cessation of bleeding was subjective and was difficult to assess in some people (such as those with intracranial bleeding) because investigators could not easily visualise or identify the bleeding site.

- In the interim analysis of RE-VERSE AD, 5/90 people had a thrombotic event during the study follow-up. Only 1 of these people had a thrombotic event within 72 hours of receiving idarucizumab; and none of these people were receiving antithrombotic treatment when the event occurred. The summary of product characteristics for idarucizumab states that people being treated with dabigatran etexilate have underlying disease states that put them at higher risk of thromboembolic events. Reversing the anticoagulant effect of dabigatran etexilate exposes people to the thrombotic risk of their underlying disease. Therefore restarting anticoagulant therapy should be considered as soon as is medically appropriate to reduce this risk. Dabigatran etexilate can be restarted after 24 hours if the person is clinically stable and adequate haemostasis has been achieved. Other antithrombotic therapy, for example low-molecular weight heparin, can be started at any time after administration of idarucizumab, if the patient is clinically stable and adequate haemostasis has been achieved.

- According to the summary of product characteristics for idarucizumab, no adverse reactions to idarucizumab were identified when safety was evaluated in 224 healthy people as well as 123 people in the ongoing RE-VERSE AD study. In the interim analysis of RE-VERSE AD, Pollack et al. 2015 reported that 21 people experienced a serious adverse event. These included the 5 thrombotic events and 18 deaths discussed above as well as gastrointestinal haemorrhage (n=2), postoperative wound infection (n=1), delirium (n=1), right ventricular failure (n=1) and pulmonary oedema (n=1). Some people had more than 1 event. The summary of product characteristics for idarucizumab states that each of the deaths that occurred could be attributed either as a complication of the index event or associated with comorbidities, and each of the thrombotic events that occurred could be attributed to the person's underlying medical condition.

- The strengths of the of the RE-VERSE AD study include its broad inclusion criteria, such as people with acute trauma and those who were expected to die within 3 days, or to require surgery within 24 hours. It also included older people (mean age 76.7 years) and a high proportion of people with intracranial bleeding (20%). However the interim analysis was based on a limited data set of only 90 people, of which only 68 to 81 people were included in the efficacy analyses. The European Medicines Agency agreed that the use of a comparator arm would have been unethical and that all standard supportive care treatments should be allowed (European public assessment report for idarucizumab). However, the uncontrolled design of the study has inherent limitations, making it difficult to assess the clinical benefit of idarucizumab in people with (or at risk of) bleeding associated with dabigatran etexilate. The primary outcome of the RE-VERSE AD study, reversal of the anticoagulant effect, was suitable to demonstrate the ability of idarucizumab to reverse the effect of dabigatran etexilate. This reversal of elevated anticoagulation effect was a surrogate for clinical efficacy, and the clinical benefit of this outcome depends on the individual patient clinical situation, disease or bleeding severity or location of the bleeding (European public assessment report for idarucizumab).

Full text of evidence review.

Context

There are currently no other licensed agents to reverse the anticoagulant effect of dabigatran etexilate (or any other NOAC).

The dabigatran etexilate summary of product characteristics states that in the event of haemorrhagic complications, treatment must be stopped and general supportive measures such as surgical haemostasis and blood volume replacement carried out. In people undergoing surgery or invasive procedures, temporarily stopping dabigatran etexilate may be required. The decision to stop dabigatran etexilate and when to stop it will depend on the person's risk of having a thromboembolic event, their renal function and the bleeding risk associated with the procedure (see the dabigatran etexilate summary of product characteristics for more information).

The dabigatran etexilate summary of product characteristics now also states that when rapid reversal of the anticoagulant effects of dabigatran is required (for emergency surgery, urgent procedures, or life-threatening or uncontrolled bleeding) the specific reversal agent idarucizumab is available. Idarucizumab can be used in conjunction with

standard supportive measures, which should be considered as medically appropriate.

The cost per 5 g (2×2.5 g/50 ml) dose of idarucizumab is £2,400 excluding VAT (MIMS, April 2016).

Full text of context.

