Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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idarucizumab 2.5g/50mL solution for injection/infusion (Praxbind®)

SMC No. (1178/16)

Boehringer Ingelheim Ltd

05 August 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

idarucizumab (Praxbind®) is accepted for use within NHS Scotland.

Indication under review: idarucizumab is a specific reversal agent for dabigatran and is indicated in adult patients treated with dabigatran etexilate when rapid reversal of its anticoagulant effects is required for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding.

In a phase III, non-randomised, case series study, treatment with idarucizumab reversed the effect of dabigatran, with a median maximum percentage reversal of 100%.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

idarucizumab is a specific reversal agent for dabigatran and is indicated in adult patients treated with dabigatran etexilate when rapid reversal of its anticoagulant effects is required:

- For emergency surgery/urgent procedures
- In life-threatening or uncontrolled bleeding.

Dosing Information

Restricted to hospital use only.

Idarucizumab 5g (two, 2.5g/50mL) is administered intravenously as two consecutive infusions over 5 to 10 minutes each or as a bolus injection.

In a subset of patients, recurrence of plasma concentrations of unbound dabigatran and concomitant prolongation of clotting tests have occurred up to 24 hours after administration of idarucizumab.

Administration of a second 5g 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/urgent procedure and have prolonged clotting times.

Relevant coagulation parameters are activated partial thromboplastin time (aPTT), diluted thrombin time (dTT) or ecarin clotting time (ECT).

A maximum daily dose has not been investigated.

Product availability date

17 December 2015.

Summary of evidence on comparative efficacy

Idarucizumab, a humanised monoclonal antibody fragment, is a specific reversal agent for dabigatran etexilate. The binding affinity of idarucizumab to dabigatran is around 300-fold more potent than the binding affinity of dabigatran for thrombin.[1] Prior to the licensing of idarucizumab, no recognised antidote to the anticoagulant effect of dabigatran etexilate existed. [2, 3]

Evidence of efficacy comes from RE-VERSE AD (1321.3), an ongoing, open-label, single arm, phase III case series (prospective cohort) study conducted in adult patients taking dabigatran etexilate. Patients had either overt, uncontrollable, or life-threatening bleeding that was judged by the treating clinician to require a reversal agent (group A), or they required surgery or other invasive procedures that could not be delayed for at least eight hours and for which normal haemostasis was required (group B). Patients were treated with idarucizumab 5g intravenously (IV) administered as two, 2.5g doses, 15 minutes apart. [4, 5]

The primary endpoint was maximum percentage reversal of the anticoagulant effect of dabigatran, as determined at any point from the end of the first idarucizumab infusion to four hours after the second infusion. It was calculated using the following equation (where inputs were measured in seconds): percentage reversal = (pre-dose test result – minimum post dose test result) / (pre-dose test result – upper limit of the normal range) × 100. The percentage reversal was assessed on the basis of the measurement of the diluted thrombin time (dTT) or ecarin clotting time (ECT) from a central laboratory, where only patients with baseline dTT or ECT outwith the upper limit of normal were included. Patient recruitment commenced in June 2014, and at the most recent pre-planned interim analysis (cut-off April 2015), 123 patients (66 in group A and 57 in group B) had been recruited out of 300 planned.[4, 5]

A total of 90 patients had central laboratory data and, of these, 68 patients with elevated dTT at baseline and 81 patients with elevated ECT at baseline were considered evaluable. The median maximum percentage reversal was 100% (95% confidence interval [CI]: 100 to 100) for group A and group B, as assessed by dTT and ECT. Reversal was evident on the sample taken after the first infusion. The proportion of evaluable patients with normalised dTT was 98% in group A and 93% in group B and with normalised ECT was 89% in group A and 88% in group B.[4, 5]

