Edoxaban tosylate for prevention of stroke and systemic embolic events in non-valvular atrial fibrillation

December 2011

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Edoxaban tosylate for prevention of stroke and systemic embolic events in non-valvular atrial fibrillation

Target group
- Atrial fibrillation (AF): non-valvular – prevention of stroke and systemic embolic events.

Technology description
Edoxaban tosylate (DU 176b) is a direct factor Xa inhibitor. Edoxaban tosylate is intended to be used for the prevention of stroke and systemic embolic events in patients with non-valvular AF. It is administered orally at 30mg or 60mg once daily (doses used in clinical trial1).

Edoxaban tosylate is in phase III clinical trials for the treatment and prevention of recurrent thromboembolic events in patients with deep-vein thrombosis and/or pulmonary embolism. Edoxaban tosylate is launched in Japan for the prevention of venous thromboembolism after major orthopaedic surgery.

Innovation and/or advantages
If licensed, edoxaban tosylate may offer a new option for prevention of stroke and systemic embolic events in patients with non-valvular atrial fibrillation that does not require anticoagulation monitoring.

Developer
Daiichi Sankyo.

Availability, launch or marketing dates, and licensing plans
In phase III clinical trials.

NHS or Government priority area
This topic is relevant to The National Stroke Strategy (2007), The National Service Framework for Older People (2001) and The National Service Framework for Coronary Heart Disease (2000).

Relevant guidance
- NICE technology appraisal in development. Dabigatran etexilate for the prevention of stroke or systemic embolism in people with atrial fibrillation. Expected December 20112.
- NICE clinical guideline. The management of atrial fibrillation. 20064.
- SIGN. Management of patients with stroke: Rehabilitation, prevention and management of complications, and discharge planning. 20105.
- European Society of Cardiology. Guidelines for the management of atrial fibrillation. 20106.
- SIGN. Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention. 20088.
Clinical need and burden of disease

AF is the most common sustained cardiac arrhythmia\(^{13}\). Its prevalence increases with age from 0.5% at age 50-59 to almost 9% at age 80-89\(^{5}\). The prevalence of AF is increasing due to an ageing population and increasing survival from conditions predisposing to AF (e.g. hypertension, coronary heart disease and heart failure)\(^{14}\). In Scotland, the prevalence of AF has been estimated at 8.4 cases per 1,000 population, and is higher amongst men (men 9.4 per 1,000 vs women 7.9 per 1,000)\(^{15}\). Applying this prevalence to England and Wales equates to around 450,000 people with the condition. There were 94,850 inpatient admissions resulting in 130,218 finished consultant episodes and 281,550 bed days for AF (ICD I48) in NHS hospitals in England in 2010/11\(^{16}\).

AF increases the overall risk of stroke five-fold\(^{17}\) and accounts for approximately 15% of all thromboembolic strokes\(^{18}\). Comorbid factors such as hypertension, diabetes mellitus, congestive heart failure and prior stroke, all serve to increase the risk of stroke in AF, and the risks are additive\(^{19}\).

Each year in England approximately 110,000 people have a first or recurrent stroke and stroke accounts for 11% of all deaths in England and Wales\(^{20}\). Ischaemic and haemorrhagic stroke accounts for about 87% and 13% of all stroke cases respectively\(^{21}\). When strokes occur in association with AF, patients may experience a greater level of mortality, morbidity, disability and longer hospital stays than patients without AF\(^{22}\).

Existing comparators and treatments

For the prevention of stroke and systemic embolic events in patients with non-valvular AF, guidelines recommend the use of adjusted-dose oral anticoagulation with vitamin K antagonists (VKA) such as warfarin, and antiplatelet agents such as aspirin if oral anticoagulants are inappropriate\(^{4,23,24}\). NICE has recently recommended dabigatran etexilate as an option for the prevention of stroke and systemic embolism in people with this condition and one or more additional risk factors\(^{25}\).

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>ENGAGE AF-TIMI 48, NCT00781391, DU176b-C-U301; edoxaban tosylate or warfarin; phase III.</th>
<th>NCT00829933, DU176b-C-J225; edoxaban tosylate or warfarin; phase II.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Daiichi Sankyo Inc.</td>
<td>Daiichi Sankyo Inc.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Complete and published.</td>
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<tr>
<td>Source of information</td>
<td>Publication(^{1}), trial registry(^{26}).</td>
<td>Trial registry(^{27}), manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (inc UK), USA, Canada and other countries.</td>
<td>Japan.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
<td>Randomised, active-controlled.</td>
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<tr>
<td>Participants and schedule</td>
<td>n=20,500; adults; AF (paroxysmal, persistent or permanent) confirmed by electrical tracing within 12 mths; no significant mitral stenosis, unresected atrial myxoma or mechanical heart valve;</td>
<td>n=536, adults; non-valvular AF confirmed by ≥2 ECG tracings at an interval of ≥1 weeks; presence of ≥1 risk factors for embolism; not on treatment with anticoagulant other than warfarin;</td>
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</table>
medium to high risk of thromboembolic events (CHADS<sub>2</sub> risk score ≥2); VKA naive or experienced; anticoagulation therapy indicated for the study duration. Randomised to edoxaban tosylate 30mg or 60mg once daily, both in combination with warfarin placebo, or warfarin titrated to an INR<sup>b</sup> of 2.0 to 3.0, with edoxaban tosylate placebo.
edoxaban tosylate naive; no contraindication to anticoagulation therapy. Randomised to edoxaban tosylate 30mg, 45mg or 60mg once daily or warfarin once daily titrated to an INR of 2.0 to 3.0 for age <70 or 1.6 to 2.6 for age ≥70 (in line with Japanese guidelines).