Estimated impact for the NHS

Idarucizumab is licensed for use in adults when rapid reversal of dabigatran etexilate's anticoagulant effects is required for emergency surgery or urgent procedures, or in life-threatening or uncontrolled bleeding. Idarucizumab is likely to be an important treatment option for people with life-threatening bleeding and those who need urgent surgery associated with a bleeding risk. The decision on whether to treat people with idarucizumab will need to be made on an individual patient basis, taking into account factors such as the location, size and severity of the bleeding (or the risk of bleeding associated with the surgical intervention or invasive procedure), the thrombotic risk of their underlying disease, and any comorbidities the person has. Standard supportive measures should be considered as medically appropriate.

Dabigatran etexilate has a half-life of approximately 12–14 hours in people with normal renal function, but this is increased in people with renal impairment. Therefore the timing of the last dose of dabigatran etexilate is likely to be a factor in whether reversal of its anticoagulant effect is needed.

People who are treated with idarucizumab may still need other supportive measures, for example blood products, to manage their bleeding. These should be considered as medically appropriate. In certain clinical situations, administration of a second 5 g dose of idarucizumab may be considered (see the idarucizumab summary of product characteristics for details). This would be, at an additional cost of £2,400 excluding VAT per 5 g dose (MIMS, April 2016).

Full text of estimated impact for the NHS.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

Full evidence summary

Introduction and current guidance

Anticoagulant therapy is used for preventing and treating thromboembolism across various clinical indications. Licensed oral anticoagulants that are used in the UK include warfarin, and the non-vitamin K antagonist oral anticoagulants (NOACs) apixaban, dabigatran etexilate, edoxaban and rivaroxaban.

The most common adverse effect of anticoagulants is bleeding, ranging from mild events to serious and fatal haemorrhage. Until recently, there were no specific antidotes for the NOACs unlike warfarin. Idarucizumab is the first agent to be licensed to reverse the anticoagulant effect of a NOAC, and it is a specific reversal agent for dabigatran etexilate. Antidotes for the other licensed NOACs are in development but are not currently available (April 2016).

The dabigatran etexilate summary of product characteristics states that excessive anticoagulation may require dabigatran etexilate treatment to be stopped. In the event of haemorrhagic complications, treatment must be stopped and the source of bleeding investigated. General supportive measures such as surgical haemostasis and blood volume replacement should be carried out. Because dabigatran etexilate is excreted predominantly by the kidneys, adequate diuresis must be maintained. Dabigatran etexilate can be dialysed because protein binding is low, but there is limited clinical experience to demonstrate using this approach in clinical studies. There is some experimental evidence to support using coagulation factor concentrates (activated or non-activated) or recombinant Factor VIIa to reverse the anticoagulant effect of dabigatran etexilate. However data on their usefulness in clinical settings and also on the possible risk of rebound thromboembolism is very limited. Giving platelet concentrates should also be

considered in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used.

The dabigatran etexilate summary of product characteristics states that people who undergo surgery or invasive procedures are at increased risk of bleeding, and temporarily stopping dabigatran etexilate may be required. The decision to stop dabigatran etexilate and when to stop it will depend on the person's risk of having a thromboembolic event, their renal function and the bleeding risk associated with the procedure. Stopping dabigatran etexilate between 24 and 96 hours before the procedure is generally recommended for elective surgery. For subacute surgery or interventions it is recommended that the procedure should be delayed if possible until at least 12 hours after the last dose. For emergency surgery or urgent procedures, dabigatran etexilate should be temporarily discontinued. See the dabigatran etexilate summary of product characteristics for more information.

The dabigatran etexilate summary of product characteristics now also states that in situations when rapid reversal of the anticoagulant effects of dabigatran etexilate are required (for emergency surgery, urgent procedures, or life-threatening or uncontrolled bleeding) the specific reversal agent idarucizumab is available. This evidence summary looks at the evidence for the efficacy and safety of idarucizumab for reversing the anticoagulant effect of dabigatran etexilate.

Product overview

Drug action

Idarucizumab is a humanised monoclonal antibody fragment (Fab) with a very high affinity to dabigatran. It potently and specifically binds to dabigatran and its metabolites, thereby preventing dabigatran from exerting its anticoagulant effect. Its action is specific to dabigatran etexilate and so it will not reverse the action of other anticoagulants (idarucizumab summary of product characteristics).

