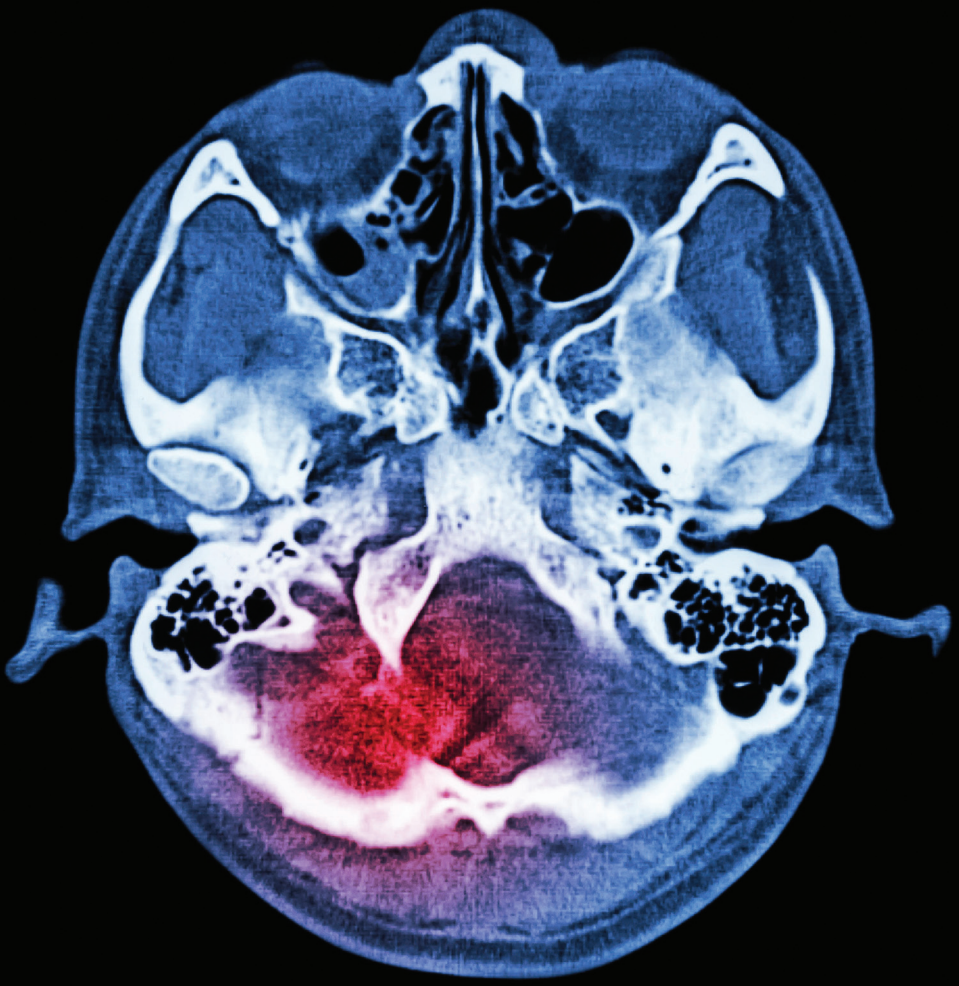
Edoxaban

Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation



PULSE Nursing IN PRACTICE

Introduction

Edoxaban is recommended, within its marketing authorisation, as an option for preventing stroke and systemic embolism in adults with non-valvular atrial fibrillation with one or more risk factors, including:

- congestive heart failure
- hypertension
- diabetes
- prior stroke or transient ischaemic attack
- age 75 years or older.

The decision about whether to start treatment with edoxaban should be made after an informed discussion between the clinician and the person about the risks and benefits of edoxaban compared with warfarin, apixaban, dabigatran etexilate and rivaroxaban. For people considering switching from warfarin, edoxaban's potential benefits should be considered against its potential risks, taking into account the person's level of international normalised ratio (INR) control.

1 The technology

Edoxaban (Lixiana, Daiichi Sankyo) is an anticoagulant that directly inhibits factor X (factor Xa), which is a key component in the formation of blood clots. It is administered orally. Edoxaban has a marketing authorisation for the 'prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, prior stroke or transient ischaemic attack (TIA)'. The summary of product characteristics states that the recommended dose is 60 mg once daily. The recommended dose is 30 mg once daily in people with one or more of the following clinical factors: moderate or severe renal impairment (creatinine clearance 15-50 ml/min); body weight of 60 kg or less; concomitant use of the P-glycoprotein inhibitors ciclosporin, dronedarone, erythromycin or ketoconazole.

