Northern Treatment Advisory Group

Andexanet alfa - Factor Xa inhibitor antidote

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Summary

- Around 1-2% of patients treated with DOACs might experience significant or life-threatening bleeding that would require rapid reversal of anticoagulation. The prevalence of life-threatening bleeding in these patients has increased as the use of those agents has increased. ICH and GI bleeding carry the highest risk of life-threatening or uncontrolled bleeding requiring urgent anticoagulation reversal.
- Licensed DOACs in the UK include the FXa inhibitors rivaroxaban, apixaban and edoxaban, and the direct thrombin inhibitor, dabigatran.
- Idarucizumab was the first specific DOAC reversal agent approved in the EU in 2015, specifically binding and inhibiting anticoagulation activity of dabigatran.
- Andexanet alfa is a first-in class FXa inhibitor antidote licensed in the EU for use in adult patients treated with a direct FXa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
- Recent guidelines recommend the use of specific antidotes for the management of severe/life-threatening bleeding in DOAC/FXa inhibitor-treated patients. In their absence, PCC is recommended, in addition to standard pro-haemostatic measures.
- Use of andexanet alfa is currently indicated in apixaban and rivaroxaban-treated patients only. Edoxaban-treated patients will be additionally analysed in the extension phase of the ANNEXA-4 study, the currently ongoing prospective phase IIIb/IV trial open-label study to evaluate haemostatic efficacy of andexanet alfa in patients receiving a FXa inhibitor with an acute major bleeding episode requiring urgent reversal of FXa anticoagulation.
- ANNEXA-4 trial has evaluated 352 adult patients with acute major bleeding taking apixaban (n=194, 54%), rivaroxaban (n=128, 36%), edoxaban (n=10, 3%) and enoxaparin (n=20, 6%). A 92% reduction of anti-FXa activity was observed in patients that had been treated with apixaban or rivaroxaban. Excellent or good haemostasis occurred in 204 of 249 patients (82% of efficacy population) over a 12-hour period following infusion. Of the safety population (n=352), 14% (n=49) of died and 10% (n=34) had a TE within 30 days.
- The main limitation of the ANNEXA-4 trial is the lack of randomisation or comparison with a control group, There is therefore no clear evidence whether it is more effective in achieving haemostasis than conventional care alone. However, andexanet alfa is the only licensed product for this indication.
- Two dose regimens of andexanet alfa are approved: a low and a high dose regimen, requiring 5 or 9 vials respectively. The listed NHS price for 4 vials of Ondexxya®▼ 200 mg powder for solution for infusion is £11,100, exclusive of VAT. Prices for low and high dose will therefore be £13,875 and £24,975 per patient, respectively. It is not yet known whether any commercial arrangements will be offered. From data extracted of patients prescribed FXa inhibitors in North East and North Cumbria, it is estimated that around £16-20 million would be the yearly cost for around 1,050 eligible patients per year.
- No direct licensed comparators are available. Alternatives in the absence of andexanet alfa include 4-PCC, a-PCC and recombinant FVII, alongside standard supportive measures.

Contents

Indication

Andexanet alfa (Ondexxya®▼, Portola Pharmaceuticals) was granted a conditional marketing authorisation in April 2019 for use in adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.[1]

Life-threatening or uncontrolled bleeding is defined by the site of the bleed in consultation with UK clinical experts as follows:[2]

- Intracranial haemorrhage (ICH): bleeding inside the skull
- Severe gastrointestinal (GI) bleed: hemodynamically unstable bleeding originating from the GI tract
- Intraocular bleed: bleeding into the eye
- Intraspinal bleed: bleeding within the spinal column
- Pericardial bleed: bleeding within the pericardial space
- Retroperitoneal bleed: bleeding within the retroperitoneal cavity

There are limited clinical data for treatment of life-threatening bleeding associated with edoxaban and enoxaparin. Likewise, no data for this indication are available for fondaparinux, and no clinical data at all are available with andexanet alfa in patients undergoing urgent surgery/invasive procedures. Therefore, the final indication leaves out patients treated with edoxaban, enoxaparin and fondaparinux and also emergency surgery/urgent procedures.[3]

Dosage and administration

Andexanet alfa is available as a 200 mg powder for solution for infusion vials. Reconstituted solution has a 10 mg/mL concentration, which is administered by intravenous (i.v.) infusion. It is first administered as an i.v. bolus at 30 mg/minute over 15 to 30 minutes, followed by a continuous infusion of 4 mg (low dose, total of 880 mg) or 8 mg (high dose, total of 1,760 mg) per minute for 120 minutes (Table 1).[4]

Table 1. Dosing regimens

	Initial intravenous bolus	Continuous intravenous infusion	Total number of 200 mg vials needed
Low dose	400 mg at a target rate of 30 mg/min	4 mg/min for 120 minutes (480 mg)	5
High dose	800 mg at a target rate of 30 mg/min	8 mg/min for 120 minutes (960 mg)	9

The recommended dose regimen for andexanet alfa is based on the dose of apixaban or rivaroxaban the patient is taking at the time of anticoagulation reversal, as well as on the time since the patient's last dose (Table 2).[4]

Table 2. Summary of dosing for reversal of apixaban or rivaroxaban.

