Andexanet alfa for acute major bleeding episodes requiring reversal of anticoagulation, including reversal of factor Xa inhibition – first line

LAY SUMMARY

Anticoagulants are drugs which prevent the blood from clotting. This can be important for the treatment of some patients, but it also increases the risks of bleeding, which can be very serious or even life-threatening. Andexanet alfa reverses the effects of anticoagulants, allowing the blood to clot normally again in an emergency.

Andexanet alfa is injected directly into the bloodstream of patients who are taking anticoagulants and bleeding.

Andexanet alfa is currently being studied to see how well it works and whether it is safe to use. If andexanet alfa is licensed in the UK, it will offer a new treatment for people with serious bleeding while taking anticoagulants.

NIHR HSRIC ID: 8020
TARGET GROUP

- Acute major bleeding episode requiring urgent reversal of anticoagulation: patients treated with a direct or indirect factor Xa inhibitor; reversal of anticoagulation required due to life-threatening or uncontrolled bleeding or emergency surgery/urgent procedures.

TECHNOLOGY

DESCRIPTION

Andexanet alfa (PRT-064445; PRT-4445; PRT064445; PRT4445) is a first-in-class factor Xa (FXa) inhibitor antidote. It is a recombinant form of the FXa clotting protein that has been modified to lack FXa enzymatic activity\(^a\). Andexanet alfa binds to direct FXa inhibitors with high affinity, and also binds to indirect FXa inhibitors complexed with antithrombin III, making them unavailable to exert their anticoagulant effects\(^a\). It is intended for emergency administration in order to reverse the activity of direct or indirect FXa inhibitors and low molecular weight heparin.

In the phase III clinical trial, andexanet alfa is administered to older healthy subjects as a single 400mg intravenous (IV) bolus followed by a continuous IV infusion at 4mg/min for 2 hours to reverse apixaban anticoagulation activity, and as a single 800mg IV bolus followed by a continuous IV infusion at 8mg/min for 2 hours to reverse rivaroxaban anticoagulation activity. The total duration of treatment was 133 and 147 minutes for apixaban and rivaroxaban treated subjects, respectively.

Andexanet alfa does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, andexanet alfa will offer an additional treatment option for acute major bleeding episodes requiring urgent reversal of anticoagulation. It would be the first universal antidote for direct and indirect FXa inhibitors and may offer the advantage of neutralising the effects of these anticoagulants without the need to increase the plasma concentration of coagulation factors through exogenous administration\(^a\).

DEVELOPER

Portola Pharmaceuticals.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

\(^a\) Company provided information.
PATIENT GROUP

BACKGROUND

A recent advance in anticoagulation therapy has been the introduction of novel oral anticoagulants (NOACs), which act by targeting specific components of the coagulation cascade, such as FXa. However, major bleeding events can occur in any patient taking these or other forms of anticoagulant. One of the potential drawbacks of FXa inhibitors is the absence of a specific antidote to reverse anticoagulation in case of life-threatening bleeding or emergency surgery.

CLINICAL NEED and BURDEN OF DISEASE

Major bleeding involving the gastrointestinal tract, urinary tract or soft tissue occurs in up to 6.5% of patients on anticoagulant therapy. The incidence of fatal bleeding, such as intracranial haemorrhage, is approximately 1% annually.

Non-vitamin K antagonist oral anticoagulants (NOACs) are an option for the treatment and secondary prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE). It is estimated that 53,040 people in England are eligible to receive NOACs for these indications. These anticoagulants are also recommended as an option for use after orthopaedic surgery for the prevention of venous thromboembolism; in England in 2009, the NHS carries out approximately 70,000 elective total knee replacements and 55,000 elective total hip replacements. NOACs are also recommended as an option to prevent stroke and systemic embolism in patients with non-valvular atrial fibrillation. The number of people with atrial fibrillation estimated to be eligible for anti-coagulation services, including apixaban, was 800 per 100,000 population in 2011, representing approximately 440,000 people in England.

In 2014-15, there were 193 hospital admissions for haemorrhagic disorder due to circulating anticoagulants (ICD-10 D68.3), resulting in 1,409 bed days and 319 finished consultant episodes.

The population likely to be eligible to receive andexanet alfa could not easily be estimated from available routine published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal. Edoxaban for treating and for preventing deep vein thrombosis and pulmonary embolism (TA354). August 2015.
• NICE technology appraisal. Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism (TA327). December 2014.
• NICE technology appraisal. Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism (TA287). June 2013.
• NICE technology appraisal. Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults (TA245). January 2012.
• NICE technology appraisal. Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (TA170). April 2009.

• NICE clinical guideline. Myocardial infarction: cardiac rehabilitation and prevention of further MI (CG172). November 2013.
• NICE clinical guideline. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing (CG144). June 2012.

• NICE advice. Non-vitamin K antagonist oral anticoagulants (NOACs) (KTT16). Published February 2016.