Licensed therapeutic indication

Idarucizumab (Praxbind, Boehringer Ingelheim Limited) was launched in the UK in December 2015. It is licensed for use in adults treated with dabigatran etexilate (Pradaxa, Boehringer Ingelheim Limited) when rapid reversal of its anticoagulant effects is required:

- for emergency surgery or urgent procedures
- in life-threatening or uncontrolled bleeding.

Idarucizumab is for hospital use only. It can be used in conjunction with standard supportive measures, which should be considered as medically appropriate.

Course and cost

The recommended dose of idarucizumab is 5 g given intravenously as 2 consecutive infusions of 2.5 g/50 ml over 5 to 10 minutes each or as 2 consecutive 2.5 g bolus injections (idarucizumab summary of product characteristics).

A second 5 g dose of idarucizumab may be considered in the following situations:

- recurrence of clinically relevant bleeding together with prolonged clotting times **or**
- if potential re-bleeding would be life-threatening and prolonged clotting times are observed **or**
- patients require a second emergency surgery or urgent procedure and have prolonged clotting times.

The cost per 5 g (2×2.5 g/50 ml) dose of idarucizumab is £2,400 excluding VAT (MIMS, April 2016).

Evidence review

This evidence summary is based on a phase III, prospective, cohort study (NCT02104947; RE-VERSE AD) which has published interim results (Pollack et al. 2015). At the time of the interim analysis 90 people had been enrolled and had results that could be analysed. It is planned that up to 500 people will be enrolled at more than 400 centres in 38 countries.

Three phase I studies have been completed in 283 volunteers to assess the safety, efficacy, tolerability, pharmacokinetics and pharmacodynamics of idarucizumab, given alone or after administration of dabigatran etexilate (idarucizumab summary of product characteristics). One of these studies has been published; NCT01688830 (Glund et al. 2015a and Glund et al. 2015b).

The European public assessment report for idarucizumab concluded that the results of pooled data in volunteers from the phase I studies demonstrated that idarucizumab completely reversed the effect of dabigatran etexilate in nearly all participants.

Because these studies were completed in volunteers rather than patients they are not discussed further in this evidence summary.

Pollack et al. 2015

- Design: ongoing, multicentre, phase III, uncontrolled, prospective cohort study.
- Population: adults aged 18 years and above taking dabigatran etexilate (median patient-reported time since last dose 15.4 hours) with either overt, uncontrollable or life-threatening bleeding that was judged by a clinician to require a reversal agent (group A: n=51, median age 77 years, median creatinine clearance 54 ml/minute); or require surgery or other invasive procedures that cannot be delayed for at least 8 hours and for which normal haemostasis is required (group B: n=39, median age 76 years, median creatinine clearance 60 ml/minute). The vast majority of participants in the interim analysis (96%) had atrial fibrillation and were taking dabigatran etexilate for stroke prevention. In group A (n=51), 20 participants (39%) had gastrointestinal bleeding, 18 (35%) had intracranial bleeding, 9 (18%) had trauma-related bleeding and 11 (22%) had other causes of bleeding.
- Intervention: participants received 5 g of idarucizumab, given as 2×50 ml bolus intravenous infusions containing 2.5 g of idarucizumab each, no more than 15 minutes apart. All standard supportive care treatments were allowed.

- Outcomes: the primary end point was the maximum percentage reversal of the anticoagulant effect of dabigatran etexilate at any point from the end of the first infusion of idarucizumab to 4 hours after the second infusion. Percentage reversal was assessed based on the measurement of the dilute thrombin time or ecarin clotting time at a central laboratory. Values of 100% or more were considered as complete reversal. Secondary endpoints included clinical outcomes such as the severity and extent of bleeding (including the time to cessation of bleeding where this could be assessed), haemodynamic instability, and for those with intracranial haemorrhage, comparison of the baseline score on the modified Rankin scale for assessment of post-stroke disability with the score at 90 days. In people in group B, haemostasis during the intervention was classified as normal, or as mildly, moderately or severely abnormal. Safety outcomes included evaluation of adverse events, deaths and thrombotic events. Participants were followed up until death or for at least 1 month.