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Active treatment period 24 mths.</th>
<th>Active treatment period 12 weeks.</th>
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</thead>
<tbody>
<tr>
<td>Primary outcome/s</td>
<td>Composite of stroke and systemic embolic events (SEE).</td>
<td>Major bleeding; CRNM bleeding; minor bleeding.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Individual and composite outcome of stroke, SEE, and cardiovascular mortality or all cause mortality; major bleeding&lt;sup&gt;c&lt;/sup&gt;; major plus clinically relevant non major (CRNM) bleeding&lt;sup&gt;d&lt;/sup&gt;; liver enzyme and bilirubin abnormalities.</td>
<td>Thromboembolic events; changes in D-dimer.</td>
</tr>
<tr>
<td>Key results</td>
<td>-</td>
<td>The mean (95% CI) incidence of all bleeding events for edoxaban tosylate 30mg, 45mg, 60 mg and warfarin were 18.5% (12.7, 26.0), 22.4% (16.2, 30.2), 27.7% (20.7, 35.9) and 20.0% (13.9, 27.9) respectively. A trend of dose-related increase in bleeding was observed for edoxaban tosylate, but there was no statistically significant difference between any edoxaban tosylate dose and warfarin. A multivariate analysis suggested that low body weight (&lt;60 kg) is an important co-variable for bleeding. D-dimer levels decreased similarly in all treatment groups, among warfarin naive patients.</td>
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<tr>
<td>Adverse effects (AEs)</td>
<td>-</td>
<td>One episode of cerebral infarction observed in the edoxaban tosylate 45mg arm.</td>
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<tr>
<td>Expected reporting date</td>
<td>Study expected to complete Feb 2012.</td>
<td>-</td>
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<tr>
<th>Trial</th>
<th>NCT00504556, DU176b-PRT018; edoxaban tosylate or warfarin; phase II.</th>
<th>NCT00806624, DU176b-C-J226; edoxaban tosylate or warfarin; phase II.</th>
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<td>Publication&lt;sup&gt;30&lt;/sup&gt;, trial registry&lt;sup&gt;31&lt;/sup&gt;.</td>
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<td>Location</td>
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<td>China, Republic of Korea, Singapore and other countries.</td>
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<sup>a</sup> The long-term risk of stroke in AF depends on clinical predictors, which are collectively assessed in the CHADS<sub>2</sub> scoring scheme, an acronym for congestive heart failure, hypertension, age>75, diabetes mellitus, and prior Stroke.
<sup>b</sup> International Normalised Ratio.
<sup>c</sup> Major bleeding was defined as bleeding that was fatal or in a critical site or overt and associated with a decline in haemoglobin of ≥2g/dl or requiring transfusion of ≥2 units of blood.
<sup>d</sup> Clinically relevant non-major (CRNM) bleeding was defined as bleeding that did not meet the definition of major bleeding, but was considered clinically significant and/or resulted in discontinuation of study medication.
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<th>Design</th>
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<td>Participants and schedule</td>
<td>n=1,146; adults; persistent non-valvular AF confirmed by 2 ECG tracings; no mitral valve disease, endocarditis, atrial myxoma or mechanical heart valve; CHADS₂ risk score ≥2; warfarin naive or experienced; edoxaban tosylate naive; no contraindication to anticoagulation therapy. Randomised to edoxaban tosylate 30mg once daily, 30mg twice daily, 60mg once daily, 60mg twice daily or warfarin titrated to an INR of 2.0 to 3.0.</td>
<td>n=235, adults; non-valvular AF confirmed by ≥2 ECG tracings within 12 mths; no left ventricular aneurysm or atrial myxoma; CHADS₂ risk score ≥1; not on treatment with an antiplatelet agent; no contraindication to anticoagulation therapy. Randomised to edoxaban tosylate 30mg once daily, 60mg once daily or warfarin titrated to an INR of 2.0 to 3.0.</td>
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<th>Follow-up</th>
<th>Active treatment period 12 weeks.</th>
<th>Active treatment period 12 weeks, then 2 mths follow up.</th>
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<tbody>
<tr>
<td>Primary outcome/s</td>
<td>Major bleeding; CRNM bleeding; minor bleeding; alanine aminotransferase (ALT); aspartate aminotransferase (AST); bilirubin abnormalities.</td>
<td>All bleeding events; major bleeding; CRNM bleeding; minor bleeding.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Major adverse cardiovascular events; composite of stroke, SEE, myocardial infarction, cardiovascular death and hospitalisation for any cardiac condition.</td>
<td>Major adverse cardiovascular events consisting of stroke, SEE, myocardial infarction, cardiovascular death and hospitalisation for any cardiac condition; AEs; laboratory variables.</td>
</tr>
</tbody>
</table>