The summary of product characteristics includes the following adverse reactions for edoxaban: bleeding, anaemia, nausea, rash, hepatobiliary disorders (increased blood bilirubin and gamma-glutamyl transferase) and abnormal liver function test. For full details of adverse reactions and contraindications, see the summary of product characteristics.

Edoxaban costs £58.80 for a 28-tablet pack (60 mg or 30 mg) and the daily cost of treatment is £2.10 (excluding VAT). Costs may vary in different settings because of negotiated procurement discounts.

2

Summary of Appraisal Committee's key conclusions

Key conclusion

Edoxaban is recommended, within its marketing authorisation, as an option for preventing stroke and systemic embolism in adults with non-valvular atrial fibrillation with one or more risk factors, including:

- congestive heart failure
- hypertension
- diabetes
- prior stroke or transient ischaemic attack
- age 75 years or older.

Current practice

Clinical need of patients, including the availability of alternative treatments

The Committee was aware that that non-valvular atrial fibrillation is well-managed with warfarin for many people but it is associated with a number of problems including the need for regular monitoring and dose adjustment, and it has multiple food and drug interactions. The NICE guideline *Atrial fibrillation: management* no longer recommends aspirin for the treatment of non-valvular atrial fibrillation, which has led to a higher uptake of both warfarin and newer oral anticoagulants.

The technology – proposed benefits of the technology

How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?

The Committee accepted the limitations of warfarin therapy and the considerable impact it may have on the people who take it, and recognised the potential benefits of edoxaban for people with atrial fibrillation.

What is the position of the treatment in the pathway of care for the condition?

Edoxaban is used as an alternative to warfarin, apixaban, rivaroxaban and dabigatran etexilate and is an anticoagulant treatment for preventing stroke and systemic embolism in


IntelliVue
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people with non valvular atrial fibrillation with 1 or more risk factors for stroke.

Adverse reactions
The Committee concluded that the risk-benefit profile of edoxaban was acceptable because it resulted in statistically significantly fewer bleeds than warfarin, and a statistically significant reduction in several secondary bleeding endpoints including fatal, intracranial and clinically relevant non-major bleeds. The Committee recognised the particular importance of the reduction in intracranial bleeding compared with warfarin.

Evidence for clinical effectiveness

Availability, nature and quality of evidence
The Committee considered the clinical effectiveness data from the ENGAGE AF-TIMI 48 trial that compared edoxaban with warfarin. It considered that the trial was of good quality.

Relevance to general clinical practice in the NHS
Although ENGAGE AF-TIMI 48 used CHADS2 to assess risk of stroke rather than CHADS2-VASc (which is now used in clinical practice, as recommended in the NICE guideline *Atrial fibrillation: management*), the Committee concluded that the trial was well designed and generalisable to clinical practice.

Uncertainties generated by the evidence
The Committee considered the results of the network meta-analysis in the light of the methodological issues and noted that all the newer oral anticoagulants appeared to have comparable efficacy for the composite primary and bleeding outcomes. The Committee concluded that the network meta-analysis results should be interpreted with caution, but edoxaban is unlikely to be different from rivaroxaban, apixaban and dabigatran etexilate in clinical practice.

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?
The Committee concluded that there was insufficient evidence to consider different treatment effects according to centre-level time in therapeutic range (TTR).

The Committee concluded that there was no biologically plausible reason to indicate that the relative treatment effect would be dependent on baseline risk of stroke.

The Committee concluded that if edoxaban is used in accordance with the summary of product characteristics, there is no reason to make differential recommendations based on creatinine clearance.

Estimate of the size of the clinical effectiveness including strength of supporting evidence
The Committee concluded that edoxaban was as clinically effective as warfarin for the primary efficacy outcome of reducing stroke (ischaemic and haemorrhagic) and systemic embolism, and had nearly half the rate of haemorrhagic stroke events compared to warfarin.

Evidence for cost effectiveness

Availability and nature of evidence
The Committee agreed that the model structure, perspective and time horizon were appropriate, although it questioned the relevance of the inclusion of myocardial infarction. It concluded that the analysis was consistent with the NICE reference case.