Table 1 Summary of Pollack et al. 2015

	Group A – people with overt, uncontrollable or life-threatening bleeding that was judged by a clinician to require a reversal agent	**Group B – people requiring surgery or other invasive procedures that could not be delayed for at least 8 hours and for which normal haemostasis was required**
Enrolled	n=51	n=39
Primary outcome: median maximum percentage reversal of anticoagulant effect of dabigatran etexilate based on dilute thrombin time	100% (n=40) 11 people were excluded from the efficacy analysis because their baseline dilute thrombin times were normal	100% (n=28) 11 people were excluded from the efficacy analysis because their baseline dilute thrombin times were normal

Primary outcome: median maximum percentage reversal of anticoagulant effect of dabigatran etexilate based on ecarin clotting time	100% (n=47) 4 people were excluded from the efficacy analysis because their baseline ecarin clotting times were normal	100% (n=34) 5 people were excluded from the efficacy analysis because their baseline ecarin clotting times were normal
Secondary outcomes		
Median investigator-assessed time to cessation of bleeding	11.4 hours (n=35) 3 people did not have a bleeding assessment at baseline, and time to cessation of bleeding could not be determined in 13 people because the nature of the bleeding made it difficult to assess	n/a
Number of people with normal intraoperative haemostasis	n/a	92% (33/36) 3 people did not have surgery, 2 because they were too unstable for surgery despite idarucizumab administration and 1 because administration of idarucizumab removed the need for emergency dialysis
Number of people who died	17.6% (9/51)	23.1% (9/39)
Safety	n=51	n=39

Number of people who experienced a serious adverse event (including death and thrombotic events)	25.5% (13/51)	20.5% (8/39)
Number of people who experienced a thrombotic event	5.9% (3/51)	5.1% (2/39)

Clinical effectiveness

At the time of the interim analysis of the RE-VERSE AD study, a total of 90 people had been enrolled into the study, 51 people in group A (serious bleeding), and 39 people in group B (urgent procedure). At baseline, a total of 22 people were found to have normal dilute thrombin times, and 9 of these were also found to have normal ecarin clotting times. These people had better renal function (median creatinine clearance 67 ml/minute compared with 48 ml/minute) and a longer patient-reported time since the last dose of dabigatran etexilate (median 30.3 hours compared with 12.8 hours) than those people with abnormal clotting times at baseline. These 22 people were enrolled into the study and given idarucizumab because they met the inclusion criteria; however, they were excluded from the efficacy analysis because of their normal clotting parameters.

In the 68 people with elevated dilute thrombin time, and 81 people with elevated ecarin clotting time at baseline, the median maximum reversal of the anticoagulant effect of dabigatran etexilate was 100% (95% confidence interval [CI] 100 to 100%).

After a 5 g dose of idarucizumab, the dilute thrombin time returned to normal in 98% of people in group A who could be evaluated and 93% of people in group B who could be evaluated. The ecarin clotting time returned to normal in 89% of people in group A who could be evaluated and 88% of people in group B who could be evaluated. However, by 12 and 24 hours after idarucizumab was given, both the dilute thrombin time and ecarin clotting time started to increase in some people. At 12 and 24 hours, the dilute thrombin time was above the upper limit of normal in 10% of people in group A who could be evaluated and 19% in group B. The ecarin clotting time was above the upper limit of normal in 28% of people in group A who could be evaluated and 46% of people in group B.

The median plasma concentration of unbound dabigatran etexilate at baseline was

84 nanograms per ml (range 3 to 641 nanograms per ml) in group A, and 76 nanograms per ml (range 4 to 2880 nanograms per ml) in group B. After the first of the two 2.5 g doses of idarucizumab, the plasma concentration of unbound dabigatran etexilate was less than 20 nanograms per ml in all but 1 person, a level that the study authors (Pollack et al. 2015) report produces little or no anticoagulant effect. At 24 hours after idarucizumab was given, median plasma levels of unbound dabigatran etexilate had risen in some people and were above 20 nanograms per ml in 16/78 (21%) people who were evaluable.

