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# Dabigatran Etexilate (Pradaxa) for secondary stroke prevention in patients with embolic stroke of undetermined source – first line

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## LAY SUMMARY

A stroke is a life threating medical condition which occurs when the blood supply to the brain is cut off. This can be as a result of the bursting of a weakened blood vessel in the brain (haemorrhagic stroke) or a blockage of one of the blood vessels in the brain by a blood clot (embolic stroke). Embolic stroke is the most common type of stroke. Strokes are a major cause of death and are the fourth largest cause of death in the UK. Once someone has had a stroke, they have a high risk of having another stroke, especially within 30 days of the original stroke. Therefore it is important to have stroke prevention treatments available after a stroke to prevent another one occurring.

Dabigatran etexilate is an oral drug that acts by preventing clots from forming and blocking blood vessels. It is already available for the treatment and prevention of stroke and other types of blood clots affecting blood vessels and organs in the body. By preventing clots from forming, it can prevent future embolic strokes. This could be particularly useful for people who have just experienced an embolic stroke who are at high risk of having another subsequent stroke.



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## TARGET GROUP

Secondary stroke prevention in patients with embolic stroke of undetermined source (ESUS) – first line

## DESCRIPTION

Dabigatran etexilate (Pradaxa; BIBR 1048) is a prodrug which, after absorption, is converted to dabigatran by esterase-catalysed hydrolysis in the plasma and liver. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma. By inhibiting thrombin, this prevents the conversion of fibrinogen into fibrin and prevents the development of thrombus. In addition to this, dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin induced platelet aggregation.[1]

In the phase III clinical trial, RE-SPECT ESUS (NCT02239120), dabigatran etexilate is administered orally at a total of 150mg (or 110mg in patients >75 years old or with a creatinine clearance > or = 30 to less than 50ml/min) taken as a twice daily dose.[2]

Dabigatran etexilate is currently licensed and marketed in the UK for the following indications:[3, 4]

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.
- Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

There are no recorded very common (≥ 1/10) adverse events reported for dabigatran etexilate across a variety of licensed indications. Common (prevalence >1/100, <1/10) adverse events reported for dabigatran etexilate across a variety of indications include: anaemia, haemoglobin decreased, epistaxis, gastrointestinal haemorrhage, abdominal pain, diarrhoea, dyspepsia, nausea, rectal haemorrhage, skin haemorrhage and genitourinary haemorrhage (including haematuria).[1]

Dabigatran etexilate is currently in phase III trials for prevention of secondary stroke in patients with embolic stroke of undetermined origin and Cerebral Venous Sinus Thrombosis (CVST).[5]

## INNOVATION and/or ADVANTAGES

If licensed, dabigatran etexilate will offer an additional treatment option for patients who have experienced an embolic stroke and who are at high risk of experiencing a subsequent embolic stroke. Through the drug's mechanism of action, it may prevent the formation of future emboli, thereby preventing future embolic stroke and the associated impact that would have on the individual and society.

## DEVELOPER

Boehringer Ingelheim Ltd

## AVAILABILITY, LAUNCH or MARKETING

Dabigatran etexilate was designated Priority review for prevention of stroke and systemic embolism in patients with atrial fibrillation by the US FDA in October 2010.

## PATIENT GROUP

### BACKGROUND

A stroke is a life threatening medical condition which occurs when the blood supply to part of the brain is cut off. There are two main types of stroke: ischaemic stroke (where the blood supply to the brain is stopped due to a blood clot), which accounts for 85% of stroke cases, and haemorrhagic strokes (occurring when a weakened blood vessel supplying the brain bursts). The treatment received will mainly depend on the type of stroke, for example, treatment for ischaemic stroke focus on dissolving blood clots while treatment for haemorrhagic stroke will focus on preventing further bleeding.[6] In the UK, primary stroke (appearing for the first time) occurs in approximately 230/100, 000 people per year. Once a person has had a stroke they are at high risk of another vascular event (secondary stroke).[7] It is estimated that 30% of stroke survivors will experience a recurrent stroke or transient ischaemic attack (TIA), with the greatest risk of a recurrent stroke in the first 30 days after the first stroke. 25-33% of strokes are estimated to be recurrent or secondary strokes.[8]

Recognising the symptoms of a stroke in a timely manner is important in order to receive prompt treatment. Symptoms usually start suddenly and will depend on the area of the brain affected. Main symptoms include drooping of the face, weakness/numbness of the arm and slurred speech or inability to speak. Other symptoms can include paralysis of one side of the body, loss or blurring of vision, dizziness, confusion, difficulty understanding what others are saying, problems with balance and co-ordination, dysphagia (problems swallowing), sudden and very severe headache and loss of consciousness.[9] The most important non-modifiable risk factors for stroke is age, with the risk of having a stroke doubling every decade after 55 years of age, and ethnicity, with people of black and south Asian origin at a higher risk of stroke at a younger age compared to white people. Modifiable risk factors for stroke include hypertension (a contributing factor in 54% strokes), diabetes (a contributing factor in 20% strokes), atrial fibrillation/irregular heart beat (a contributing factor in 20% strokes), high cholesterol, sickle cell disease, physical inactivity, obesity, smoking, alcohol and illegal drug use.[8] Strategies for preventing secondary strokes focus on targeting any modifiable risk factors with pharmacological treatment or lifestyle changes.

