New Medicine Assessment

Idarucizumab (Praxbind®)

For adult patients treated with Pradaxa (dabigatran etexilate) when rapid reversal of its anticoagulant effects is required for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding.

Recommendation: RED

Idarucizumab (Praxbind®) is recommended for adult patients treated with Pradaxa (dabigatran etexilate) when rapid reversal of its anticoagulant effects is required for emergency surgery/urgent procedures (which cannot be performed safely while anticoagulated or reasonably be delayed) or in life-threatening or uncontrolled bleeding.

- Supplied by the hospital for the duration of the treatment course.

Red medicines are those where primary care prescribing is not recommended. These treatments should be initiated by specialists only and prescribing retained within secondary care. They require specialist knowledge, intensive monitoring, specific dose adjustments or further evaluation in use.

Please note, this recommendation is **not** restricted to gastrointestinal bleeding.

Summary of supporting evidence:

- The European Medicines Agency (EMA) concluded that the efficacy of administration of idarucizumab with the proposed dose regimen of 2 times 2.5g was supported by the totality of the presented data in healthy volunteers as well as in treated patients. [1]
- Adverse events directly attributable to idarucizumab appear to be rare based on clinical evidence submitted to the EMA.
- A meta-analysis of studies comparing idarucizumab, andexanet alfa and 4-PCC found high rates of effective haemostasis for all agents and that it is a plausible conclusion that, in the event of insufficient response, additional attempts and/or combination with other treatment modalities aimed at achieving effective haemostasis should be considered. [2]
- NICE recommends the use of another reversal agent (andexanet alfa) for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threating or uncontrolled bleeding. [3]
- The acquisition price of idarucizumab is significantly lower than andexanet alfa (approximately 20% cost).
- Clinical experts consulted by the SMC considered idarucizumab to be a therapeutic advancement relative to standard, supportive care and expect it to be used infrequently in avoiding major bleeds. [4]

Date: July 2021

Details of Review

Name of medicine (generic & brand name)**:** Idarucizumab (Praxbind®).

Strength(s) and form(s): 2.5 g/50 mL solution for injection/infusion.

Dose and administration:

The recommended dose is 5 g idarucizumab (2 vials of 2.5 g/50 mL).

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 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/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). [5]

BNF therapeutic class / mode of action:

Antidotes / humanised monoclonal antibody fragment that binds specifically to dabigatran.

Licensed indication(s):

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

• For emergency surgery/urgent procedures.

• In life-threatening or uncontrolled bleeding. [5]

Proposed use (if different from, or in addition to, licensed indication above):

N/A

Course and cost:

£2400 for a single treatment (PbR excluded high cost drug - CCG commissioned).

Under certain circumstances a second dose of idarucizumab may be considered (see above).

Current standard of care/comparator therapies:

- No comparator
- Standard care involves stopping dabigatran treatment and providing general supportive measures such as surgical haemostasis and blood volume replacement. [6]

- 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 should be temporarily discontinued. [6]

Relevant NICE guidance:

NICE evidence summary ESNM73 - Reversal of the anticoagulant effect of dabigatran: idarucizumab [6]

NICE guideline NG 39 - Major trauma: assessment and initial management [7]

"Consult a haematologist immediately for advice on adults (16 or over) who have active bleeding and need reversal of any anticoagulant agent other than a vitamin K antagonist."

Background and context

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 also known as direct oral anticoagulants (DOACs) apixaban, dabigatran etexilate, edoxaban and rivaroxaban. [6]

The most common adverse effect of anticoagulants is bleeding, ranging from mild events to serious and fatal haemorrhage. Idarucizumab was the first agent to be licensed to reverse the anticoagulant effect of a DOAC, and it is a specific reversal agent for dabigatran etexilate. Andexanet alfa is licensed for reversing anticoagulation by apixaban and rivaroxaban. NICE produced technology appraisal guidance in May 2021 recommending the use of andexanet alfa in adults with life-threatening or uncontrolled bleeding only if the bleed is in the gastrointestinal tract. [8]

The summary of product characteristics (SPC) for dabigatran etexilate 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. [9]

The LSCMMG prioritised idarucizumab following use of idarucizumab in local trusts.

Summary of evidence

Summary of efficacy data in proposed use:

Scottish Medicines Consortium (SMC) review [4]

The SMC completed an assessment of idarucizumab for its licensed uses in 2016 and accepted idarucizumab for use in NHS Scotland. The basis of the recommendation was a phase III, non-randomised, case series interim analysis study [10] which was submitted by the manufacturer.

Pollack et al interim analysis [10]

In this 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 5 g intravenously (IV) administered as two, 2.5 g doses, 15 minutes apart.

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. A total of 90 patients had central laboratory data and, of these, 68 patients with elevated diluted thrombin time (dTT) at baseline and 81 patients with elevated ecarin clotting time (ECT) at baseline were considered evaluable.

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.

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, intraoperative 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.

Pollack et al – Full Cohort Analysis [11]

The level of reversal observed in the full cohort analysis is consistent with the results of the interim analysis of this study [10] and with the results of studies of the use of idarucizumab in healthy volunteers.