In the 35/51 people in group A who could be evaluated, the median investigator-reported time to cessation of bleeding was 11.4 hours. Three people had no bleeding assessment at baseline, and the time to cessation of bleeding could not be ascertained in 13 people with intracranial haemorrhage, gastrointestinal bleeding, intramuscular bleeding, pericardial bleeding or retroperitoneal bleeding.

In group B, administration of idarucizumab removed the need for emergency dialysis in 1 person who had taken a large overdose of dabigatran etexilate. Another 2 people remained unstable and so were unsuitable for surgical procedures despite receiving idarucizumab. In the remaining 36 people in group B who underwent urgent surgical procedures, normal intraoperative haemostasis was reported in 33 people (92%). Mildly abnormal haemostasis was reported in 2 people and moderately abnormal haemostasis in 1 person.

A total of 18/90 (20%) people died; 9 in group A and 9 in group B. Ten of the deaths were because of vascular causes including 5 fatal bleeding events. Half of the deaths occurred within 96 hours of treatment with idarucizumab and appeared to be related to the index event (3 people had an intracranial haemorrhage, 2 people had septic shock, 1 had multiorgan failure, 1 had haemodynamic collapse, 1 had respiratory failure, and 1 had cardiac arrest). The remaining deaths occurred later than this and appeared to be associated with existing comorbidities.

Blood products (such as packed red cells, fresh frozen plasma, platelets, volume expanders and pro-haemostatic agents) were given to 33/51 (65%) people in group A and 17/39 (44%) people in group B.

Safety and tolerability

The summary of product characteristics states that idarucizumab binds specifically to dabigatran and its metabolites and therefore will not reverse the effects of any other

anticoagulant. It also states that people being treated with dabigatran etexilate have underlying disease states that put them at higher risk of thromboembolic events. Reversing the anticoagulant effect of dabigatran etexilate exposes people to the thrombotic risk of their underlying disease. Therefore restarting anticoagulant therapy should be considered as soon as is medically appropriate to reduce this risk.

In the interim analysis of the RE-VERSE AD study which included 90 people, 5 people had a thrombotic event during study follow-up (3 people in group A and 2 people in group B). Only 1 of these people had a thrombotic event within 72 hours of receiving idarucizumab; a deep-vein thrombosis (DVT) and pulmonary embolism (PE) 2 days after treatment. Additionally 1 person had a DVT, PE and left atrium thrombus 9 days after treatment, 1 person had a DVT 7 days after treatment, 1 person had a non-ST segment elevation myocardial infarction 13 days after treatment and 1 person had an ischaemic stroke 26 days after treatment. None of these people were receiving antithrombotic treatment when the event occurred.

After administration of idarucizumab, treatment with dabigatran etexilate can be restarted after 24 hours if the person is clinically stable and adequate haemostasis has been achieved. Other antithrombotic therapy, for example low-molecular weight heparin, can be started at any time after administration of idarucizumab, if the patient is clinically stable and adequate haemostasis has been achieved (summary of product characteristics for idarucizumab).

According to the summary of product characteristics for idarucizumab, no adverse reactions to idarucizumab were identified when safety was evaluated in 224 healthy people as well as 123 people in the ongoing RE-VERSE AD study. Of these 123 people, 26 people died but each of the deaths that occurred could be attributed either as a complication of the index event or associated with comorbidities. Thrombotic events were reported in 5 people (as discussed above) and each could be attributed to the person's underlying medical condition.

In the interim analysis of the RE-VERSE AD study, Pollack et al. report that a total of 21 people experienced a serious adverse event. These included the 5 thrombotic events and 18 deaths discussed above as well as gastrointestinal haemorrhage (n=2), postoperative wound infection (n=1), delirium (n=1), right ventricular failure (n=1) and pulmonary oedema (n=1). Some people had more than 1 event.

In the European public assessment report for idarucizumab, it is highlighted that the

amount of sorbitol contained in each dose of idarucizumab is very high. This is reflected in the summary of product characteristics which advises that treatment with idarucizumab must be weighed against the potential benefit of such an emergency treatment in people with hereditary fructose intolerance.