Secondary endpoints included duration of reversal, bleeding status and use of blood products. At 12 hours after the idarucizumab infusion, 90% of patients had dTT values and 72% of patients had ECT values less than the upper limit of normal, and at 24 hours, the proportions were 81% and 54% respectively. Bleeding cessation was assessed subjectively by the investigator, based on what could be seen or measured, although computed tomography (CT) or magnetic resonance imaging (MRI) scans or other tests were not always repeated for several days. In group A, bleeding cessation data were available for 48 patients. Bleeding stopped within 72 hours for 92% (44/48) of patients and the median time for bleeding to stop was 9.8 hours (range: 0.2 hours to 62 days). In group B, intra-operative status of bleeding was determined in 52 patients and was judged to be normal haemostasis in 92% (48/52) of patients. The median time from administration of first dose of idarucizumab to surgery was 1.7 hours (range: -0.2 to 26.4 hours). The proportion of patients that received blood products was 68% in group A and 40% in group B. Packed red blood cells were used in 42% and fresh frozen plasma in 24% of all patients.[4]

A total of 96 patients restarted anticoagulant or antithrombotic therapy: 47 in group A and 49 in group B. Dabigatran was restarted in 26% (17/66) of patients in group A and 60% (34/57) of patients in group B. Bridging therapy was used prior to dabigatran being restarted in eight (of 17 patients) in group A and 25 (of 34 patients) in group B.[4]

Supportive data come from two, phase I studies conducted in healthy (1321.1) and healthy, elderly or renally-impaired volunteers (1321.2). The studies demonstrated that, at doses greater than 2g, the reversal effect was quickly observed after administration of idarucizumab, and lasted for 72 hours.[4]

Summary of evidence on comparative safety

In RE-VERSE AD the proportion of patients that reported any adverse event was 89% (59/66) in group A and 77% (44/57) in group B, and investigator-defined, drug-related adverse events occurred in 6.1% (4/66) and 1.8% (1/57) of patients respectively. Serious adverse events occurred in 47% (31/66) and 39% (22/57) of patients in group A and B respectively. Adverse events, reported in at least 5% of patients were: hypokalaemia (7.3% [9/123]), delirium (7.3% [9/123]), constipation (6.5% [8/123]), pyrexia (5.7% [7/123]) and pneumonia (5.7% [7/123]). Five patients (three in group A and two in group B) not on antithrombotic therapy at the time of the event reported a thrombotic event which could be attributed to the underlying medical condition of the patient [4]

Data on anti-drug antibodies were available for 47 patients and, although limited, indicate a low level of immunogenicity for idarucizumab. This is consistent with the levels of immunogenicity identified in the healthy volunteer population from the phase I studies.[4] There were 26 deaths; 13 in group A and 13 in group B. There were 13 deaths within the first five days of the study (6 in group A and 7 in group B) which were because of progression of the index events or underlying pre-treatment conditions. In group A, of 24 patients with intracranial haemorrhage, 25% (n=6) were fatal, and of 27 gastro-intestinal bleeds, 11% were fatal [4]

Summary of clinical effectiveness issues

Idarucizumab is the first treatment specifically licensed for reversal of the anticoagulant effect of dabigatran. Treatments to enhance the clearance of dabigatran include haemodialysis, haemofiltration and charcoal haemoperfusion. When life-threatening bleeding is present, prothrombin complex concentrates (PCC), activated PCC (aPCC) and recombinant activated factor VII (rFVIIa) may be considered.[3]

Interim results of the ongoing RE-VERSE AD study indicate that idarucizumab reverses the effect of dabigatran, with a median maximum 100% reversal of laboratory test abnormalities. However, the comparative efficacy versus off-label treatments that are currently used is unknown. The European Medicines Agency (EMA) considered this surrogate endpoint was appropriate and also considered the non-comparative design of the study was acceptable given the absence of a proven alternative to idarucizumab. However, this means that the clinical benefit provided by idarucizumab is difficult to assess.[6] Furthermore, prognosis depends greatly on the individual patient's clinical situation, co-existing conditions and bleeding severity and location.[4, 6] Blood products were given to 68% of patients in group A and 40% of patients in group B, in addition to idarucizumab. Therefore other supportive measures will still be required by patients who receive idarucizumab.