Uncertainties around and plausibility of assumptions and inputs in the economic model
The Committee noted that for the comparison of edoxaban with the other newer oral anticoagulants, hazard ratios obtained from the network meta-analysis were used in the economic model and

that these estimates were considered unreliable by the Evidence Review Group (ERG) (see consideration of evidence in clinical effectiveness section in the NICE guideline, *Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation*). The Committee concluded that data from ENGAGE AF-TIMI 48 were appropriate for calculating the cost effectiveness of edoxaban compared with warfarin, but that estimates of the cost effectiveness of edoxaban compared with dabigatran etexilate, apixaban and rivaroxaban were based on data that were associated with a high degree of uncertainty.

Incorporation of health-related quality-of-life benefits and utility values

Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?

The Committee heard from the ERG that there were differences in the utility values used in the economic model compared with other technology appraisals for atrial fibrillation. The Committee concluded that the utility values used in the model, although open to debate, were not key drivers of the cost effectiveness.

No health-related benefits were identified that were not included in the economic model.

Are there specific groups of people for whom the technology is particularly cost effective?

The Committee concluded that there was insufficient evidence to consider different treatment effects according to centre-level TTR.

The Committee concluded that if edoxaban is used in accordance with the summary of product characteristics, there is no reason to make differential recommendations based on creatinine clearance.

What are the key drivers of cost effectiveness?

The Committee noted the ERG's exploratory analyses, in which the change that had the largest single impact on the incremental cost-effectiveness ratio (ICER) for edoxaban compared with warfarin was applying the hazard ratio from ENGAGE AF-TIMI 48 for haemorrhagic stroke (which increased the ICER to £17,100 per QALY gained).

The Committee concluded that there was insufficient evidence to distinguish between the clinical and cost effectiveness of edoxaban and the newer oral anticoagulants recommended in previous appraisals (apixaban, dabigatran etexilate and rivaroxaban). Therefore, edoxaban could be recommended as a cost-effective treatment for non valvular atrial fibrillation in people who have 1 or more risk factors for stroke.

Most likely cost-effectiveness estimate (given as an ICER)

The Committee noted that the inclusion of all the ERG's preferred values in the model resulted in a deterministic ICER of £16,000 per QALY gained and a probabilistic ICER of £22,100 per QALY gained.

Additional factors taken into account

Patient access schemes (PPRS)

The Committee concluded that the PPRS payment mechanism was irrelevant for the consideration of the cost effectiveness of edoxaban.

End of life considerations

Not applicable.

Equalities considerations and social value judgements

No equalities issues were identified.

3 Implementation

Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has non-valvular atrial fibrillation and the doctor responsible for their care thinks that edoxaban is the right treatment, it should be available for use, in line with NICE's recommendations. ●

Resources

For the full nice NICE guideline *Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation*, visit www.nice.org.uk/guidance/ta355.

LIXIANA®
PRESCRIBING INFORMATION

Indicated for:[3]

Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA)

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults

LIXIANA▼ (edoxaban) 60 mg/30 mg/15 mg film coated tablets
See summary of product characteristics prior to prescribing for full list of adverse events

Presentation: 60 mg (yellow)/30 mg (pink)/15 mg (orange) edoxaban film coated tablets (as tosilate). **Indications:** Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA) and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. **Posology and method of administration:** *NVAF* – The recommended dose is 60 mg edoxaban once daily with or without food. Therapy with edoxaban in NVAF patients should be continued long term. *VTE* – The recommended dose is 60 mg edoxaban once daily following initial use of parenteral anticoagulant for at least 5 days with or without food. Duration of therapy (at least 3 months) should be based on risk profile of the patient. For NVAF and VTE the recommended dose is 30 mg edoxaban once daily in patients with one or more of the following clinical factors: moderate or severe renal impairment (creatinine clearance (CrCL) 15–50 ml/min), low body weight ≤60 kg and/or concomitant use of the following P-glycoprotein (P-gp) inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole. The 15 mg dose of edoxaban is not indicated as monotherapy, and should only be used during a switch from edoxaban to VKA (see SmPC for full details). If a dose of edoxaban is missed, the dose should be taken immediately and then continued once daily on the following day. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients; clinically significant active bleeding. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal (GI) ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. Uncontrolled severe hypertension. Concomitant treatment with any other anticoagulants e.g. UFH, low molecular weight heparins, heparin derivatives (fondaparinux, etc.), VKA or NOACs except under specific circumstances of switching oral anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter. Pregnancy and breastfeeding. **Special warnings and precautions for use:** Haemorrhagic risk: Use with caution in patients with increased risk of bleeding such as elderly on ASA and should be discontinued if severe haemorrhage occurs. The anticoagulant effect of edoxaban cannot be reliably monitored with standard laboratory testing. A specific anticoagulant reversal agent for edoxaban is not available. Haemodialysis does not significantly clear edoxaban. Renal impairment: Renal function should be assessed prior to initiation of edoxaban and afterwards when clinically indicated. Not recommended in patients with end-stage renal disease or on dialysis. Renal function and NVAF: A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin. Edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful benefit risk evaluation. Hepatic impairment: Not recommended in patients with severe hepatic impairment and should be used with caution in patients with mild or moderate hepatic impairment. Edoxaban should be used with caution in patients with elevated liver enzymes (ALT/AST >2 x ULN) or total bilirubin ≥1.5 x ULN. *Surgery or other interventions*: discontinue edoxaban at least 24 hours before the procedure. If the procedure cannot be delayed, the increased risk of bleeding should be weighed against the urgency of the procedure. Edoxaban should be restarted as soon as haemostasis is achieved. *Prosthetic heart valves and moderate to severe mitral stenosis*: Not recommended. *Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy*: Not recommended. *Patients with active cancer*: Not recommended. **Drug interactions:** The *P-gp inhibitors* ciclosporin, dronedarone, erythromycin, or ketoconazole result in increased concentration of edoxaban and a dose reduction of 30 mg is required. Edoxaban should be used with caution with concomitant *P-gp inducers* (e.g. phenytoin, carbamazepine, phenobarbitol or St John's Wort). Concomitant high dose ASA (325 mg) or chronic NSAIDs is not recommended. There is very limited experience with dual antiplatelet therapy or fibrinolytic agents. **Pregnancy:** Not recommended. *Breastfeeding*: discontinue breastfeeding or edoxaban therapy. **Undesirable effects:** Common: anaemia, epistaxis, lower GI haemorrhage, upper GI haemorrhage, oral/pharyngeal haemorrhage, nausea, blood bilirubin increased, gamma GT increased, cutaneous soft tissue haemorrhage, rash, pruritus, macroscopic haematuria/urethral haemorrhage, vaginal haemorrhage, puncture site haemorrhage, liver function test abnormal. Uncommon: hypersensitivity, intracranial haemorrhage (ICH), intraocular haemorrhage, other haemorrhage, haemoptysis, surgical site haemorrhage. Rare: anaphylactic reaction, allergic oedema, subarachnoid haemorrhage, pericardial haemorrhage, retroperitoneal haemorrhage, intramuscular haemorrhage (no compartment syndrome), intra-articular haemorrhage, subdural haemorrhage, procedural haemorrhage. **Legal category:** POM. **Package quantities and basic NHS costs:** 60 mg/30 mg – 28 tablets £58.80; 15 mg – 10 tablets £21.00. **Marketing Authorisation (MA) number:** EU/1/15/993/001–16. **MA holder:** Daiichi Sankyo Europe GmbH, Zielstattstrasse 48, 81379 Munich, Germany. **Date of prep:** July 2015.

Adverse events should be reported.
Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Daiichi Sankyo UK Medical Information on 0800 028 5122, medinfo@daiichi-sankyo.co.uk

References: 1. Giugliano RP *et al. NEJM* 2013;369(22):2093–2104. **2.** The Hokusai-VTE Investigators. *NEJM* 2013;369(15):1406–1415. **3.** LIXIANA®, Summary of Product Characteristics, July 2015. **4.** NICE Technology Appraisal 355. Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation. September 2015. Available at: www.nice.org.uk/guidance/ta355 Accessed September 2015. **5.** NICE Technology Appraisal 354. Edoxaban for treating and for preventing deep vein thrombosis and pulmonary embolism. August 2015. Available at: www.nice.org.uk/guidance/ta354/ Accessed September 2015.

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NOW NICE RECOMMENDED IN NVAF AND VTE

NEW ONCE-DAILY LIXIANA®▼ (edoxaban)

Only LIXIANA® combines:

- Proven efficacy comparable to well-controlled warfarin[1,2]
- Superior reduction in clinically relevant bleeding vs. well-controlled warfarin[1,2]
- Once-daily dosing across both NVAF and VTE indications[3]

NICE guidance:

- Edoxaban is recommended, within its marketing authorisation, as an option for preventing stroke and systemic embolism (blood clots) in adults with NVAF who have one or more risk factors[4]
- Edoxaban is recommended, within its marketing authorisation, as an option for treating and for preventing recurrent DVT and PE in adults[5]

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once-daily Lixiana® edoxaban

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Prescribing information and references can be found overleaf