Stroke is a major cause of mortality being the fourth largest cause of death in the UK and second largest cause of death worldwide. 1 in 8 strokes are fatal within the first 30 days and 1 in 4 are fatal within a year. Stroke is also one of the largest causes of disability with half of all stroke survivors with disability and a third of stroke survivors dependant on others for care. Stroke causes a greater range of disabilities than any other condition, affecting walking, talking, speech, balance, co-ordination, vision, spatial awareness, swallowing, bladder and bowel control.[8]

## CLINICAL NEED and BURDEN OF DISEASE

In the UK, stroke (appearing for the first time) occurs in approximately 230/100, 000 people per year and is the fourth largest single cause of mortality.[7]

There are over 1.2 million (1 in 53 people) stroke survivors in the UK and around 1 in 4 of these survivors will experience another stroke within 5 years.[8] It is estimated that 30% of stroke survivors will experience a recurrent stroke or TIA, with the greatest risk of a recurrent stroke in the first 30 days after the first stroke. [10]

According to the 2016/2017 Sentinel Stroke National Audit Programme (SSNAP) Report, there were 74, 216 strokes in the UK due to infarction from April 2016 to March 2017 (87.2% of total number of stokes).[11] The incidence of cryptogenic stroke (stroke without known cause) is estimated to comprise 25% of all ischemic (or embolic) stroke, equating to 300,000 incidence cases per year in Europe and North America.[12] If applied to the SSNAP data for 2016/2017, this would estimate the incidence of embolic strokes of unknown cause at 18, 554.

Stroke can cause significant disability. Of stroke survivors, 60% will suffer from visual problems after their stroke (reducing to 20% in 3 months after the stroke), 75% report arm weakness, 75% report leg weakness and a third report aphasia (disorder of language or communication). Stroke can also seriously impact on quality of life. 40% of stroke survivors require help with activities of daily living on discharge from hospital, 42% of people report a negative change in their relationship with their partner after stroke and 25% report their stroke had a negative effect on their family. People of working age who have a stroke are also 2-3 times more likely to be unemployed 8 years after their stroke and 1 in 6 will experience loss of income after their stroke.[8]

## PATIENT PATHWAY

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE Interventional procedures guidance. Percutaneous closure of patent foramen ovale to prevent recurrent cerebral embolic events (IPG472). December 2013.
- NICE Interventional procedure guidance. Percutaneous closure of patent foramen ovale for the secondary prevention of recurrent paradoxical embolism in divers (IPG371). December 2010.

### NHS ENGLAND and POLICY GUIDANCE

No relevant guidance identified

### OTHER GUIDANCE

- AHA/ASA Guideline: Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack – A guideline for healthcare professionals from the American heart association/American stroke association. 2014.
- AHA/ASA Practice Guidelines. AHA/ASA Guidelines on prevention of recurrent stroke. 2011.
- NICE Clinical knowledge summary. Stroke and TIA. March 2017.

## CURRENT TREATMENT OPTIONS

Secondary prevention after ischaemic stroke is initiated at stroke diagnosis (in secondary care) and is followed up in primary care at 6 months and then annually after the original stroke. Several different strategies are involved in the secondary prevention of stroke, including:[7]