The clinical data on cessation of bleeding and haemostasis during surgery provide evidence that reversal may result in clinically meaningful outcomes. The study population was, in general, representative of patients who may be eligible for idarucizumab in clinical practice, with a median age of 77 years and a median creatinine clearance of 55mL/min. However, of the 90 patients with central laboratory data available, around 25% did not have an elevated baseline dTT value and 10% did not have an elevated baseline ECT. These patients were not included in analysis of the primary endpoint and would not be expected to benefit from idarucizumab in clinical practice. It is not clear whether, in clinical practice, coagulation assays would be available to guide treatment initiation; the summary of product characteristics (SPC) does not state that these should be available prior to administering idarucizumab.[1] Clinical experts consulted by SMC considered that idarucizumab would be initiated before results of dTT or other tests are known, given the life-threatening situation.

The majority of patients (around 66%) were being treated with dabigatran at a dose of 110mg twice daily, which may not be representative of the usual dose in clinical practice, where patients are likely to receive dabigatran 150mg twice daily. There are very limited data in patients with severe renal impairment.

The EMA considered the phase I studies were pivotal for marketing authorisation. They noted that results from these studies, as well as the phase III case series study, demonstrated efficacy for the licensed dose of idarucizumab.[4]

The availability of idarucizumab would have advantages for the service as it offers a highly effective treatment for the reversal of the anticoagulant effect of dabigatran. Idarucizumab should be stored in its original packing at 2 to 8°C and unopened vials have a shelf life of 24 months.[1] Idarucizumab treatment will be required to be administered urgently and therefore stocked in acute hospitals.

Administration of a second 5g dose of idarucizumab may be considered in specific circumstances.[1] Two patients, enrolled in the RE-VERSE AD study, required re-treatment with a second dose of idarucizumab 5g due to re-bleeding, but were not included in the analysis presented previously. Results for these patients are the basis for the statement on re-treatment included in the SPC.[4]

Vitamin K antagonists are the most predominant anticoagulants used currently in clinical practice. Patients treated with these, and who have major bleeding, should have immediate reversal of the anticoagulant with intravenous vitamin K or prothrombin complex concentrate.[7] Prothrombin complex concentrates are licensed for use in overdose of vitamin K antagonists when rapid correction of the deficiency is required.[8] These cost in the region of £800 to £1,800 per treatment (source: DM&D).

Clinical experts consulted by SMC reported the use of a range of treatments (often off-label), although they noted that rationale and evidence for these are very limited. Treatments include blood volume expanders, blood transfusion, tranexamic acid, factor concentrates and haemodialysis. They considered that idarucizumab is a therapeutic advancement, being the first agent to reverse the effect of a direct oral anticoagulant. Idarucizumab is not expected to be used very often, but its availability was considered to be potentially valuable in avoiding a major bleed.

Summary of comparative health economic evidence

The company submitted a cost analysis of idarucizumab when used in adult patients treated with dabigatran when rapid reversal of its anticoagulant effects is required for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding. The comparator included a number of other treatments used off-label, including PCC, aPCC, and dialysis. No treatment was also included as a comparator for a proportion of patients. Subgroup analyses were presented according to the type of bleeding event. The subgroups included were: gastrointestinal (GI) bleed (39.2%), intracranial haemorrhage (ICH, 35.3%), other bleeds (25.5%), and emergency surgery (1%).

The analysis was a simple cost analysis which compared the cost associated with treating a major bleed using a mixture of treatments (including off-label) with the cost of treating a major bleed if idarucizumab were available. The company described these scenarios in terms of ‘world with’ and ‘world without’ idarucizumab. The analysis assumes idarucizumab is 100% effective at reversing the anticoagulant effects of dabigatran and, as a result, standard treatments are either not required or reduced. The company noted that the nature of the clinical evidence (ie single-arm case series study for idarucizumab and limited evidence of the efficacy of off-label treatments) meant it was not possible to conduct an indirect comparison with current treatments and, therefore, a standard economic evaluation was also not possible. The diverse patient population covered by the idarucizumab licence was also noted as being a complicating factor in conducting a standard economic analysis.

The cost analysis included the costs of aPCC and PCC treatments as the main treatments currently used in practice. Other costs included a range of hospital visits, tests and procedures, blood transfusions and blood products, surgical procedures, and other procedures such as dialysis. The only medicine cost included in the analysis was idarucizumab. It was noted that rFVIIa may also be used in practice but this was not included as a displaced cost in the analysis as the company argued that there was no evidence of rFVIIa use in these patients. The resource use estimates were based on a combination of clinical guidelines, published studies, and expert opinion.