Evidence strengths and limitations

The strengths of the RE-VERSE AD study include its broad inclusion criteria, enrolling people with acute trauma and those who were expected to die within 3 days, or to require surgery within 24 hours. The RE-VERSE AD study also included older people (mean age 76.7 years) and a high proportion of people with intracranial bleeding (20%). However the interim analysis was based on a limited data set of only 90 people, of which only 68 to 81 people were included in the efficacy analyses.

The study has inherent limitations due to its uncontrolled design and, as discussed in an editorial by Bauer (2015), the absence of a control group makes it difficult to assess the clinical benefit of idarucizumab in people with (or at risk of) bleeding associated with dabigatran etexilate. The uncontrolled design was agreed by the European Medicines Agency because the use of a comparator arm would have been unethical. There is no licensed alternative to idarucizumab and the target treatment population were treated in emergency situations where all standard supportive care treatments should be allowed (European public assessment report for idarucizumab).

The mortality rate in the RE-VERSE AD study was high at 20%. However, participants included people with conditions such as intracranial bleeding, in whom the mortality rate is expected to be high. Half of the deaths occurred after 96 hours and appeared to be related to existing comorbidities rather than the index event. The RE-VERSE AD study was not designed to assess the impact of idarucizumab on mortality and it is not possible to say what effect idarucizumab has on mortality compared with existing standard supportive measures alone in these high risk populations.

Five people experienced thrombotic events during the interim analysis of the RE-VERSE AD study. However, only one of these occurred within 72 hours of receiving treatment with idarucizumab and none of the people who experienced a thrombotic event were receiving antithrombotic therapy at the time of the event. The European public assessment report for idarucizumab states that the occurrence of these events after reversal of the anticoagulant effect was not unexpected, and was not linked to the action of idarucizumab. The summary of product characteristics for idarucizumab states that if

the patient is clinically stable and adequate haemostasis has been achieved, dabigatran etexilate treatment can be re-initiated 24 hours after administration of idarucizumab. Other antithrombotic therapy (such as low-molecular weight heparin) can be started at any time, if the patient is clinically stable and adequate haemostasis has been achieved.

The European public assessment report for idarucizumab states that the chosen end points in the RE-VERSE AD study to demonstrate the ability of idarucizumab to reverse the effect of dabigatran etexilate were suitable. However, the primary outcome, reversal of the anticoagulant effect, is a surrogate for clinical efficacy. The clinical benefit of this outcome depends on the individual patient, clinical situation, disease or bleeding severity and location of the bleeding. Secondary clinical outcomes reported in the study were median investigator-reported time to cessation of bleeding and intraoperative haemostasis. The European public assessment report for idarucizumab reports that cessation of bleeding was difficult to assess in some people (such as those with intracranial bleeding) because the investigators could not visualise or identify the bleeding site. Also cessation of bleeding was subjective and based upon whatever the investigator could visualise or measure.

Other planned secondary clinical outcomes, such as severity and extent of bleeding, and for those with intracranial haemorrhage, comparison of the baseline score on the modified Rankin scale with the score at 90 days, were not reported in the interim analysis because of the small number of people with available follow-up data.

Nearly a quarter of people enrolled into the RE-VERSE AD study (who were given idarucizumab because they met the inclusion criteria) were subsequently found to have a normal dilute thrombin time at baseline and 10% were found to have a normal ecarin clotting time. These people were excluded from the efficacy analyses, further limiting the data set on which the efficacy analyses were based. An editorial by Bauer (2015) suggests that this group of people would have little or no circulating anticoagulant in their blood and would not be expected to benefit from idarucizumab. The editorial suggests that it may be useful to have procedures in place to ensure activity measurements for dabigatran etexilate are evaluated where the clinical situation allows before idarucizumab is given. However, the summary of product characteristics for idarucizumab has no requirement for clotting parameters to be measured.

Blood products (such as packed red cells, fresh frozen plasma, platelets, volume expanders and pro-haemostatic agents) were given to 65% of people in the serious bleeding group and 44% of the urgent procedure group. Therefore people who are given

idarucizumab may still require other treatments to manage their bleeding.