FXa inhibitor	Last dose	Timing of last dose before andexanet alfa initiation	
		< 8 hours or unknown	≥ 8 hours
Apixaban	≤ 5 mg	Low dose	Low dose
	> 5 mg/ Unknown	High dose	
Rivaroxaban	≤ 10 mg	Low dose	Low dose
	> 10 mg/ Unknown	High dose	

Therapeutic background

The most common adverse effect of anticoagulants is bleeding, ranging from mild events to serious and fatal haemorrhage.[5] There is an estimated risk of bleeding in 1-4% of the patients treated with direct oral anticoagulants (DOACs), and around 1-2% might experience significant or life-threatening risk of bleeding requiring rapid reversal of the anticoagulant effect.[6,7]

DOAC use is increasingly replacing warfarin or other vitamin K antagonists (VKAs), particularly as the preferred choice in patients newly started on anticoagulation. Although the risk of haemorrhagic complications - including life-threatening bleeding - might be less common than with VKAs, concerns such as the lack of specific reversal agents have been raised.[8,9] Approved DOACs include the FXa inhibitors rivaroxaban, apixaban and edoxaban, and the direct thrombin inhibitor, dabigatran. Apixaban, rivaroxaban and edoxaban are indicated for:[3]

- Prevention of stroke in patients with atrial fibrillation (AF) (all)
- Prevention of venous thromboembolism (VTE) in hip and knee replacement surgery (rivaroxaban and apixaban)
- Prevention of recurrence of VTE (all)
- Treatment of deep vein thrombosis (DVT) (all)
- Treatment of pulmonary embolism (PE) (all)
- Prevention of atherothrombotic events after acute coronary syndrome (ACS) (rivaroxaban only)

Andexanet alfa is a first-in-class FXa inhibitor antidote licensed in the EU for life-threatening or uncontrolled bleeding in patients treated with apixaban or rivaroxaban, with future likely inclusion of edoxaban. Andexanet alfa is a recombinant protein that restores the activity of FXa by reversing the anticoagulant effects of FXa DOACs through the specific binding and sequestration of those agents. Andexanet alfa also reverses indirect FXa inhibitors such as fondaparinux, by binding to antithrombin-fondaparinux complex, and may inhibit the tissue factor pathway inhibitor (TFPI) activity through binding to TFPI. However, these interactions have not been fully characterized, and are not reflected in the granted indication.[4,6]

Previously in 2015, idarucizumab (Praxbind®▼), a monoclonal antibody that neutralises the anticoagulant effect of dabigatran, was the only specific DOAC antidote approved in the EU.[3] It is indicated in adult patients treated with Pradaxa® (dabigatran etexilate) when rapid reversal of its anticoagulant effects is required for

emergency surgery/urgent procedures and in life-threatening or uncontrolled bleeding.[10]

Cirapantag, a specific reversal agent for FXa and low molecular weight heparin (LMWH), is currently in a fast track development phase II status in the US.[8,11]

Management of severe/life-threatening bleeding

Institutions should have an agreed procedure in place for management of severe or life-threatening bleeding. General principles are as follows.

1) Analysis of clinical situation – general assessment: type of bleeding, bleeding site onset, type and time of last DOACs, and other factors influencing haemostasis (e.g. other antithrombotic drugs, alcohol abuse).

The European Society of Cardiology (ESC) Guidelines for management of AF (2016), propose a general assessment to manage bleeding events in patients with DOACs, that includes mechanical intervention (compression of bleeding sites) followed by the assessment of haemodynamic status, blood pressure, basic coagulation parameters, blood count and kidney function, and other factors influencing bleeding risk. Similar measures are advised in the European Heart Rhythm Association (EHRA) practical guide on the use of DOACs in patients with AF (2018) (Figure 1 A and B). Both, however, state that conventional coagulation tests might be non-informative in patients taking DOACs, are not always readily available and are often unnecessary for bleeding management.[9,12]

2) Severe/life-threatening bleeding.

In urgent situations when immediate reversal is required, general measures and drug-specific management are advised.[9,13] In this scenario, a specific antidote is indicated in severe or life-threatening bleeding events.[12] In case specific antidotes are not available, administration of coagulation factor concentrates, such as prothrombin complex concentrates (PCC), may be considered for severe bleeding on DOACs; however this is an unlicensed indication (Figure 1 A and B). [9,12-14]

Severe bleeding may be also managed with fluid replacement, red blood cells and platelet substitution, fresh frozen plasma, anti-fibrinolytic (e.g. tranexamic acid), or treatment interventions directed against the cause of the bleeding (e.g. gastroscopy) may be still considered in severe bleeding. [9,12] However, specific recommendations for ICH should be considered (see below).