The total cost per patient per event based on current treatment was estimated to be £5,776 compared to £6,562 with idarucizumab. The weighted average incremental cost of idarucizumab treatment across the four subgroups was estimated to be £786 per patient. The incremental cost is driven by the cost of idarucizumab, with some cost-offsets due to reductions in other resource use. The analysis assumes idarucizumab treatment will result in a reduction in the use of aPCC and PCC, reduce the length of stay in hospital by one day and reduce stay in intensive care by between 0.43 and 0.71 days depending on the type of bleed. The results of each subgroup are presented in the table below.

Table: Cost per patient by subgroup

	GI bleed (39.2%)	ICH (35.3%)	Other bleed (25.5%)	Emergency surgery (1%)	Weighted average cost/pt
Idarucizumab	£6,301	£6,598	£6,574	£8,843	£6,562
Current treatments	£5,734	£5,642	£5,728	£7,772	£5,776
Incremental cost	£567	£957	£846	£1,071	£786

The following limitations were noted:

- The company provided a simple cost analysis which showed idarucizumab treatment is associated with an average incremental cost per patient of £786, but the impact of idarucizumab treatment on patient outcomes was not explored. The emergency nature of the clinical situations where idarucizumab would be used combined with the lack of data to support the efficacy of current treatments provide particular challenges in conducting an economic analysis. Nonetheless, the submitting company may have been able to use clinical expert opinion or explore some clinical scenarios in order to aid decision-making and justify the increase in cost. SMC clinical experts were asked to provide an estimate of the potential reduction in mortality associated with idarucizumab treatment compared to current standard of care. Responses from clinical experts indicated it was a difficult question to answer given the rarity of the clinical situation and the lack of data on patient outcomes. There was a general view that idarucizumab treatment would be likely to result in a reduction in mortality and morbidity compared to standard treatments but quantifying this benefit was particularly challenging. Experts noted that, while idarucizumab would reverse the anticoagulant effects of dabigatran, patient outcomes would be determined largely by the underlying cause of the bleed.
- It is not clear that the assumptions made in the analysis regarding current treatment options fully reflect clinical practice in Scotland. Sensitivity analysis was provided which increased the proportion of patients receiving no treatment and reduced the proportion of patients receiving aPCC by 40%, and this increased the incremental cost to £836.

Despite the increased cost of idarucizumab and the lack of analysis exploring the benefits of treatment to justify the increase in cost, the Committee considered idarucizumab to be a useful treatment option for a limited number of patients.

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from Pumping Marvellous Foundation, Stroke Association and Anticoagulation Europe, which are all registered charities.

- Pumping Marvellous Foundation has received 75% pharmaceutical company funding in the last two years, but none from the submitting company. The Stroke Association has received <3% and Anticoagulation Europe has received 46% pharmaceutical company funding in the past two years, including from the submitting company.

- Anticoagulation therapy increases risk of bleeding. Until recently, there has been no known reversal agent available for the anticoagulant treatment, dabigatran. With no antidote, the risk of uncontrolled or life threatening bleeding to those currently taking this medicine can impact patients' quality of life both physically and mentally.

- Warfarin is currently used for those who require an anticoagulant with an available reversal agent. Warfarin requires frequent monitoring which may impact on the lifestyle of patients and carers. Frequent dosing adjustments may be required and can also be challenging.

- Idarucizumab is a reversal agent for dabigatran. It can enable those who may require a reversal at short notice to benefit from treatment with dabigatran.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence published an evidence summary, Reversal of the anticoagulant effect of dabigatran: idarucizumab, in May 2016. [9]

The Neurocritical Care Society and Society of Critical Care Medicine published; Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage, in 2016. The guideline notes that idarucizumab is in development and has recently being approved by the Food and Drug Administration. It recommends idarucizumab as first-line treatment for intracranial haemorrhage, and, when not available, 4-factor PCC or aPCC may be used. [10]

The following guidelines predate the licensing of idarucizumab by the EMA.