Although after a 5 g dose of idarucizumab the dilute thrombin time and ecarin clotting time returned to normal in about 90% or more of people who could be evaluated, in some people these values had deteriorated by 12 and 24 hours. At these time points, the dilute thrombin time was above the upper limit of normal in 10–19% of people who could be evaluated and the ecarin clotting time was above the upper limit of normal in 28–46% of people who could be evaluated. Additionally, the median plasma concentration of unbound dabigatran, which had fallen to a level that produces little or no anticoagulant effect after the first of the two 2.5 g doses idarucizumab, had risen again in some people at 24 hours after idarucizumab. Pollack et al. suggest that these findings may reflect the redistribution of extravascular dabigatran into the intravascular compartment. The summary of product characteristics for idarucizumab states the clinical situations where consideration of an additional 5 g dose of idarucizumab may be considered in people with prolonged clotting times.

Context

Alternative treatments

There are currently no other licensed agents to reverse the anticoagulant effect of dabigatran etexilate (or any other NOAC).

The dabigatran etexilate summary of product characteristics states that in the event of haemorrhagic complications, treatment must be stopped and general supportive measures such as surgical haemostasis and blood volume replacement carried out. In people undergoing surgery or invasive procedures, temporarily stopping dabigatran etexilate may be required. The decision to stop dabigatran etexilate and when to stop it will depend on the person's risk of having a thromboembolic event, their renal function and the bleeding risk associated with the procedure (see the dabigatran etexilate summary of product characteristics for more information).

The dabigatran etexilate summary of product characteristics now also states that in situations when rapid reversal of the anticoagulant effects of dabigatran are required (for emergency surgery, urgent procedures, or life-threatening or uncontrolled bleeding) the specific reversal agent idarucizumab is available.

Costs of alternative treatments

There are no other licensed agents to reverse the anticoagulant effect of dabigatran etexilate. Managing haemorrhagic complications and reversing anticoagulant effects is multifactorial and various agents are used. The cost of alternative treatments will depend on the preparation chosen, and it is not possible to provide a comprehensive list of costs for alternative treatments in this evidence summary. The summary of product characteristics for idarucizumab states that idarucizumab can be used in conjunction with standard supportive measures, which should be considered as medically appropriate.

The cost per 5 g (2×2.5 g/50 ml) dose of idarucizumab is £2,400 excluding VAT (MIMS, April 2016).

Estimated impact for the NHS

Likely place in therapy

The interim analysis of the RE-VERSE AD study (Pollack et al. 2015), demonstrated that idarucizumab completely reversed the anticoagulant effect of dabigatran etexilate. Idarucizumab is licensed for use in adults when rapid reversal of dabigatran etexilate's anticoagulant effects is required for emergency surgery or urgent procedures, or in life-threatening or uncontrolled bleeding.

Idarucizumab is likely to be an important treatment option for people with life-threatening bleeding and those who need urgent surgery associated with a bleeding risk. The decision on whether to treat people with idarucizumab will need to be made on an individual patient basis, taking into account factors such as the location, size and severity of the bleeding (or the risk of bleeding associated with the surgical intervention or invasive procedure), the thrombotic risk of their underlying disease, and any comorbidities the person has.

Dabigatran etexilate has a half-life of 12–14 hours in people with normal renal function, but this is increased in people with renal impairment. Therefore the timing of the last dose of dabigatran etexilate is likely to be a factor in whether reversal of its anticoagulant effect is needed. The bleeding risk from elective surgery can generally be managed by stopping dabigatran etexilate between 24 and 96 hours before a surgical procedure, with timing dependent on the person's risk of having a thromboembolic event, their renal function and the bleeding risk associated with the procedure. Idarucizumab is not indicated for elective

surgery, only for emergency surgery or urgent procedures where the surgery cannot be delayed (see the summaries of product characteristics for dabigatran etexilate and idarucizumab for more information).

People who are treated with idarucizumab may still need other supportive measures, for example blood products, to manage their bleeding. The summary of product characteristics for idarucizumab states that idarucizumab can be used in conjunction with standard supportive measures, which should be considered as medically appropriate.

The summary of product characteristics states that a second dose of idarucizumab may be considered in people with a recurrence of clinically relevant bleeding together with prolonged clotting times, in people in whom potential re-bleeding would be life-threatening who also have prolonged clotting times, or in people requiring a second emergency procedure who have prolonged clotting times. This would incur an additional cost of £2,400 excluding VAT per 5 g dose (MIMS, April 2016).