ICH bleeding

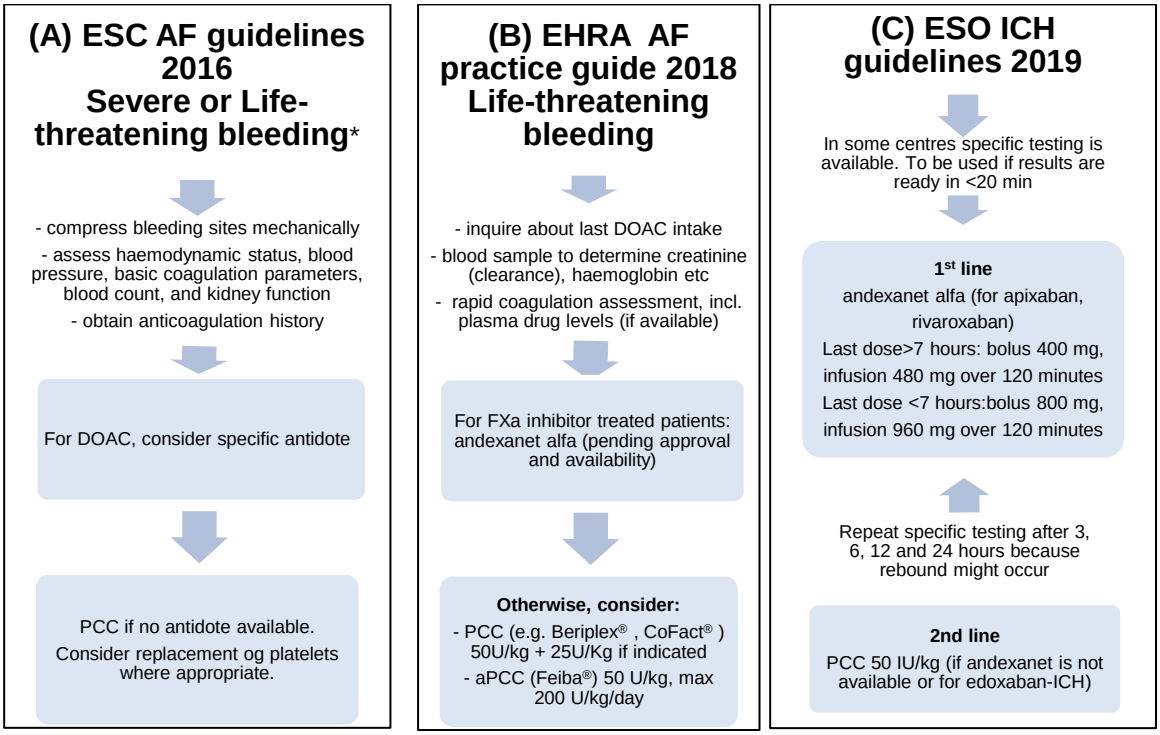
ICH rates in patients treated with DOACs range from 0.3-0.5%, based on clinical trial results.[6] Extracranial haemorrhages represent a similar proportion, gastrointestinal (GI) bleeding being the most common (90%).[3] However, ICH is associated with high mortality and severe disability rates.[8,15] Therefore, although not specifically indicated, the scope for the NICE guidance addresses the wording of the therapeutic

indication and notes that NICE may give consideration to subgroups with IC bleeding if the evidence allows for it.[6]

Based on clinical studies for idarucizumab and andexanet alfa, severe bleeding with DOACs will be IC in 33-64% of cases, 26-46% gastrointestinal, while trauma and others will represent the remaining cases. [16-18] Most of patients were been treated for AF (80-90%) followed by VTE (10-18%) as the primary indication for anticoagulation treatment at baseline.[16,18]

New guidelines on reversal of oral anticoagulants in acute intracerebral haemorrhage from the European Stroke Organisation (ESO) recommend using preferably andexanet alfa in patients with rivaroxaban and apixaban-related ICH (2019)(Figure 1, C). A weak recommendation is given for high dose of PCC (50IU/Kg) for all patients taking edoxaban, and for patients on apixaban or rivaroxaban where andexanet alfa is not available, due to likely increased risk of thrombosis. Likewise, recombinant factor VII a (FVIIa) is not recommended, outside clinical trials. Tranexamic acid is not recommended due to its unlikely benefit as monotherapy in DOAC-related ICH.[19]

Figure 1. Flowcharts for the management of severe/life-threatening and ICH in DOACs/FXa inhibitor-treated patients according with ESC (A), EHRA (B) and ESO (C) recommendations.



* This guideline was published on 2016, when andexanet alfa was still in development and before its approval.

Clinical efficacy

Efficacy of andexanet alfa has been reported in two phase III studies (ANNEXA-A and ANNEXA-R) and a phase IIIb/IV study (ANNEXA-4).

ANNEXA-A and ANNEXA-R in healthy volunteers

ANNEXA-A and ANNEXA-R, both were randomized placebo-controlled studies to evaluate change in anti-FXa activity in old healthy volunteer, aged 50 to 75 years, receiving apixaban or rivaroxaban, respectively. Both studies were designed to evaluate the ability of andexanet alfa to reverse anticoagulation with apixaban (ANNEXA-A) or rivaroxaban (ANNEXA-R), in two consecutive parts: part 1, to examine i.v. andexanet bolus alone, and part 2, to examine i.v. bolus followed by a continuous 120-minute infusion. A total of 101 (48 in ANNEXA-A, and 53 in ANNEXA-R) were randomised to andexanet alfa and 44 participants (17 in ANNEXA-A, and 27 in ANNEXA-R) were randomised to placebo. The primary endpoint for both studies was the percent change in anti-factor FXa activity.[20]

Anti-FXa activity was significantly reduced in both groups treated with andexanet alfa within 2 to 5 min after bolus injection (ANNEXA-A: 94% with andexanet alfa vs. 21% with placebo, p<0.001; ANNEXA-R: 92% with andexanet vs. 18% with placebo, p<0.001). Reversal activity was maintained during the continuous infusion (1-2 hours), followed by a return to placebo levels.[20]

ANNEXA-4 in bleeding patients

ANNEXA-4 was a global prospective, open-label study to evaluate the haemostatic efficacy of andexanet alfa in patients receiving a FXa inhibitor with an acute major bleeding episode requiring urgent reversal of FXa anticoagulation. The co-primary outcomes were the percent change of anti-FXa activity after andexanet treatment and the proportion of patients with excellent or good haemostasis at 12 hours after the end of the andexanet alfa infusion. Haemostatic efficacy was assessed by an independent adjudication committee, based on pre-specified criteria for each bleed type, scoring from excellent or good efficacy (effective), to poor or no efficacy (not-effective).[18]