The Scottish Intercollegiate Guidelines Network (SIGN) updated guideline number 129; Antithrombotics: indications and management, in June 2013. The guideline states notes that no recognised antidote to the anticoagulant effect of dabigatran etexilate is available but notes that dialysis may be of benefit in an emergency situation due to dabigatran being 35% plasma protein bound.[2]

SIGN updated guideline number 122; Prevention and management of venous thromboembolism, in October 2015. The guideline notes that lack of reversibility for dabigatran (and other new oral anticoagulants) should be taken into consideration when selecting the most appropriate treatment. [7]

The British Committee for Standards in Haematology (BCSH) published a guideline on the management of bleeding in patients on antithrombotic agents in 2012. For dabigatran the following recommendations are made:

- There is no specific antidote for dabigatran. Management of bleeding should be through cessation of treatment and general haemostatic measures
- In bleeding patients who have taken a dose of dabigatran in the last 2 hours, consider oral activated charcoal to prevent further absorption
- If rapidly deployable, haemodialysis, haemofiltration and charcoal haemoperfusion offer the possibility of enhanced clearance of the active drug
- In situations with ongoing life-threatening bleeding PCC, aPCC and rFVIIa should be considered.[3]

The European Heart Rhythm Association (EHRA) published EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary, in 2013. Treatment of non-life threatening bleeding in patients taking dabigatran include, when necessary/indicated; fluid replacement, RBC substitution, platelet substitution, FFP as plasma expander, tranexamic acid, desmopressin and dialysis. In addition, the following treatments may be considered in patients with life threatening bleeding; PCC, aPCC or rFVIIa. In patients requiring a surgical intervention the guidelines state that the anticoagulant should be stopped and surgery/intervention deferred, if possible, until at least 12 hours and ideally 24 hours after the last dose. [11]

Additional information: comparators

There are no medicine comparators. There is some off-label use of PCC, aPCC and rFVIIa.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Idarucizumab	**Two, 2.5g/50mL intravenous infusions**	**2,400**

Costs from DM&D on 27 April 2016.

Additional information: budget impact

The submitting company estimated there would be would be 46 patients eligible for treatment with idarucizumab in year 1 and 57 patients in year 5. The estimated uptake rate was 100% in all years with 46 patients in year 1 and 57 patients in year 5

The gross impact on the medicines budget was estimated to be £110k in year 1, rising to £137k in year 5. No medicines were assumed to be displaced. However, assuming displacement of blood-related products aPCC and PCC, the net budget impact was estimated to be £73k in year 1, rising to £90k in year 5.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Idarucizumab (Praxibind®) summary of product characteristics. Boehringer Ingelheim Limited. Electronic Medicines Compendium Last updated November 2015.

2. Scottish Intercollegiate Guidelines Network. Antithrombotics: indications and management, guideline number 129. Updated June 2013.

3. Makris M VVJ, Tait C, et al,. The British Committee for Standards in Haematology. Guideline on the management of bleeding in patients on antithrombotic agents. British Journal of Haematology. 2012;160:35-46.

4. European Medicines Agency. European Public Assessment Report. Idarucizumab (Praxibind) EMEA/H/C/003986/0000. 24 September 2015.

5. Pollack CV, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA*, et al.* Idarucizumab for dabigatran reversal. New England Journal of Medicine. 2015;373(6):511-20.

6. Bauer K. Targeted Anti-Anticoagulants [editorial]. New England Journal of Medicine. 2015;373:569-71.

7. Scottish Intercollegiate Guidelines Network. Prevention and management of venous thromboembolism, guideline number 122. Updated October 2015.

8. Keeling D, Baglin T, Tait C et al. Guidelines on oral anticoagulation with warfarin – fourth edition. British Journal of Haematology. 2011.

9. National Institute for Health and Care Excellence. Reversal of the anticoagulant effect of dabigatran [evidence summary]. 2015.

10. Frontera JA, Lewin IJJ, Rabinstein AA, Aisiku IP, Alexandrov AW, Cook AM*, et al.* Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Neurocritical Care. 2016;24(1):6-46.

11. Heidbuchel H PVP, Alings M, et al,. EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. European Heart Journal. 2013.

This assessment is based on data submitted by the applicant company up to and including 21 July 2016.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.