Estimated usage

The manufacturer of idarucizumab (Praxbind, Boehringer Ingelheim Limited) estimates that approximately 0.98% of people per year may need emergency surgery whilst they are being treated with dabigatran etexilate, and therefore may be eligible for treatment with idarucizumab. Similarly they estimate that 1.34% of people per year may experience life-threatening or severe bleeding during treatment with dabigatran etexilate that may warrant the use of idarucizumab. These figures are based on estimates from the RE-LY study (Connolly et al. 2009) which compared dabigatran etexilate with warfarin in people with atrial fibrillation.

Relevance to NICE guidance programmes

NICE has issued the following technology appraisal guidance relating to dabigatran etexilate:

- Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults (2008) NICE technology appraisal guidance 157
- Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (2012) NICE technology appraisal guidance 249

- Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism (2014) NICE technology appraisal guidance 327

NICE has issued guidelines on:

- Venous thromboembolic diseases: diagnosis, management and thrombophilia testing (2012) NICE guideline CG144
- Venous thromboembolism: reducing the risk for patients in hospital (2010) NICE guideline CG92
- Atrial fibrillation: management (2014) NICE guideline CG180

References

Bauer K (2015) Targeted anti-anticoagulants. New England Journal of Medicine 373: 569–71

Boehringer Ingelheim (2015) Praxbind 2.5 g/50 mL solution for injection/infusion summary of product characteristics [online; accessed 13 April 2016]

Boehringer Ingelheim (2016) Pradaxa 75 mg hard capsules summary of product characteristics [online; accessed 13 April 2016]

Boehringer Ingelheim (2016) Pradaxa 110 mg hard capsules summary of product characteristics [online; accessed 13 April 2016]

Boehringer Ingelheim (2016) Pradaxa 150 mg hard capsules summary of product characteristics [online; accessed 13 April 2016]

Connolly SJ, Ezekowitz MD, Yusuf S et al. (2009) Dabigatran versus warfarin in patients with atrial fibrillation. New England Journal of Medicine 361: 1139–51

Glund S, Stangier J, Schmohl M et al. (2015a) Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial. Lancet 386: 680–90

Glund S, Moschetti V, Norris S et al (2015b) A randomised study in healthy volunteers to investigate the safety, tolerability and pharmacokinetics of idarucizumab, a specific antidote to dabigatran. Thrombosis and Haemostasis 113: 943–51

Pollack CV, Reilly PA, Eikelboom J et al. (2015) Idarucizumab for dabigatran reversal. New England Journal of Medicine 373: 511–20

US National Institutes of Health (2016) ClinicalTrials.gov Identifier NCT02104947 [online; accessed 13 April 2016]

Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

Expert advisers

Dr Joe Martins, Consultant Cardiologist, Medical Service Head for Cardiology, The Dudley Group NHS Foundation Trust

Professor Martin R Cowie, Professor of Cardiology, Imperial College London

Dr Will Lester, Consultant Haematologist, University Hospital Birmingham, Queen Elizabeth

Daniel Horner, Consultant in Emergency Medicine and Intensive Care, Salford Royal NHS Foundation Trust

Declarations of interest

Joe Martins has received speaker honoraria, payments for consultancy on an advisory board and educational sponsorships for presenting at conferences from Bayer.

Martin Cowie has provided consultancy advice, and been paid honoraria for educational events for Boehringer Ingelheim, Bayer, Pfizer/BMS and Daiichi-Sankyo. He is on the medical advisory committee of the Atrial Fibrillation Association (non-fee paying) and chaired groups for NICE on the patient decision aid for the NICE atrial fibrillation

guidelines, and the implementation collaborative on NOACs (both non-remunerative).

Will Lester has received speaker honoraria from Boehringer Ingelheim, Bayer, Bristol Myers Squibb, and Pfizer. He has been on advisory boards for Boehringer Ingelheim, Bayer, Bristol Myers Squibb, Daiichi Sankyo and Pfizer. He has also received support from Boehringer Ingelheim to attend a scientific meeting.

Daniel Horner has no relevant interests to declare.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

ISBN: 978-1-4731-1862-1