The trial, still recruiting, has evaluated 352 adult patients (mean age: 77 years) with acute major bleeding, who had received any dose of apixaban (n=194, 55%), rivaroxaban (n=128, 36%), or edoxaban (n=10, 3%), or at least 1 mg/Kg/day of enoxaparin (n=20, 6%), within the last 18 hours.[18] Acute major bleeding was defined as: potentially life-threatening bleeding with signs or symptoms of haemodynamic compromise (e.g. severe hypotension), bleeding with decrease in haemoglobin levels (≥ 2g/dL, or ≤ 8 g/dL if baseline level was not available), or bleeding in a critical area or organ (e.g. IC bleeding). The primary sites of bleeding were IC (64%) and GI (26%). The primary indication for anticoagulation was AF (80%) and VTE (17%).[18]

Eligible patients received an initial bolus followed by a 2-hour infusion of andexanet alfa, and were followed for at least 30 days or until death. Andexanet alfa doses were determined by the type, dose and timing of the FXa inhibitor received prior to enrolment, consisting of low (400 mg bolus at 30mg/min + 4 mg/min infusion for 2 hours) or high doses (800 mg bolus at 30mg/min + 8 mg/min infusion for 2 hours).[18]

Efficacy was assessed in those patients who met the bleeding severity criteria and whose baseline anti-FXa activity was ≥75 ng/mL, or ≥0.25 IU/mL for those receiving enoxaparin (efficacy population, n=254). Rapid reversal of FXa inhibition was observed at the end of the bolus administration (15-30 minutes). Anti-FXa activity was reduced by 92% in patients treated with apixaban (n=134; 95% CI, 91-93) and rivaroxaban (n=100; 95% CI, 88-94), and 75% with enoxaparin (n=16; 95% CI, 66-79). After 12 hours of andexanet alfa infusion, mean reductions in levels were 38%

(95% CI, 34-41), 62% (95% CI, 58-65) and 61% (95% CI, 49-67), respectively. Haemostatic efficacy at 12 hours could be evaluated in 249 patients. Excellent or good efficacy was adjudicated to 171 (68.7%) and 33 (13.2%) patients, respectively, achieved by 85% (95% CI, 76-94) in GI bleeding and 80% (95% CI, 74-86) in IC bleeding.[18] Overall, excellent or good haemostasis was achieved in 82% of patients over a 12-hour period following infusion, with consistent effects across all subgroups (Table 3).

Poor or no efficacy was observed in 45 (18.1%) patients (Table 4). Median reduction of anti-FXa activity in those patient was 94% with apixaban (n=22, 95% CI, 87-95), 90% with rivaroxaban (n=20, 95% CI, 78-95), and 78% with enoxaparin (n=2, 95% CI, 74-82) (Table 2). In addition, there were no significant relationship between haemostatic efficacy and change in anti–factor Xa activity. These data did not confirm the initial hypothesis that a reduction in anti-FXa activity could predict clinical responses (AUC 0.53, 95% CI, 0.44-0.62). Only predictability was found in ICH sub-population (AUC 0.64, 95% CI, 0.53-0.74). Despite these results, the authors consider that change in anti-FXa activity is not likely to be useful for clinical response prediction in clinical practice.[18] A prospective randomised phase IV trial in acute ICH in patients receiving an oral FXa inhibitor (apixaban, rivaroxaban or edoxaban) is ongoing (NCT03661528).

Table 3. Anti-FXa activity and haemostatic efficacy.

Subgroup	Anti–FXa activity reduction (end of bolus administration, 15-30 min)		Excellent or Good Haemostasis (12 h post-infusion)	
	n	% (95% CI)	n/N	% (95% CI)
All	-	-	204/249	82% (77-87)
Apixaban	134	92% (91-93)	109/131	83% (77-90)
Rivaroxaban	100	92% (88-94)	79/99	80% (72-88)
Enoxaparin	16	75% (66-79)	13/15	87% (69-100)
Edoxaban	10	-	-	-
ICH	-	-	135/168	80% (74-86)
GI bleeding	-	-	51/60	85% (76-94)
Other site bleeding	-	-	18/21	86% (71-100)
Low Dose	-	-	172/208	83% (78-88)
High Dose	-	-	32/41	78% (65-91)

(-) No specific data available in the published study.

Table 4. Haemostatic efficacy and anti-FXa activity for patients with poor or no haemostatic efficacy.

Subgroup	Poor or no efficacy		
	n/N	%	Anti-FXa activity reduction % (95% CI)
All	45/249	18.1%	-
Apixaban	22/131	16.8%	94% (87-95)
Rivaroxaban	20/99	20.2%	90% (78-95)
Enoxaparin	2/15	13.3%	78% (74-82)
Edoxaban	1/4	25%	-
ICH	33/168	19.6%	-
GI bleeding	9/60	15%	-
Other site bleeding	3/21	14.3%	-
Low Dose	36/208	17%	-
High Dose	9/41	18.1%	-

(-) No specific data available in the published study.

