Briefing Paper for Surrey Heartlands Integrated Care System (ICS) Area Prescribing Committee (APC)

NICE Technology Appraisals: Local implementation

NICE TA Guidance	Andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban (TA697)		
Available at	https://www.nice.org.uk/guidance/ta697		
Date of issue	12 May 2021	**Implementation deadline**	August APC

Medicine details	
Name, brand name	Andexanet alfa (Ondexxya)
Manufacturer	Portola
Licensed indication	For 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.
Formulation	Powder for solution for infusion
Usual dosage	Andexanet alfa is administered as an intravenous bolus at a target rate of approximately 30 mg/min over 15 minutes (low dose) or 30 minutes (high dose), followed by administration of a continuous infusion of 4 mg/min (low dose) or 8 mg/min (high dose) for 120 minutes (see table 1).

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

Reversal of apixaban

The recommended dose regimen of Ondexxya is based on the dose of apixaban the patient is taking at the time of anticoagulation reversal, as well as on the time since the patient's last dose of apixaban (see table 2).

Table 2: Summary of dosing for reversal of apixaban

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

Reversal of rivaroxaban

The recommended dose regimen of Ondexxya is based on the dose of rivaroxaban the patient is taking at the time of anticoagulation

	reversal, as well as on the time since the patient's last dose of rivaroxaban (see table 3). **Table 3: Summary of dosing for reversal of rivaroxaban**

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

NICE recommended dosage/schedule	The dosage schedule is the same as available in the summary of product characteristics.

Disease and potential patient group

Brief description of disease	Reversal of anticoagulation with direct factor Xa inhibitors (apixaban, rivaroxaban)
Potential patient numbers per 100,000	Based on a RSCH audit conducted in 2016, use is likely to be required approximately once per acute trust per month for NICE-approved indications. The NICE resource impact tool suggests 55 patients per year in Surrey Heartlands, which is roughly in agreement with this.

SUMMARY

NICE recommendation

1. Andexanet alfa is recommended as an option for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding, only if:
   - the bleed is in the gastrointestinal tract, and
   - the company provides andexanet alfa according to the commercial arrangement.
2. Andexanet alfa is recommended only in research for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding in the skull (intracranial haemorrhage; ICH), in the form of an ongoing randomised trial mandated by the regulator.

Cost implications*

Cost of product:
The list price for andexanet alfa is £11,100 per 4-vial pack of 200 mg of powder for solution for infusion (excluding VAT, BNF online accessed March 2021).

Cost per patient treated:
The average cost of a course of treatment at list price is £15,000 per patient. (list price)

Costing information/100,000 population and per CCG:
Using NICE costing template assumptions calculates to £95,049 per 100,000 population in year 5 after implementation.

Availability of PAS and details (if appropriate):
The company has a commercial arrangement. This makes andexanet alfa available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

**NICE funding requirements are based on Quality Adjusted Life Years (QALY) threshold. If there is evidence that the incremental cost rises above this threshold in the future, the APC may reconsider the commissioning status.*

Alternative treatments and cost per patient (per year / per month as appropriate)

Other NICE recommended products:
None for this indication, but NICE TA acknowledges the use of prothrombin complex

concentrate (PCC) in clinical practice

Options not reviewed by NICE but used in standard practice:
Comparison with current management
There have not been any studies which have directly compared andexanet with the current standard of care, prothrombin complex concentrate (PCC). Small studies have examined the efficacy and safety of PCC when used to treat bleeding in patients on apixaban and rivaroxaban. Majeed et al (Blood 2017 Oct 12;130(15):1706-1712) prospectively collected data on 84 patients. For 69.1% patients PCC was felt to achieve effective haemostasis. Most patients with ineffective haemostasis with PCC had intracranial haemorrhage (n = 16; 61.5%). Two patients developed an ischemic stroke, occurring 5 and 10 days after treatment with PCC. Twenty-seven (32%) patients died within 30 days of their major bleeding event. Schulman et al (Thromb Haemost 2018 May;118(5):842-851) evaluated 66 patients. Effectiveness of PCC was assessed as good in 65% and moderate in 20%. Efficacy for GI bleeding and ICH were similar. There were nine deaths (14%) by 30 days, and five (8%) major thromboembolic events. In a post hoc analysis, according to International Society on Thrombosis and Haemostasis criteria, reversal was effective in 68% and ineffective in 32%. For andexanet, roughly equivalent figures for efficacy and safety (from Annexa 4 trial) were: for rivaroxaban 80%, and for apixaban 83%, were assessed as having excellent or good haemostasis. The percentages of patients with excellent or good efficacy were 85% for gastrointestinal bleeding and 80% for intracranial bleeding.
There were 34 patients (10%) with a thrombotic event during the 30-day follow-up period. No thrombotic events occurred after oral anticoagulation had been restarted.

Cost for treatment of 70kg patient with Beriplex £780.
(Beriplex is human prothrombin complex made from human plasma (this is the liquid part of the blood) and it contains the human coagulation factors II, VII, IX and X.)

Impact to patients

Increased confidence in, and therefore potentially acceptance of, anticoagulation (with benefits of stroke prevention in AF, or VTE prevention).

Impact to primary care prescribers

Potential need to consider restarting anticoagulation in discussion with secondary care.

Impact to secondary care

Potential for reduced length of hospital stay if GI bleeds managed promptly with andexanet.

Impact to CCGs

Potential for reduced costs from reduced length of hospital admissions.

Implementation

As trusts have mechanisms in place for managing bleeding in patients on anticoagulation there should be no barriers to implementation. To ensure a consistent approach within Surrey Heartlands, the Area prescribing committee will recommend the Trust formulary pharmacists to work together to produce a consensus guidance on the management of bleeding emergencies. Implementation will not be dependent on this.
As the protocol for most trusts for management of anticoagulation-related bleeding already mandate discussion with the on-call haematologist it is proposed that initiation of andexanet is on the decision of a haematology SpR or consultant only.
For trusts which are part of the BSPS laboratory network, laboratory SOPs will also need updating. This does not necessarily need to happen before implementation.

Additional comments:
The limited indication approved by NICE was the result of their interpretation of the available data, and the fact that they did not feel a mortality benefit could be convincingly demonstrated for andexanet in any type of bleeding apart from GI bleeding.
They acknowledge that the available data is very limited, hence the suggestion that intracranial haemorrhage be treated in the context of a clinical trial.
Trusts will need to develop mechanisms for ensuring use is for life-threatening GI bleeding

only. This could be through restriction to
A Bluteq form could be considered to monitor use, but completion would need to be retrospective as use of andexanet will be in emergency situations.

Recommendation to APC

PbRe: Yes

Andexanet alfa is recommended as an option for reversing anticoagulation from apixaban or rivaroxaban in adults with life-threatening or uncontrolled bleeding, only if:

- the bleed is in the gastrointestinal tract, and
- the decision to use is made by a haematology SpR or consultant, and
- the company provides andexanet alfa according to the commercial arrangement.

Colour classification guidelines

Recommended traffic light status (see attached guidelines):
RED

References:

1 Andexanet alfa for reversing anticoagulation from apixaban or rivaroxaban (TA697) https://www.nice.org.uk/guidance/ta697

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Declaration of Interest: None

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Declaration of Interest:None

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