| Key results | Bleeding events, n ([%], p value vs warfarin), for edoxaban tosylate 30mg once daily, 30mg twice daily, 60mg once daily, 60mg twice daily and warfarin respectively: all bleeding, 13 [5.5%, p=0.367], 31 [12.7%, p=0.104], 17 [7.3%, p=0.864], 33 [18.3%, p=0.002], 20 (8%); major plus CRNM bleeding, 7 [3%, p=1.0], 19 [7.8%, p=0.0029], 9 [3.8%, p=0.807], 19 [10.6%, p=0.002], 8 (3.2%); major bleeding, 0 (p=1.0), 5 [2.0%] p=0.119], 1[0.4%, p=1.0], 6 [3.3%, p=0.023], 1(0.4%); CRNM bleeding, 7 (3%), 14 (5.7%), 8 (3.4%), 13 (7.2%), 7 (2.8%); minor bleeding, 6 (2.6%), 12 (4.9%), 8 (3.4%), 14 (7.8%), 12 (4.8%). | Bleeding events, n ([%], 95% CI), for edoxaban tosylate 30mg once daily, 60mg once daily and warfarin respectively: all bleeding, 16 [20.3%, (12.9, 30.4)], 19 [23.8%, (15.8, 34.1)], 22 [29.3%, (20.2, 40.4)]; major bleeding, 0 [0 (0, 4.6)], 0 [0, (0, 4.6)], 2 [2.7% (0.7, 9.2)]; CRNM bleeding, 0 [0 (0, 4.6)], 6 [7.5%, (3.5, 15.4)], 3 [4% (1.4, 11.1)]; minor bleeding, 16 [20.3% (12.9, 30.4)], 15 [18.8% (11.7, 28.7)], 17 [22.7% (14.7, 33.3)]. |

For edoxaban tosylate 30mg once daily, 30mg twice daily, 60mg once daily, 60mg twice daily and warfarin respectively: ALT or AST ≥3 times upper limit of the normal range (ULN), 1.3%, 0.9%, 3.1%, 1.7%, 1.6%; bilirubin ≥2 times ULN, 0.9%, 1.3%, 0.4%, 2.9%, 1.6%.

Adverse effects (AEs) | For edoxaban tosylate 30mg once daily, 30mg twice daily, 60mg once daily, 60mg twice daily and warfarin respectively: treatment-emergent AEs (TEAEs), 40.4%, 39.8%, 42.3%, 45.6%, 46.0%; drug related AEs, 11.1%, 13.5%, 11.5%, 22.2%, 18.4%; | AEs, n (%), for edoxaban tosylate 30mg once daily, 60mg once daily and warfarin respectively: all AEs, 59 (74.7%), 59 (73.8%), 52 (69.3%); drug related AEs, 17 (21.5%), 23 (28.8%), 25 (33.3%); serious AEs, 2 |

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* Minor bleeding was defined as any bleeding that did not meet the criteria for a major or CRNM bleeding event.

For edoxaban tosylate arms, the incidence of all bleeding events was higher in patients with body weight ≤60kg than other patients.
cardiac AEs, 1.7%, 2.5%, 4.3%, 1.1%, 2.4%. Serious TEAEs observed in 5.9% and 4.4% of participants receiving edoxaban tosylate and warfarin respectively. (2.5%), 5 (6.3%), 4 (5.3%); drug related serious AEs, 0, 1 (1.3%), 1 (1.3%); AEs leading to permanent discontinuation of study drug, 3 (3.8%), 9 (11.3%), 2 (2.7%).

Estimated cost and cost impact
The cost of edoxaban tosylate is not yet known. The annual costs of warfarin at 5mg per day and aspirin at 75mg per day are approximately £13 and £11 respectively\(^3^\), excluding the costs of monitoring warfarin anticoagulation (INR).

Claimed or potential impact – speculative

Patients
- Reduced mortality or increased length of survival
- Reduction in associated morbidity or improved quality of life for patients and/or carers
- Quicker, earlier or more accurate diagnosis or identification of disease
- None identified

Services
- Increased use
- Service organisation
- Staff requirements
- Decreased use: reduced need for anticoagulation monitoring
- None identified

Costs
- Increased unit cost compared to alternative
- Increased costs: more patients coming for treatment
- Increased costs: capital investment needed
- New costs:
  - Savings: reduced need for anticoagulation monitoring
  - Other: uncertain unit cost compared to alternative

Other issues
- Clinical uncertainty or other research question identified:
  - Expert opinion suggests it may be difficult to manage overdose or bleeding
- None identified

References


American College of Cardiology, American Heart Association and European Society of Cardiology. Guidelines for the management of patients with atrial fibrillation. Europace 2006;8:651–745.


NHS. Hospital episode statistics, NHS England -Primary diagnosis: 3 character, 2010-11. HES data www.hesonline.nhs.uk