Based on the patients included in ANNEXA-4, who were mainly treated with apixaban and rivaroxaban, the Committee for Medicinal Products for Human use (CHMP) decided to exclude patients treated with edoxaban and enoxaparin from the final indication.[3] An extension of the ANNEXA-4 trial is ongoing to further evaluate the efficacy and safety of andexanet alfa (NCT02329327). It is expected that additional patients taking edoxaban will be included. At the moment, only limited preclinical data supporting edoxaban-reversal with andexanet has been published.[3,21]

Limitations

The main limitation of ANNEXA-4 study is the lack of randomisation and comparison with a control group. It is therefore unclear if a targeted reversal of anti-FXa inhibitor is more effective in achieving effective haemostasis than conventional care alone. The company is running a randomized, controlled clinical trial evaluating the efficacy and safety of andexanet versus usual standard of care in patients with ICH anticoagulated with a direct oral anticoagulant, that will be completed in 2023 (NCT03661528).[18]

Safety

From a safety population of 352 patients in ANNEXA-4, death occurred in 49 patients (14%) and a thrombotic event (TE) in 34 (10 %) within 30 days. Deaths mostly occurred of cardiovascular causes (71%). TEs reported included myocardial infarction in 7 patients, ischemic stroke in 14, DVT in 13, and pulmonary embolism in 5.[18]

No serious or severe adverse drug reactions (ADR) were reported in the clinical trials with healthy subjects (ANNEXA-A and –R). The most frequently observed ADRs in healthy subjects were mild or moderate infusion-related reactions (e.g. flushing, feeling hot, cough, dysgeusia, and dyspnoea) occurring within a few minutes to a few hours of the infusion.[4]

Antibodies to FX or FXa did not develop in any participant from any of the trials with healthy or bleeding subjects. Non-neutralising antibodies were detected in 1 of 44 healthy participants with placebo (2%) and in 17 of 101 with andexanet alfa (17%).[18,20]

Comparison with other standard care options

There are limited treatment options for patients suffering an acute major bleeding episode taking FXa inhibitors, and there is no licensed alternative to andexanet alfa. Established clinical management of uncontrolled or life-threatening bleeding without andexanet alfa included non-specific pro-haemostatic agents such as prothrombin complex concentrate (PCC) and activated PCC (aPCC).[6]

Meta-analysis PCC for the management of direct factor Xa inhibitor–related major bleeding (2019)

In a recent meta-analysis,[14] 10 case-series studies evaluating the efficacy of PCCs in the reversal of direct FXa-associated bleeding were found. From those, only 2, Majeed et al. 2017 and Schulman et al, 2018,[22,23] followed the International Society of Thrombosis and Haemostasis (ISTH) recommendations for the assessment of effectiveness of major bleeding management,[24] similar to the criteria used in ANNEXA-4 trial (see Appendix 1). The median dose of 4-PCC given to apixaban and rivaroxaban- treated patients was 2,000 IU. The median proportion of patients with effective haemostasis in apixaban- or rivaroxaban-associated major bleeding treated with 4-PCC reported in those 2 trials was 69% (n=150, 95% CI, 61-76).[14,18] The authors concluded that this result is similar to the ANNEXA-4 trial (82%), and suggest that PCC may continue to be used given the limited availability and high cost of andexanet alfa, at least in reference to US and Canada.

In addition, rate of TEs during the follow-up period (≤30 days) in the pooled analysis (9 studies, 249 patients) was 4%, which was below the incidence found in ANNEXA-4 (10%). However, in the pooled analyses (8 studies, n=190) the proportion of all-cause mortality was slightly higher (16%) than that reported in ANNEXA-4 trial (14%). Death and TE rates ranged from 9 to 27% and from 3 to 5%, respectively, in the 2 studies using the ISTH criteria (Table 5). [22,23]

Safety, efficacy and cost analysis of 4-PCC in patients with FXa-inhibitor-related bleeding: a retrospective study (2019)

This study aimed to perform a comprehensive analysis of the safety and efficacy of 4-PCC for the management of serious bleeding related to oral FXa inhibitors.[25] The primary outcome was to evaluate the effectiveness of 4-PCC for the management of FXa inhibitor-related major bleeding. Doses ranged from 25 to 50 U/kg (5,000 U max). Haemostatic efficacy was assessed using the criteria described in Sarode et al.[26] the same study used to adapt the prespecified criteria for effectiveness in ANNEXA-4. The study included 31 patients that were taking apixaban (n=17, 54.8%)

or rivaroxaban (n=14, 45.2%). Effective haemostasis was achieved in 80.6% of patients. Five patients (16%) died due to acute bleeding and no TEs were observed. Similar patient populations to this cohort and similar effectiveness assessments were included in the two main prospective studies discussed above, although mean doses were lower (2,000 U).[22,23]

Table 5 shows a summary of the trials with similar criteria for effectiveness evaluation to those used in ANNEXA-4. However, the differences between the intrinsic thrombotic risk in baseline population, and the percentage of patients with ICH at enrolment, are factors that are likely to influence those outcomes, and direct comparison cannot be made.

Table 5. Summary characteristics and outcomes from ANNEXA-4 and 4-PCC trials.

