NIHR | Innovation Observatory

# HEALTH TECHNOLOGY BRIEFING AUGUST 2020

# Tecarfarin for preventing venous thromboembolism

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| **NIHRIO ID** | 3018 | **NICE ID** | 10188 |
| **Developer/Company** | Espero BioPharma | **UKPS ID** | N/A |

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| **Licensing and market availability plans** | Currently in phase III clinical trials. |

## SUMMARY


Tecarfarin is in clinical development for the prevention of thromboembolism in patients requiring long-term blood thinning treatment. Venous thromboembolism (VTE) refers to a blood clot that develops in a vein. There are two types of VTE: deep vein thrombosis (DVT) which refers to a blood clot in a vein and pulmonary embolism (PE) which refers to a blood clot that has broken free and travelled to the lungs.. Some patients who have had a VTE require long- term treatment with blood-thinning medication to reduce the risk of VTE recurrence.

Tecarfarin, a vitamin K reductase, is given by oral administration and works by blocking the liver from using vitamin K to make clotting factors. Clotting factors work with blood cells called platelets that trigger the clotting process to form a blood clot. Stopping the activation of these vitamin K dependent clotting factors means the blood takes much longer to clot so there is a decreased risk of VTE. Tecarfarin works in the same way as warfarin, which is the current best treatment option for preventing VTE, but is expected to be safer and deliver more predictable clotting. If licensed, tecarfarin would offer an additional treatment option for preventing VTE in patients who require long-term anticoagulation therapy.

# PROPOSED INDICATION

Prevention of thromboembolism in patients requiring chronic anticoagulation.[1-3]

# TECHNOLOGY

## DESCRIPTION

Tecarfarin (ATI-5923) is an orally active and non-competitive vitamin K reductase (VKOR) antagonist that impairs the activation of the vitamin K-dependent clotting factors II, VII, IX and X.[4] Clotting factors are made by the liver and work with blood cells called platelets to trigger the clotting process (coagulation). Anticoagulants like warfarin and tecarfarin make the blood clot more slowly.[5,6] Tecarfarin is a structural analogue of warfarin with the same mechanism and duration of action. Like for warfarin, anticoagulant efficacy is monitored using the international normalized ratio (INR). Unlike warfarin, which is metabolized by the cytochrome R 450 (CYP450) pathway, tecarfarin undergoes hydrolysis mediated by human carboxylesterase 2 (Hce-2), yielding a single inactive carboxylic acid metabolite (ATI-5900), which is excreted by the kidney.[7]

Tecarfarin is currently in clinical development for the prevention of thromboembolism in patients who require chronic anticoagulation treatment. In the phase III clinical trial (TACT; NCT02522221) participants are given an oral dose of tecarfarin which will be dose adjusted by the investigator in accordance with a target INR range.[1]

## INNOVATION AND/OR ADVANTAGES

Tecarfarin has a similar pharmacological profile to warfarin but was designed to provide more uniform and stable anticoagulation. Tecarfarin is metabolized by an esterase to a single inactive metabolite and thus is expected to have less variable metabolism, drug-drug interactions and reduce instances of under/over coagulation, making the response safer and more predictable.[3]

## DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Tecarfarin does not currently have Marketing Authorisation in the EU/UK for any indication.

Tecarfarin is not currently in phase II or phase III clinical development for any other indication.[8]

In March 2019, tecarfarin was granted an orphan designation by the US FDA for the prevention of systemic thromboembolism of cardiac origin in patients with end stage renal disease and atrial fibrillation.[9]

# PATIENT GROUP

## DISEASE BACKGROUND

Venous thromboembolism (VTE), refers to a blood clot that starts in a vein. There are two types of VTE: deep vein thrombosis (DVT) and pulmonary embolism (PE).[10] DVT refers to a blood clot that starts in a vein and may occur if the flow of blood slows down in the body's veins, if something damages the blood vessel lining, or if the makeup of the blood itself changes to that blood clots form more easily.[10,11] DVT usually occurs in the legs but can occasionally occur in the arm. Signs and symptoms of a DVT include: swelling (usually in one leg or arm), leg pain or tenderness, reddish or blue skin discoloration, leg or arm being warm to touch. PE is a very serious condition that can be fatal.[12] It occurs when a DVT clot breaks free from a vein wall, travels to the lungs and then blocks some or all of the blood supply. Blood clots originating in the thigh are more likely to break off and travel to the lungs than blood clots in the lower leg or other parts of the body.[10] The signs and symptoms of PE include: sudden shortness of breath, a chest pain – sharp stabbing that may get worse with deep breaths, rapid heart rate or an unexplained cough, sometimes with blood-streaked mucus.[12]

VTE is a significant cause of mortality, long-term disability and chronic health problems.[13] Almost anyone can have DVT. However, risk factors like surgery, medical conditions such as cancer or spinal cord injury, pregnancy, paralysis, long periods of immobilization, increased oestrogen, previous or family history of DVT or PE, older age, obesity, having a catheter located in a central vein or inherited clotting disorders can increase the risk of developing the condition. The more risk factors a person has, the greater the chance a person has of developing venous thromboembolism.[11,14]

## CLINICAL NEED AND BURDEN OF DISEASE

In England, the incidence of VTE is 1-2 per 1,000 of the population and the risk increases with age. 1 in 20 people will have a VTE at some time in their life and approximately half of the cases are associated with prior hospitalisation for medical illness or surgery.[13] Around 30% of people who have had a VTE develop further problems within the next 10 years, despite treatment.[15]

In England, in 2018-19, there were 17,728 diagnoses of venous embolism and thrombosis (ICD-10 code I82) resulting in 2,920 finished consultant episodes (FCE), 2,440 hospital day cases and 7,083 FCE bed days.[16] Over the three year period from 2013-2015 the average number of deaths from VTE in England was 12,640 per annum.

# PATIENT TREATMENT PATHWAY

## TREATMENT PATHWAY

Anticoagulation is indicated for patients with proximal DVT and PE as it reduces the development of PE and extension of DVT.[17]

Following VTE, anticoagulant treatment is given for three months, as standard. Prolonged treatment may be given for patients at high risk of recurrence. However, clinicians must balance the risk of bleeding against the risk of recurrence.[18] Patients with provoked VTE (caused by surgery or immobilisation) have a low risk of recurrent VTE after discontinuing VTE.

Patients with unprovoked VTE have a higher risk of recurrent VTE and these are the patients indicated for long term anticoagulation therapy.[19]

The benefits and risks of continuing anticoagulant therapy should be assessed and discussed with people who have had anticoagulation treatment for 3 months (3 to 6 months for people with active cancer) after a proximal DVT or PE. Continuing anticoagulation therapy beyond the 3 to 6 months should be considered following an unprovoked DVT or PE because the benefit of reducing VTE recurrence risk outweighs the risk of bleeding.[20]

## CURRENT TREATMENT OPTIONS

The anticoagulants currently recommended by NICE for the prevention of recurrent DVT and PE are:[21]

- Apixaban
- Dabigatran
- Edoxaban
- Rivaroxaban
- Warfarin

## PLACE OF TECHNOLOGY

If licensed, tecarfarin will offer an additional treatment option to prevent VTE in patients who require chronic anticoagulation.

# CLINICAL TRIAL INFORMATION

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| **Trial** | **TACT,** NCT02522221; A Real-World, Randomized, Open-Label, Study on the Efficacy, Safety and Tolerability of Tecarfarin (ATI-5923) a Novel Vitamin K Antagonist, Versus Warfarin in Subjects Requiring Chronic Anticoagulation<br>**Phase III** – unknown status<br>**Location:** No locations provided<br>**Estimated primary completion date:** 30 March 2019 |
| **Trial design** | Randomised, Parallel Assignment, Open-Label |
| **Population** | N=1000; adults aged 18 to 85 years; requiring chronic anticoagulation therapy; has one or more of the following indications for chronic oral anticoagulation:<br>• atrial fibrillation/flutter not due to a reversible cause, documented by electrocardiography<br>• aortic and/or mitral prosthetic HV<br>• history of myocardial infarction or cardiomyopathy<br>• any other indication for which warfarin is approved or recommended |
| **Intervention(s)** | Tecarfarin (oral administration) dose adjusted by the investigator in accordance with a target International Normalized Ratio (INR) range pre-specified by the investigator |

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| **Comparator(s)** | Warfarin (oral administration) dose adjusted by the investigator in accordance with a target INR range pre-specified by the investigator |
| **Outcome(s)** | Primary outcome measure:<br>• Percentage of time in the therapeutic range (TTR) for tecarfarin vs warfarin for each treatment group in the randomized population [ Time Frame: From the date of randomization until study termination, up to 24 months (1st month not included)]<br><br>See trial record for full list of other outcomes |
| **Results (efficacy)** | - |
| **Results (safety)** | - |

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| **Trial** | **EmbraceAC**, NCT00691470; A Randomized, Double Blind Comparison of ATI-5923, a Novel Vitamin K Antagonist, With Warfarin in Patients Requiring Chronic Anticoagulation<br>**Phase II/III** – unknown status<br>**Location:** United States<br>**Estimated primary completion date:** June 2009 |
| **Trial design** | Randomised, Double Blind Comparison of ATI-5923, a Novel Vitamin K Antagonist, With Warfarin in Patients Requiring Chronic Anticoagulation |
| **Population** | N=600; adults aged 18 years and older; patients with one or more of the following indications for chronic warfarin anticoagulation (the patient may either be a new candidate for anticoagulation or may already be receiving warfarin):<br>• atrial fibrillation or atrial flutter<br>• a prosthetic heart valve in the aortic or mitral position that requires chronic anticoagulation<br>• a history of venous thromboembolic disease (deep vein thrombosis and/or pulmonary embolism) requiring long term anticoagulation ( > 6months)<br>• a history of myocardial infarction or cardiomyopathy requiring anticoagulation<br>• currently receiving chronic warfarin therapy for another indication not listed, with sponsor approval |
| **Intervention(s)** | Tecarfarin (ATI-5923). Dose adjusted based on INR |
| **Comparator(s)** | Warfarin (Coumadin). Dose adjusted based on INR |
| **Outcome(s)** | Primary outcome measure:<br>• Percent of time INR is in therapeutic range after the exclusion of the first 4 weeks of treatment, using the linear interpolation method of Rosendaal (Rosendaal, 1993) [ Time Frame: After the first month through end of study ]<br><br>See trial record for full list of outcomes |
| **Results (efficacy)** | - |
| **Results (safety)** | - |

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| **Trial** | NCT00431782; An Open-Label Multi-Center Study of ATI-5923 for Anticoagulation in Patients With Atrial Fibrillation<br>**Phase II**<br>**Location:** United States<br>**Study Completion Date:** October 2007 |
| **Trial design** | Single Group Assignment, Open-Label |
| **Population** | N=60; adults aged 18 years and older; documented atrial fibrillation; candidate for anticoagulation or currently receiving warfarin at screening |
| **Intervention(s)** | Tecarfarin (ATI-5923) |
| **Comparator(s)** | No comparator |
| **Outcome(s)** | International normalized ratio (INR) |
| **Results (efficacy)** | After the initial 3 weeks of tecarfarin treatment, the mean interpolated time in therapeutic range was 71.4%. Only 10.9% of patients had time in therapeutic range of <45%. Times in extreme INR ranges of <1.5 and >4.0 were 1.2% and 1.2%, respectively. The median daily dose (for an individual patient) to maintain an INR between 2 and 3 was 15.6mg (range, 6mg to 29mg).[22] |
| **Results (safety)** | Tecarfarin was generally well tolerated; adverse events were reported in 45 patients (68%) overall, with 95% of adverse events categorized as mild or moderate in severity. Of these, 72% were not related to study drug. The adverse events regarded as related to study drug were expected effects of anticoagulation: increased INR, bruising, epistaxis, hematoma and positive stool occult blood tests. Six patients experienced serious adverse events: exacerbation of AF, atrioventricular node ablation (2 patients), pacemaker replacement, traumatic hematoma of elbow, bronchogenic carcinoma, exacerbation of pre-existing idiopathic pulmonary fibrosis and pneumonia. Three patients discontinued study drug treatment because of: elevated blood pressure, non-therapeutic INR, traumatic hematoma of elbow and bronchogenic carcinoma.[22] |

# ESTIMATED COST

The estimated cost of tecarfarin is not yet known.

# RELEVANT GUIDANCE

## NICE GUIDANCE

- NICE technology appraisal guidance. Edoxaban for treating and preventing deep vein thrombosis and pulmonary embolism (TA354). August 2015.
- NICE technology appraisal guidance. Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism (TA341). June 2015

- NICE technology appraisal guidance. Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism (TA327). December 2014.
- NICE technology appraisal guidance. Revaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism (TA287). June 2013.
- NICE technology appraisal guidance. Revaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism (TA261). July 2012.
- NICE technology appraisal guidance. Apizaban for the prevention of venous thromboembolism after total hip or knee replacement in adults (TA245). January 2012.
- NICE technology appraisal guidance. Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults (TA170). April 2009.
- NICE technology appraisal guidance. Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults (TA157). September 2008.
- NICE clinical guideline. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism (NG89). March 2018.
- NICE clinical guideline. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing (CG144). November 2015.
- NICE clinical guideline. Venous thromboembolism: reducing the risk for patients in hospital (CG92). June 2015.
- NICE clinical guideline. Venous thromboembolism (surgical) (CG46). April 2007.
- NICE quality standard. Venous thromboembolism in adults: reducing the risk in hospital (QS3). March 2018.
- NICE quality standard. Venous thromboembolism in adults: diagnosis and management (QS29). April 2016.
- NICE intervention procedures guidance. Thoracoscopic exclusion of the left atrial appendage (with or without surgical ablation) for non-valvular atrial fibrillation for the prevention of thromboembolism (IPG400). June 2011.
- NICE intervention procedures guidance. Percutaneous occlusion of the left atrial appendage in non-valvular atrial fibrillation for the prevention of thromboembolism (IPG349). June 2010.

## NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified

## OTHER GUIDANCE

- American Society of Haematology. 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. December 2019.[23]
- Scottish Intercollegiate Guidelines Network. Prevention and management of venous thromboembolism: a national clinical guideline (SIGN 122). October 2010.[24]

# ADDITIONAL INFORMATION

Espero BioPharma did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisation on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain

data from other sources. UK PharmaScan is an essential tool so support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

# REFERENCES


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