Ciraparantag is a new drug to treat bleeding in people taking new oral anticoagulants (NOACs). Anticoagulants are medicines which are given to people to thin the blood and prevent blood clots. Anticoagulation can become a problem when patients experience major bleeding, have a traumatic injury or require emergency surgery. There are currently no licensed treatments that can quickly reverse the effects of NOACs in an emergency.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.
TARGET GROUP

• Haemorrhage: in patients receiving new oral anticoagulants (NOACs).

TECHNOLOGY

DESCRIPTION

Ciraparantag (Aripazine; PER 977) is a water soluble, small molecule that re-establishes normal blood coagulation by directly binding to factor Xa and IIa inhibitors. It is intended for use as a broad-spectrum reversal agent for anticoagulants, including low molecular weight heparin, unfractionated heparin and NOACs that target both factor Xa and IIa. In clinical trials, ciraparantag was administered via 2 single bolus intravenous (IV) injections on consecutive days, at a dose ranging from 25mg to 300mg per dose, following anticoagulation with edoxaban.

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

INNOVATION and/or ADVANTAGES

If licensed, ciraparantag will address an unmet clinical need for a broad spectrum NOAC reversal agent as well as providing a reversal drug for unfractionated and low molecular weight heparin.

DEVELOPER

Perosphere.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Anticoagulants are medications that interact with the body’s natural blood-clotting system to treat and prevent abnormal blood clots. They are widely used to prevent and treat a variety of thromboembolic events. Anticoagulation becomes a clinical problem when patients experience major bleeding, have a traumatic injury or require emergency surgery. For decades, warfarin was the primary oral anticoagulant in use, however in recent years a number of NOACs have become available as alternatives to warfarin. NOACs are shorter-acting than warfarin, which takes several days for the anticoagulant effect to wear off. However, unlike warfarin, no specific antidotes are currently available to rapidly reverse the anticoagulant effect of NOACs in patients who experience a major bleeding event.

CLINICAL NEED and BURDEN OF DISEASE

Major bleeding involving intracranial haemorrhages, the gastrointestinal tract, urinary tract or soft tissue occurs in up to 6.5% of patients on anticoagulant therapy, and the annual
The incidence of fatal bleeding is approximately 1% in this population. 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. NOACs are also recommended as an option for use after orthopaedic surgery for the prevention of venous thromboembolism. In 2009, around 70,000 elective total knee replacements and 55,000 elective total hip replacements were carried out in England. 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 anticoagulation services, was 800 per 100,000 population in 2011, representing approximately 440,000 people in England.

In 2014-15, there were 193 hospital admissions in England for haemorrhagic disorder due to circulating anticoagulants (ICD10 D68.3), resulting in 319 finished consultant episodes and 1,409 bed days.

### PATIENT PATHWAY

### RELEVANT GUIDANCE

**NICE Guidance**


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. Prothrombin complex concentrate is given to patients who are taking warfarin and actively bleeding.

Currently, there are no licensed broad-spectrum reversal agents for NOACs or for low molecular weight heparin.

**Efficacy and Safety**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02207257, PER977-02-001; ciraparantag vs placebo; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Perosphere, Inc.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry(^1), manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>USA.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=69 (planned); aged 18-65 years; healthy volunteers.</td>
</tr>
<tr>
<td>Schedule</td>
<td>All participants receive edoxaban 60mg oral in the morning on days 1-4. Participants randomised to receive ciraparantag IV at 25mg, 50mg, 100mg or 300mg, or placebo IV on days 3-4, approximately 3 hrs following dose of edoxaban.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Observed in hospital for 24 hrs and followed up 1 wk later.</td>
</tr>
</tbody>
</table>
Primary outcome/s | Whole blood clotting time as a measure of edoxaban anticoagulation reversal.
---|---
Secondary outcome/s | Pharmacokinetics; safety coagulation measures; safety and tolerability.
Key results | Ciraparantag at 100mg and 300mg IV produced complete and sustained reversal of anticoagulation.
Adverse effects (AEs) | Not reported.
Expected reporting date | Currently being prepared for publication.

**ESTIMATED COST and IMPACT**

**COST**
The cost of ciraparantag is not yet known.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**
- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- No impact identified
- Other:

**Impact on Health and Social Care Services**
- Increased use of existing services
- Decreased use of existing services
- Need for new services
- None identified
- Re-organisation of existing services
- Other:

**Impact on Costs and Other Resource Use**
- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
- Other reduction in costs:
- None identified
- Other:

**Other Issues**
- Clinical uncertainty or other research question identified

**REFERENCES**


a Information from manufacturer.


9 All Wales Medicines Strategy Group. All Wales advice on the role of oral anticoagulants. Llandough: AWMSG; February 2016.