Source study	Intervention	Baseline characteristics				Effective haemostasis		Deaths n (%)	TEs n (%)
		N	ICH n (%)	Apixaban n (%)	Rivaroxaban n (%)	Total	ICH		
ANNEXA-4, Connolly et al. (2019)[14]	Andexanet alfa	249	227 (64)	194 (55)	128 (36)	82%+	80%+	49 (14)‡	34 (10)
Majeed et al. (2017)[22]	4-PCC	84	59 (70)	39 (46)	49 (54)	69%#	73%#	27 (32)	3 (3.6)
Schulman et al. (2018)[23]	4-PCC	66	36 (54)	29 (44)	37 (56)	68%#	67%*	9 (14)	5 (8)
Smith et al. (2019)[25]	4-PCC	31	18 (58)	17 (55)	14 (45)	80.6 %#	88%#	5 (16)	0 (0)

* Defined as good haemostasis. + Defined as good or excellent haemostasis, # Defined as effective according with ISTH recommendations, ‡ from a safety population of 352 patients.

aPCC - Factor Eight Inhibitor Bypassing Activity (FEIBA) (2018, 2019)

Two recent small retrospective case studies on the use of the aPCCs FEIBA® (Shire Pharmaceuticals, now part of Takeda) for reversal of DOAC-related haemorrhage showed it to be an effective management strategy. One of them found excellent and good responses in GI bleeds when using the ANNEXA-4 definition of haemostatic efficacy (n=15). However, main outcomes were safety, and the assessment of efficacy is generally not comparable with ANNEXA-4 criteria. TEs were reported in 8 to 10% of patients within 30 days after aPCC administration and 14-29% had died.[27,28]

DOACs anticoagulation reversal by rFVIIa

The evidence on using recombinant factor VIIa (rFVIIa) in reversal of FXa-inhibitors is very limited, and mostly carried out in animals or in vitro experiments with human blood.[29] Despite the improvements in coagulation parameters, there is a general high rate of TEs, and certain concerns about its weak effect on preventing expansion of intracerebral haemorrhages. The benefit of using rFVIIa to reverse anticoagulation of DOACs is therefore uncertain.[29,30]

Overall, the evidence is limited and no comparative studies are available to determine whether 4-PCC or aPCC would still constitute a comparable effective alternative to andexanet alfa in the management of direct FXa-related major bleeding.

Cost analysis

This section contains data that are confidential to the NHS and commercially sensitive, and should not be disclosed to third parties outside of NTAG.

Population likely to receive andexanet alfa

In 2015, it was estimated that 350,000 people were treated with DOACs, of whom 1-2% will experience a significant or life-threatening bleeding yearly.[3] These numbers are consistent with the company estimates of total eligible population in the UK of 4,500 – 4,800 through year 1 to 5, respectively.[2]

Prescribing data in NHS North East and North Cumbria regarding apixaban, rivaroxaban and edoxaban have been evaluated for the last 3 years (Table 5).[31]

Table 6. Items prescribed and identified patient counts from CCGs: Darlington; Durham Dales, Easington and Sedgefield; Hartlepool and Stockton-on-Tees; North Durham; North Tyneside; Northumberland; South Tees; South Tyneside CCG; Sunderland; Newcastle Gateshead; and North Cumbria.

Year	Items (%)				Identified Patient Count			
	Total	A	R	E	Total	A	R	E
2016	310,809	108,226 (34.8)	202,119 (65)	464 (0.2)	[redacted]	[redacted]	[redacted]	[redacted]
2017	457,150	202,721 (44.3)	252,096 (55.2)	2,333 (0.5)	[redacted]	[redacted]	[redacted]	[redacted]
2018	616,322	323,237 (52.5)	286,246 (46.4)	6,839 (1.1)	[redacted]	[redacted]	[redacted]	[redacted]

A: apixaban; R: rivaroxaban; E: edoxaban

The use of specific FXa inhibitors is increasing rapidly, at an annual rate of 32%. Therefore, estimates for 2019 in North East and North Cumbria would be for around 70,000 patients, of whom 1-2%, 700-1400 (mean 1,050) patients per year would experience a bleeding event eligible for treatment with andexanet alfa. Although

edoxaban is not included in the licensed indication, it has been included in the calculation. Its proportion of use is now very low compared to apixaban and rivaroxaban (1.6% in 2018); however, numbers are progressively increasing, and it is likely to be included in future license extensions.

Price of andexanet alfa in the UK

All prices exclude VAT, unless otherwise specified. It is not known whether any commercial agreements are planned to reduce the cost.

The NHS list price of 4 vials of Ondexxya 200 mg powder for solution for infusion has been established at £11,100.[32] Two dose regimens can be used: a low dose requiring 5 vials, and a high dose requiring 9 vials. Prices for the low and high dose will be £13,875 and £24,975 per patient, respectively.

Calculations based on an eligible population

Scenario 1: Based on patients receiving low or high dose andexanet alfa in ANNEXA-4 trial.

In the efficacy population in ANNEXA-4 (n=249), 208 subjects received the low dose (83.5%) and 41 subjects received the high dose (16.5%).[18] If those percentages are transferable to the general population, from 1,050 eligible patients per year, 876 and 174 patients would be receiving the low and the high dose of andexanet, respectively. The total cost would then be around £16.5 million per year for a single treatment.

Scenario 2: Based on doses generally prescribed for apixaban and rivaroxaban.