Other Guidance

• West Suffolk Hospital Clinical Guidelines for Reversal of Oral Anticoagulants including Warfarin and Phenindione. (CG10142-2)².
• National Collaborating Centre for Acute Care. Venous Thromboembolism – reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery. April 2007¹⁴.
CURRENT TREATMENT OPTIONS

Guidelines recommend that patients with substantial bleeding are transfused with blood, platelets and clotting factors in line with local protocols for managing this acute medical emergency\textsuperscript{15}. Prothrombin complex concentrate is given to patients who are taking warfarin and actively bleeding. Recombinant factor VIIa is used only when all other methods have failed.

The company have stated that there are currently no approved treatments to specifically reverse the anticoagulant effects of oral FXa inhibitors\textsuperscript{b}.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02207725, ANNEXA-A; andexanet alfa vs placebo; phase III.</th>
<th>NCT02220725, ANNEXA-R; andexanet alfa vs placebo; phase III.</th>
<th>NCT02329327; andexanet alfa; phase III.</th>
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</thead>
<tbody>
<tr>
<td>Status</td>
<td>Published.</td>
<td>Published.</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Publication\textsuperscript{16}, trial registry\textsuperscript{17}, manufacturer.</td>
<td>Publication\textsuperscript{16}, manufacturer.</td>
<td>Trial registry\textsuperscript{16}, manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>USA.</td>
<td>USA.</td>
<td>Canada and USA.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=65; aged 50-75 yrs; healthy volunteers receiving apixaban 5mg twice daily for 3.5 days.</td>
<td>n= 80; aged 50-75 yrs; healthy volunteers receiving rivaroxaban 20mg once daily for 4 days.</td>
<td>n=250 (planned); aged 18 yrs or older; acute major bleeding; pts receiving a FXa inhibitor; urgent requirement for reversal of anticoagulation, defined as acute bleeding and any one of the following: potentially life-threatening bleeding; a fall in haemoglobin level by ≥2g/dL; Hbs8g/dL; or acute symptomatic bleeding in a critical organ.</td>
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<tr>
<td>Schedule</td>
<td>On day 4, 3 hrs after last dose of apixaban, pts randomised to receive andexanet alfa as a 400mg IV bolus followed by 4mg/min IV infusion for 2 hours; or placebo IV bolus followed by continuous infusion for a total of 133mins.</td>
<td>On day 4, 4 hrs after last dose of rivaroxaban, pts randomised to receive andexanet alfa as an 800mg IV bolus followed by an 8mg/min IV infusion for 147 mins; or placebo IV bolus followed by continuous infusion for a total of 147 mins.</td>
<td>Pts receiving apixaban (and pts receiving rivaroxaban &gt;7 hrs ago) received a 400mg IV bolus andexanet alfa followed by a continuous IV infusion at 4mg/min for a total treatment time of 133 mins; all other pts received a single 800mg IV bolus followed by a continuous IV infusion at 8mg/min for a total treatment time of 147 mins.</td>
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\textsuperscript{b} Company provided information.
<table>
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<tr>
<th>Follow-up</th>
<th>Active treatment for up to 133 mins. Follow-up to 43 days.</th>
<th>Active treatment for up to 147 mins. Follow-up to 43 days.</th>
<th>Active treatment, up to 147 mins. Follow-up to 51 days.</th>
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<tbody>
<tr>
<td>Primary outcomes</td>
<td>Reversal of apixaban anticoagulation effect as measured by anti-factor Xa activity.</td>
<td>Reversal of rivaroxaban anticoagulation effect as measured by anti-factor Xa activity.</td>
<td>Proportion of pts with excellent or good haemostasis; anti-FXa activity.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Unbound apixaban plasma levels and thrombin generation. No quality of life measurements were included in trial outcomes.</td>
<td>Unbound rivaroxaban plasma levels and thrombin generation. No quality of life measurements were included in trial outcomes.</td>
<td>No quality of life measurements were included in trial outcomes.</td>
</tr>
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<td>Key results</td>
<td>For subjects receiving andexanet alfa vs placebo respectively: anti-factor Xa activity reduction, 94% vs 21%; reduction in unbound apixaban concentration, 9.3ng/ml vs 1.9ng/ml; restoration of thrombin generation within 2-5 mins, 100% vs 11%.</td>
<td>-</td>
<td>-</td>
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<td>Adverse effects (AEs)</td>
<td>No serious adverse effects were reported.</td>
<td>No serious adverse effects were reported.</td>
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<td>Expected reporting date</td>
<td>-</td>
<td>-</td>
<td>Primary completion date reported as November 2022.</td>
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**ESTIMATED COST and IMPACT**

**COST**

The cost of andexanet alfa is not yet known.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Other

- Reduced symptoms or disability
- No impact identified

**Impact on Health and Social Care Services**

- Increased use of existing services
- Re-organisation of existing services
- Other

- Decreased use of existing services: if successfully reduces requirements for blood products and reduces complications of major bleeds.
- Need for new services
- None identified
Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs.
- Other reduction in costs
- Other
- None identified

Other Issues

- Clinical uncertainty or other research question identified
- None identified

REFERENCES