A total of 503 patients were enrolled: 301 in group A, and 202 in group B. The median maximum percentage reversal of dabigatran was 100% (95% confidence interval, 100 to 100), on the basis of either the diluted thrombin time or the ecarin clotting time. In group A, 137 patients (45.5%) presented with gastrointestinal bleeding and 98 (32.6%) presented with intracranial haemorrhage; among the patients who could be assessed, the median time to the cessation of bleeding was 2.5 hours. In group B, the median time to the initiation of the intended procedure was 1.6 hours; periprocedural haemostasis was assessed as normal in 93.4% of the patients, mildly abnormal in 5.1%, and moderately abnormal in 1.5%. At 90 days, thrombotic events had occurred in 6.3% of the patients in group A and in 7.4% in group B, and the mortality rate was 18.8% and 18.9%.

Meta-analysis of reversal agents [2]

A meta-analysis was conducted to investigate clinical outcomes associated with the use of 4-factor prothrombin complex concentrates (4-PCC), idarucizumab, or andexanet alfa for reversal of severe DOAC-associated bleeding (e.g., potentially life-threatening bleeding with signs or symptoms of haemodynamic compromise; major bleeding associated with a fall in haemoglobin >2 g/dl; or bleeding in a critical area or organ). Case-series with <10 patients were excluded, and patients treated with less common reversal modalities (e.g., activated prothrombin complex concentrate, recombinant factor VIIa, tranexamic acid, and/or vitamin K) and those in which the administration of the reversal agent was not indicated to treat a major bleeding.

The investigators evaluated 60 studies in 4,735 patients with severe DOAC-related bleeding who were treated with 4-factor prothrombin complex concentrates (n = 2,688), **idarucizumab (n = 1,111)**, or andexanet (n = 936). The majority of the studies were retrospective cohorts (n = 48), followed by prospective cohorts (n = 10) and clinical trials (n = 2).

There were 623 deaths in 4,169 patients evaluable for mortality (rate: 17.7%; CI95%: 15.1% to 0.4%). No relevant differences were found in death rates depending on the reversal agent used, the type of study, risk of bias, or study sponsorship. Effective haemostasis was achieved in 1,469 of 1,890 patients (rate: 78.5%; CI95%: 75.1% to 81.8%). The rate of haemostatic efficacy was high with 4-PCC (80.1%; CI95%: 75.9% to 84.2%), idarucizumab (76.7%; CI95%: 68.5% to 85%), and andexanet (80.7%; CI95%: 73.5% to 87.9%).

Summary of safety data:

The EPAR for idarucizumab concluded that the safety data for idarucizumab showed an acceptable safety profile in 283 healthy volunteers and 123 emergency patients. There were 26 deaths at the cut-off in the ongoing Phase III study, 13 each in bleeding and surgical patients. The Committee for Medicinal Products for Human Use (CHMP) agreed that the deaths were most likely related either to the index event or to co-morbidities. During the study, 5 patients developed thrombotic events, all of them not on antithrombotic therapy. In the safety database, there were

very few AEs or SAEs. All adverse events were judged by the EMA to be related to the index events or underlying diseases. [1] The SPC for idarucizumab does not therefore list any specific adverse reactions.

In RE-VERSE AD [10] the proportion of patients that reported any adverse event was 89% (59/66) in group A (emergency patients) and 77% (44/57) in group B (surgical patients), 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]

No contraindications are listed in the SPC for idarucizumab and patients with potential hypersensitivity/intolerances or who are pregnant/breastfeeding may use idarucizumab if the expected clinical benefit is likely to outweigh the risks. If an anaphylactic reaction or other serious allergic reaction occurs, administration of idarucizumab should be discontinued immediately and appropriate therapy initiated. Patients being treated with dabigatran have underlying disease states that predispose them to thromboembolic events. Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. To reduce this risk, resumption of anticoagulant therapy should be considered as soon as medically appropriate. No formal interaction studies with idarucizumab and other medicinal products have been performed. Based on the pharmacokinetic properties and the high specificity in binding to dabigatran, clinically relevant interactions with other medicinal products are considered unlikely. [5]

Strengths and limitations of the evidence:

Strengths

- The European Medicines Agency (EMA) concluded that the efficacy of administration of idarucizumab with the proposed dose regimen of 2 times 2.5g was supported by the totality of the presented data in healthy volunteers as well as in treated patients. [1]
- Adverse events directly attributable to idarucizumab appear to be rare based on clinical evidence submitted to the EMA.
- A meta-analysis of studies comparing idarucizumab, andexanet alfa and 4-PCC found high rates of effective haemostasis for all agents and that it is a plausible conclusion that, in the event of insufficient response, additional attempts and/or combination with other treatment modalities aimed at achieving effective haemostasis should be considered. [2]
- NICE recommends the use of another reversal agent (andexanet alfa) for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threating or uncontrolled bleeding. [3]
- The acquisition price of idarucizumab is significantly lower than andexanet alfa (approximately 20% of the cost).
- Clinical experts consulted by the SMC considered idarucizumab to be a therapeutic advancement relative to standard, supportive care and expect it to be used infrequently in avoiding major bleeds. [4]
- Guidance from the Society of Critical Care Medicine in the US recommend idarucizumab for patients with intracranial haemorrhage associated with dabigatran. [12]

Limitations

- 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.