The usual apixaban or rivaroxaban dose for AF – which is the primary anticoagulation indication for FXa-inhibitors– is 5 mg or 20 mg daily, respectively.[33-36] Based on this data, most patients taking apixaban would receive a low dose of andexanet alfa, while those taking rivaroxaban would receive a high dose, unless 8 hours or more have elapsed since the last dose.[4]

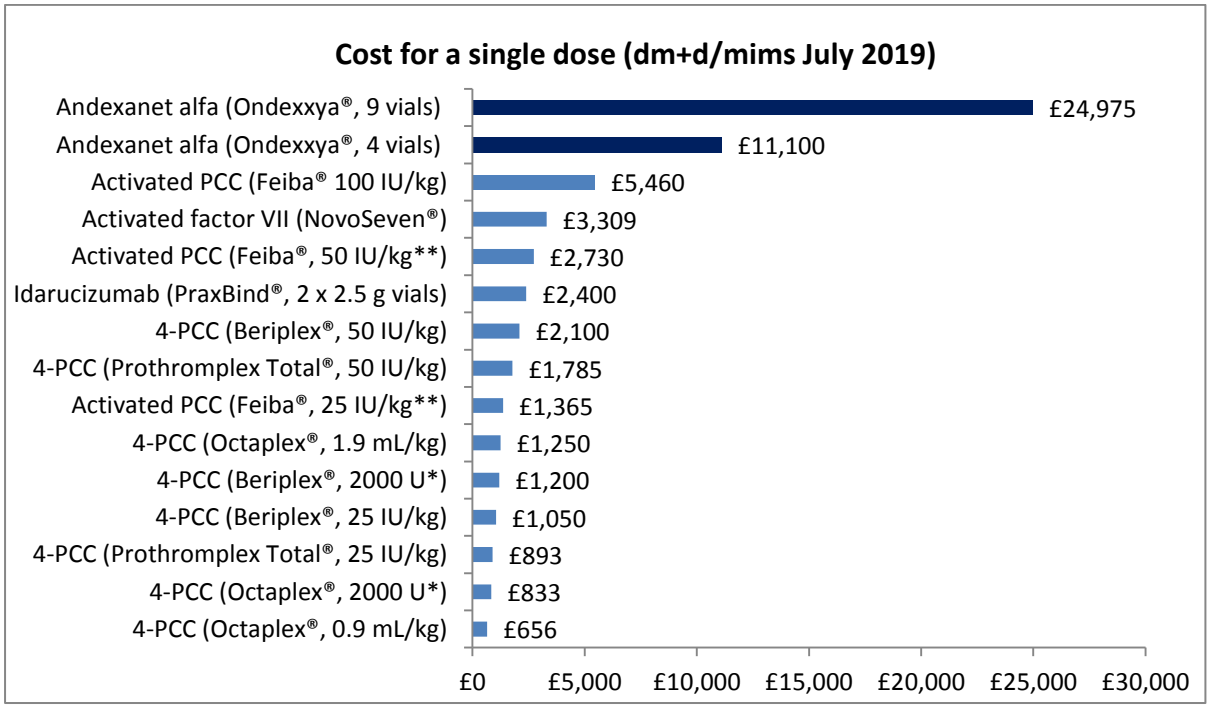
Apixaban and rivaroxaban account for almost 99% of current FXa-inhibitors prescriptions in the UK (Table 6), distributed into 51% for apixaban and 48% for rivaroxaban. So if 1,050 patients would be eligible in North East and North Cumbria in 2019, the highest expected price of andexanet alfa would be £20 million per year for a single treatment. Of note, a yearly 8% increase in the use of apixaban, to the detriment of rivaroxaban, could be expected, based on prescribing data from the last 3 years, which will increase the pool for the low dose andexanet.

Alternative treatments

The cost of alternative treatments will depend on the preparation chosen. Various agents, including inactivated or activated PCCs, are used for managing haemorrhagic complications and reversing anticoagulant effects.[5]

In two prospective cohort studies,[22,23] 4-PCCs Octaplex® and Beriplex® were given at a median dose of 2,000 IU for the management of apixaban or rivaroxaban-associated major bleeding, which would cost £833 and £1,200 per patient,

respectively (assuming a 70kg adult). The cost for a single dose of these and other agents are shown in the cost chart below. Costs shown represent the lowest and the highest dose for each medicine as stated in their respective summary of product characteristics. It should be noted that repeated doses of these agents may be needed, and the cost will vary with the weight of the patient. The cost of the mean dose used for DOAC reversal in published reports is also included, if available. Reduction in use of these agents may reduce the impact of andexanet alfa to some degree. However, the use of PCCs, or any other agents, is not licensed to reverse apixaban or rivaroxaban effects, and the use of andexanet alfa should be considered for all apixaban- or rivaroxaban-treated patients with uncontrolled or life-threatening bleeding.



Costs are for general comparison only and do not imply therapeutic equivalence. Costs for Beriplex®, Octaplex®, Prothromplex Total® and Feiba® assume treatment of a 70 kg adult. Does not include cost of administration or any local discounts. * Mean dose used in PCC meta-analysis.[14] ** Lowest and highest dose used in FEIBA studies.[27,28]

Availability and approval status in the UK

Andexanet alfa will be the subject of the NICE TA "Andexanet alfa for reversing anticoagulation", with expected publication on 4 March 2020. Since its approval in the EU, Ondexxya is available to order in the UK from 1 July 2019, but can currently only be ordered directly from the company affiliate in the Netherlands.[2]

Points to consider

Andexanet alfa is the first specific reversal agent for the FXa-inhibitors apixaban and rivaroxaban. Its use is indicated for uncontrolled or life-threatening bleeding. Current management of those patients would mainly include the unlicensed use of 4-PCC or a-PCCs, plus other standard measures additionally used for non-life threatening bleeding. However, due to the design of the main trial, ANNEXA-4, it is not clear

whether use of andexanet alfa is actually more effective than those standard procedures.

Being the only licensed product for the above mentioned indication, the use of andexanet alfa in the likely population might impart a substantial financial burden compared to standard procedures.

People who are treated with PCCs may still need other supportive measures (e.g. anti-platelet use, frozen plasma, other reversal agents, administration of more doses) in certain clinical situations. This scenario is considered medically appropriate for dabigatran-specific reversal with idarucizumab[5]. Whether andexanet alfa would need such supportive care or, on the contrary, its use may offer offsetting savings from reduction in blood products and reduced complications from major bleeds, is still unclear. Also, the reversal activity of andexanet alfa is not permanent, unlike idaricizumab, but the effect returns to placebo levels within 2–3 h after stopping infusion.[19] Therefore, continued clinical and laboratory monitoring might need to be considered since DOAC concentrations may recover and contribute to recurrent or continued bleeding.[9]

Although the indication does not refer to specific subpopulations regarding site of bleeding, ICH might particularly be given special attention if evidence allows for it.[6] Of note, in the absence of andexanet alfa, recent guidelines for ICH management recommend high-dose of PCC (50 IU/ml) in patients on FXa-inhibitors. However, since high-dose PCC is likely to increase the risk of thrombosis, the use of andexanet alfa might be particularly beneficial for that subgroup of patients.[19]

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Appendix 1

Criteria comparison for haemostatic effectiveness: ANNEXA-4 vs the International Society of Thrombosis and Haemostasis (ISTH) recommendations for the assessment of effectiveness of major bleeding management. [18,24]

Bleeding site	ANNEXA-4	ISTH
Intracerebral / Intracranial	Excellent: ≤20% increase in hematoma volume compared to baseline on a repeat **CT or MRI scan performed at both the 1 and 12 hour** post infusion time points Good: >20% but **≤35% increase in hematoma volume** compared to baseline on a repeat CT or MRI scan at +12-hour time point Poor/none: >35% increase in hematoma volume on a CT or MRI compared to baseline on a repeat CT or MRI scan at +12-hour time point	Effective haemostasis is achieved when: a.The h**ematoma volume is stable, or increased by <35%** as compared with baseline volume) , as assessed by a **CT scan within 12 h** (time window of 6–24 h after the index CT) b.No deterioration of the Extended Glasgow Outcome Scale (GOS-E) as assessed at 24 h in comparison with that at presentation. c.By 48 h after the start of the initial management, there is no need for further infusion of hemostatic agents or coagulation factors, or transfusion of other blood products. Annotation of effective hemostasis with good clinical outcome when: d.No neurologic eterioration/dysfunction is present at discharge (at discharge can be replaced by 'at day = 30', whenever applicable) as assessed with any validated scoring system (e.g. GOS-E) as compared with that at presentation.
Visible	Excellent: Cessation of bleeding ≤ 1 hour after end of infusion and no plasma, coagulation factor or blood products (excludes pRBCs). Good: **Cessation of bleeding** between > 1 and ≤ **4 hours** after end of infusion and ≤ 2 units plasma, coagulation factor or blood products (excludes pRBCs) Poor/none: Cessation of bleeding > 4 hours after end of the infusion and /or >2 units plasma, coagulation factor or blood products (excludes pRBCs)	Effective haemostasis is achieved when: a.There is **cessation of** v**isible bleeding within 4 h** after the end of the administration of the hemostatic agent b.By 48 h after the start of the initial management, there is no need for further infusion of hemostatic agents or coagulation factors, or transfusion of other blood products c.Invasive interventions are either avoided or carried out with blood loss not exceeding the expected amount in a patient with normal hemostasis .

Muscular/skeletal	Excellent: **pain relief or no increase in swelling** or unequivocal improvement in objective signs of bleeding ≤1 hour after the end of infusion; and the condition has **not deteriorated during the 12-hour period** Good: pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding >1 and ≤4 hours after end of infusion; and the condition has not deteriorated during the 12-hour period Poor/none: No improvement by 4 hours after end of infusion and/or condition has deteriorated during the 12-hour period	Effective haemostasis is achieved when: a.**Pain is reduced and swelling is improved within 24 h** b.Fasciotomy is either avoided or carried out with blood loss not exceeding the expected amount in a patient with normal hemostasis c.By 48 h after the start of the initial management, there is no need for further infusion of hemostatic agents or coagulation factors, or transfusion of other blood products Annotation of effective hemostasis with good clinical outcome when: d.No neurologic dysfunction or limb loss is present at discharge (at discharge can be replaced by 'at day = 30', whenever applicable)
GI, Urinary or nonvisible bleeding not described above	Excellent: **≤10% decrease in both corrected hemoglobin/hematocrit** at **12 hours compared to baseline** Good: >10 % to **≤20% decrease** in both corrected hemoglobin/hematocrit at **12 hours** compared to baseline Poor/none: >20% decrease in both corrected hemoglobin/hematocrit	Effective haemostasis is achieved when: a.The **hemoglobin level is stable at 48 h** after initial treatment with packed red cells and hemostatic agent (a **reduction of ≤ 10% of the initial hemoglobin level** is considered to be a stable level) b.By 48 h after the start of the initial management, there is no need for further infusion of hemostatic agents or coagulation factors, or transfusion of other blood products c.Invasive interventions are either avoided or carried out with blood loss not exceeding the expected amount in a patient with normal hemostasis
CT: computed tomography; MRI: magnetic resonance imaging; pRBCs: packed red blood cells		