- Advice and information on:
  - stroke and TIA – including information on risk factors, driving and returning to work
- Lifestyle changes:
  - physical activity - individualized exercise programmes should be prescribed, delivered and monitored by the rehabilitation team
  - Smoking cessation (where appropriate) – referral to NHS stop smoking service, drug treatment and written information
  - Diet optimisation to reduce CVD risk – aim to eat 5 portions of fruit/veg per day and 2 portions of oily fish per week, reduce saturated fat intake, reduce salt intake.
  - Alcohol intake – should remain within recommended limits (14 units per week over 3 days)
  - Advice against dietary supplement use – Vitamins A, B, C, or E, selenium and calcium (with or without vitamin D) unless required for another medical condition.
- Review of medications used for secondary prevention:
  - Anti-platelet therapy – initiated on diagnosis of stroke or TIA for long term vascular prevention. Recommendations for anti-platelet therapy as follows:
    - Clopidogrel 75mg daily - standard treatment
    - Modified release dipyridamole 200mg twice daily – if clopidogrel and aspirin are contraindicated or cannot be tolerated
    - Aspirin 75mg daily – if clopidogrel and modified release dipyridamole are contraindicated or cannot be tolerated
    - Aspirin 75 mg daily + modified-release dipyridamole 200 mg twice daily -may be used if clopidogrel cannot be tolerated.
    - Aspirin 75mg daily + clopidogrel 75mg daily - may be initiated in secondary care for the first three months following ischaemic stroke or TIA due to severe symptomatic intracranial stenosis or for another condition such as acute coronary syndrome.
  - Lipid modification drug treatment:
    - High intensity statin (e.g. atorvastatin 20–80mg daily) will be offered at diagnosis with the aim of reducing non-HDL cholesterol by more than 40% - standard treatment
    - If this reduction is not achieved within 3 months, consider adherence, diet, lifestyle, and increasing dose
  - Antihypertensive drugs:
    - Initiated following diagnosis - may include a thiazide-like diuretic, long-acting calcium channel blocker or angiotensin-converting enzyme inhibitor.
  - Anti-coagulant drugs:
    - Treatment is deferred until at least 14 days from onset in people with disabling ischaemic stroke. In the interim aspirin 300 mg daily will be used.
    - Anticoagulation for people with TIA or stroke should be with adjusted-dose warfarin (target INR 2.5, range 2.0 to 3.0) or a direct thrombin or factor Xa inhibitor (for people with non-valvular AF).

- Optimise the management of other comorbidities and risk factors – e.g. diabetes, obstructive sleep apnoea, heart failure, contraception, menopause and prevention of influenza.

| EFFICACY and SAFETY | |
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| **Trial** | RE-SPECT ESUS, NCT02239120, EudraCT-2013-003444-24, 2013-003444-24, HKUCTR-1944, CTRI/2015/05/005763, JapicCTI-152868; dabigatran vs. placebo; phase III |
| **Sponsor** | Boehringer Ingelheim Ltd. |
| **Status** | Ongoing - recruiting |
| **Source of Information** | Trial registry[2] |
| **Location** | 18 European countries (not including UK), 12 countries in Asia, 5 countries in South America, USA, Australia, Canada, Mexico, New Zealand and South Africa |
| **Design** | Randomised, placebo-controlled |
| **Participants** | n=6000 (planned); aged 18-150 years; ischaemic stroke with a brain lesion visualised by neuroimaging; up to 3 months before randomisation or up to 6 months before randomisation in people >60 years with at least one additional risk factor and patients aged 18-59 years with a stroke in the past 3 months with a least one additional risk factor for stroke. |
| **Schedule** | Randomised to one of 2 treatment arms:<br>1) Total daily dose of 150mg (or 110mg in people >75 years or with a creatinine clearance > or = 30 to less than 50ml/min) dabigatran etexilate administered orally twice daily plus acetylsalicylic acid (ASA) placebo.<br>2) 100mg ASA administered orally once per day plus dabigatran etexilate placebo twice per day (unless participant is >75 years or with a creatinine clearance > or = 30 to less than 50ml/min in which case they will receive a total daily dose 110mg dabigatran etexilate placebo as 2 oral administrations per day). |
| **Follow-up** | Follow up is up to 36 months |
| **Primary Outcomes** | •Time to first recurrent stroke (ischemic, hemorrhagic, or unspecified) – up to 36 months |
| **Secondary Outcomes** | •Time to Ischemic Stroke – up to 36 months<br><br>•Composite endpoint of (time to) nonfatal stroke, nonfatal myocardial infarction (MI) and cardiovascular death – up to 36 months<br><br>•Time to Disabling stroke (modified Rankin Scale greater than or equal to 4, as determined 3 months after recurrent stroke) - up to 36 months<br><br>•Time to All-cause death - up to 36 months<br><br>•Time to first major bleed - up to 36 months<br><br>•Time to first intracranial hemorrhage - up to 36 months<br><br>•Time to life-threatening bleed - up to 36 months |

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| | •Fatal bleed - up to 36 months<br><br>•Time to any bleed (all severities) - up to 36 months |
| **Key Results** | - |
| **Adverse effects (AEs)** | - |
| **Expected reporting date** | The study estimated primary completion date is 31 July 2018. |

## ESTIMATED COST and IMPACT

### COST

Dabigatran etexilate (Pradaxa) is already marketed in the UK at a cost of £8.50 for 10 x 110mg tablet pack, £51.00 for 60 x 110mg tablet pack and £51.00 for a 60 x 150mg tablet pack.[13]

### IMPACT – SPECULATIVE

### IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

### IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ 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: potential prevention of a secondary stroke and therefore reduces associated costs in treating secondary stroke.

☐ Other ☐ None identified

## OTHER ISSUES

☐ Clinical uncertainty or other research question identified ☒ None identified

## REFERENCES


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