- The primary outcome measure of the pivotal trial is a surrogate marker using two blood tests (dilute-thrombin-time and ecarin clotting-time) which would not normally be undertaken and interpreted in clinical practice due to the life-threatening nature of the patient presentation.
- The EMA concluded that the effect of idarucizumab therapy on reduction in morbidity or mortality (most notable bleeding complications) remained uncertain. RE-VERSE AD [10] was not powered nor designed to detect a difference between standard of care plus idarucizumab versus standard of care alone.
- The nature of the life-threatening clinical situation that idarucizumab would be used in precludes the ability to design a comparative study to measure effects against standard care.
- Measuring patient orientated outcomes relating to cessation of bleeding is often difficult and subjective especially for concealed bleeds (e.g. intracranial).
- The authors of a meta-analysis comparing reversal agents concluded that the risk of death after severe DOAC-related bleeding remains significant despite a high rate of effective haemostasis with reversal agents.

Summary of evidence on cost effectiveness:

The company submitted a cost analysis of idarucizumab to the SMC 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%). [4]

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. [4]

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. [4]

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. [4]

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

Prescribing and risk management issues:

Idarucizumab is for hospital use only. In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Idarucizumab must not be mixed with other medicinal products. A pre-existing intravenous line may be used for administration of idarucizumab. The line must be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection prior to and at the end of infusion. No other infusion should be administered in parallel via the same intravenous access. [5]

Commissioning considerations:

Innovation, need and equity implications of the intervention:

Anticoagulation therapy increases risk of bleeding. Without a reversal agent, the risk of uncontrolled or life-threatening bleeding to those currently taking dabigatran can impact patients' quality of life both physically and mentally. Idarucizumab is the only agent available for the reversal of dabigatran anticoagulation. Other management strategies for patients requiring reversal of dabigatran anticoagulation include a range of off-label treatments (e.g. factor concentrates, tranexamic acid) with limited evidence to support use.

Financial implications of the intervention:

Based on patient numbers submitted by the manufacturer to the SMC, 57 patients would require idarucizumab for its licensed indications. This equates to 18 patients in Lancashire and South Cumbria. Assuming each patient required a single treatment (£2,400) the total spend in Lancashire and South Cumbria would be approximately £43,000.

The manufacturer also assumed that displacement of blood related products may contribute to lower overall costs (by approximately 1/3).

Service Impact Issues Identified:

No additional service impact is expected. Idarucizumab is an additional treatment option for anticoagulated patients presenting with haemorrhage.

Equality and Inclusion Issues Identified:

See the attached equality form. There may be an equality issue for patients who do not wish to receive blood products.
Cross Border Issues Identified:
Idarucizumab is available as a “Red” drug in both Pan Mersey and GMMMG formularies.
Legal Issues Identified:
N/A
Media/ Public Interest:
N/A

References

[1] European Medicines Agency, "Assessment Report EMA/713107," September 2015. [Online]. Available: https://www.ema.europa.eu/en/documents/assessment-report/praxbind-epar-public-assessment-report_en.pdf. [Accessed July 2021].

[2] A Gomez-Outes et al, "Meta-Analysis of Reversal Agents for Severe Bleeding Associated With Direct Oral Anticoagulants," *Journal of the American College of Cardiology,* vol. 77, no. 24, pp. 2987-3001, 2021.

[3] NICE, "TA697 Andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban," May 2021. [Online]. Available: https://www.nice.org.uk/guidance/ta697. [Accessed July 2021].

[4] Scottish Medicines Consortium, "Idarucizumab 2.5g/50ml solution for injection/infusion (SMC No 1178/16)," August 2016. [Online]. Available: https://www.scottishmedicines.org.uk/media/1810/idarucizumab_praxbind_final_august_2016_for_website.pdf. [Accessed July 2021].

[5] Electronic Medicines Compendium, "Summary of Product Characteristics Praxbind," Boehringer Ingelheim Limited, November 2015. [Online]. Available: https://www.medicines.org.uk/emc/product/5073. [Accessed July 2021].

[6] NICE, "Reversal of the anticoagulant effect of dabigatran: idarucizumab," May 2016. [Online]. Available: https://www.nice.org.uk/advice/esnm73/chapter/Key-points-from-the-evidence. [Accessed July 2021].

[7] NICE, "Major trauma: assessment and management," February 2016. [Online]. Available:

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[11] CV Pollack et al, "Idarucizumab for Dabigatran Reversal - Full Cohort Analysis," *NEJM,* vol. 377, pp. 431-441, 2017.

[12] JA Frontera, "Guideline for Reversal of Antithrombotics in Tntracranial Hemorrhage," *Neurocrit Care,* vol. 24, pp. 6-46, 2016.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality