Lixiana® 15 mg
Lixiana® 30 mg
Lixiana® 60 mg
(Edoxaban)

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Lixiana 15 mg film-coated tablets
Lixiana 30 mg film-coated tablets
Lixiana 60 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 15 mg film-coated tablet contains 15 mg edoxaban (as tosilate).
Each 30 mg film-coated tablet contains 30 mg edoxaban (as tosilate).
Each 60 mg film-coated tablet contains 60 mg edoxaban (as tosilate).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
15 mg film-coated tablet: Orange, round-shaped film-coated tablets (6.7 mm diameter) debossed with “DSC L15”.
30 mg film-coated tablet: Pink, round-shaped film-coated tablets (8.5 mm diameter) debossed with “DSC L30”.
60 mg film-coated tablet: Yellow, round-shaped film-coated tablets (10.5 mm diameter) debossed with “DSC L60”.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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).

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (see section 4.4 for haemodynamically unstable PE patients).

4.2 Posology and method of administration

Posology

Prevention of stroke and systemic embolism
The recommended dose is 60 mg edoxaban once daily.
Therapy with edoxaban in NVAF patients should be continued long term.

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTE)
The recommended dose is 60 mg edoxaban once daily following initial use of parenteral anticoagulant for at least 5 days (see section 5.1). Edoxaban and initial parenteral anticoagulant should not be administered simultaneously.
The duration of therapy for treatment of DVT and PE (venous thromboembolism, VTE), and prevention of recurrent VTE should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4). Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.

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
Concomitant use of the following P-glycoprotein (P-gp) inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole.

Table 1: Summary of posology in NVAF and VTE (DVT and PE)

Summary Guide for Dosing		
Recommended dose		60 mg once daily
Dose recommendation for patients with one or more of the following clinical factors:		
Renal Impairment	*Moderate or severe (CrCL 15 – 50 mL/min)*	30 mg once daily
Low Body Weight	*≤ 60 kg*	
P-gp Inhibitors	*Ciclosporin, dronedarone, erythromycin, ketoconazole*	

Missed dose
If a dose of Lixiana is missed, the dose should be taken immediately and then be continued the following day with the once-daily intake as recommended. The patient should not take double the prescribed dose on the same day to make up for a missed dose.

Switching to and from Lixiana
Continued anticoagulant therapy is important in patients with NVAF and VTE. There may be situations that warrant a change in anticoagulation therapy (Table 2).

Table 2: Switching

Switching to Lixiana		
From	**To**	**Recommendation**
Vitamin K Antagonist (VKA)	Lixiana	Discontinue the VKA and start Lixiana when the international normalised ratio (INR) is ≤ 2.5.
Oral anticoagulants other than VKA • dabigatran • rivaroxaban • apixaban	Lixiana	Discontinue dabigatran, rivaroxaban or apixaban and start Lixiana at the time of the next dose of the oral anticoagulant (see section 5.1).

Switching to Lixiana		
From	**To**	**Recommendation**
Parenteral anticoagulants	Lixiana	These medicinal products should not be administered simultaneously. Subcutaneous anticoagulant (i.e.: LMWH, fondaparinux): Discontinue subcutaneous anticoagulant and start Lixiana at the time of the next scheduled subcutaneous anticoagulant dose.
		Intravenous unfractionated heparin (UFH): Discontinue the infusion and start Lixiana 4 hours later.

Switching from Lixiana		
From	**To**	**Recommendation**
Lixiana	Vitamin K Antagonist (VKA)	There is a potential for inadequate anticoagulation during the transition from Lixiana to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. *Oral option:* For patients currently on a 60 mg dose, administer a Lixiana dose of 30 mg once daily together with an appropriate VKA dose. For patients currently on a 30 mg dose (for one or more of the following clinical factors: moderate to severe renal impairment (CrCL 15 – 50 mL/min), low body weight, or use with certain P-gp inhibitors), administer a Lixiana dose of 15 mg once daily together with an appropriate VKA dose. Patients should not take a loading dose of VKA in order to promptly achieve a stable INR between 2 and 3. It is recommended to take into account the maintenance dose of VKA and if the patient was previously taking a VKA or to use valid INR driven VKA treatment algorithm, in accordance with local practice. Once an INR ≥ 2.0 is achieved, Lixiana should be discontinued. Most patients (85%) should be able to achieve an INR ≥ 2.0 within 14 days of concomitant administration of Lixiana and VKA. After 14 days it is recommended that Lixiana is discontinued and the VKA continued to be titrated to achieve an INR between 2 and 3. It is recommended that during the first 14 days of concomitant therapy the INR is measured at least 3 times just prior to taking the daily dose of Lixiana to minimise the influence of Lixiana on INR measurements. Concomitant Lixiana and VKA can increase the INR post Lixiana dose by up to 46%.

Switching from Lixiana		
From	**To**	**Recommendation**
		Parenteral option: Discontinue Lixiana and administer a parenteral anticoagulant and VKA at the time of the next scheduled Lixiana dose. Once a stable INR of ≥ 2.0 is achieved, the parenteral anticoagulant should be discontinued and the VKA continued.
Lixiana	Oral anticoagulants other than VKA	Discontinue Lixiana and start the non-VKA anticoagulant at the time of the next scheduled dose of Lixiana.
Lixiana	Parenteral anticoagulants	These agents should not be administered simultaneously. Discontinue Lixiana and start the parenteral anticoagulant at the time of the next scheduled dose of Lixiana.

Special populations

Assessment of renal function:

- Renal function should be assessed in all patients by calculating the creatinine clearance (CrCL) prior to initiation of treatment with Lixiana to exclude patients with end stage renal disease (e.g. CrCL < 15 mL/min), to use the correct Lixiana dose in patients with CrCL 15 – 50 mL/min (30 mg once daily), in patients with CrCL > 50 mL/min (60 mg once daily) and when deciding on the use of Lixiana in patients with increased creatinine clearance (see section 4.4).

- Renal function should also be assessed when a change in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products).

The method used to estimate renal function (CrCL in mL/min) during the clinical development of Lixiana was the Cockcroft-Gault method. The formula is as follows:

- For creatinine in µmol/L:

$$\frac{1.23 \times (140\text{-age [years]}) \times \text{weight [kg]} \ (\times 0.85 \text{ if female})}{\text{serum creatinine [µmol/L]}}$$

- For creatinine in mg/dL:

$$\frac{(140\text{-age [years]}) \times \text{weight [kg]} \ (\times 0.85 \text{ if female})}{72 \times \text{serum creatinine [mg/dL]}}$$

This method is recommended when assessing patients' CrCL prior to and during Lixiana treatment.

Renal impairment

- In patients with mild renal impairment (CrCL > 50 – 80 mL/min), the recommended dose is 60 mg Lixiana once daily.

- In patients with moderate or severe renal impairment (CrCL 15 – 50 mL/min), the recommended dose is 30 mg Lixiana once daily (see section 5.2).

- In patients with end stage renal disease (ESRD) (CrCL < 15 mL/min) or on dialysis, the use of Lixiana is not recommended (see sections 4.4 and 5.2).

Hepatic impairment

Lixiana is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 4.3).

In patients with severe hepatic impairment Lixiana is not recommended (see sections 4.4 and 5.2).

In patients with mild to moderate hepatic impairment the recommended dose is 60 mg Lixiana once daily (see section 5.2). Lixiana should be used with caution in patients with mild to moderate hepatic impairment (see section 4.4).

Patients with elevated liver enzymes (ALT/AST > 2 x ULN) or total bilirubin ≥ 1.5 x ULN were excluded in clinical trials. Therefore Lixiana should be used with caution in this population (see sections 4.4 and 5.2). Prior to initiating Lixiana, liver function testing should be performed.

Body weight
For patients with body weight ≤ 60 kg, the recommended dose is 30 mg Lixiana once daily (see section 5.2).

Elderly
No dose reduction is required (see section 5.2).

Gender
No dose reduction is required (see section 5.2).

Concomitant use of Lixiana with P-glycoprotein (P-gp) inhibitors
In patients concomitantly taking Lixiana and the following P-gp inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole, the recommended dose is 30 mg Lixiana once daily (see section 4.5).
No dose reduction is required for concomitant use of amiodarone, quinidine or verapamil (see section 4.5).
The use of Lixiana with other P-gp inhibitors including HIV protease inhibitors has not been studied.

Paediatric population
The safety and efficacy of Lixiana in children and adolescents less than 18 years of age have not been established. No data are available.

Patients undergoing cardioversion
Lixiana can be initiated or continued in patients who may require cardioversion. For transoesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, Lixiana treatment should be started at least **2 hours** before cardioversion to ensure adequate anticoagulation (see sections 5.1 and 5.2). Cardioversion should be performed no later than 12 hours after the dose of Lixiana on the day of the procedure.
For all patients undergoing cardioversion: Confirmation should be sought prior to cardioversion that the patient has taken Lixiana as prescribed. Decisions on initiation and duration of treatment should follow established guidelines for anticoagulant treatment in patients undergoing cardioversion.

Method of administration
For oral use.
Lixiana can be taken with or without food (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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 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. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, rivaroxaban, apixaban etc.) except under specific circumstances of switching oral anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).
- Pregnancy and breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Lixiana 15 mg is not indicated as monotherapy, as it may result in decreased efficacy. It is only indicated in the process of switching from Lixiana 30 mg (patients with one or more clinical factors for increased exposure; see table 1) to VKA, together with an appropriate VKA dose (see table 2, section 4.2).

Haemorrhagic risk

Edoxaban increases the risk of bleeding and can cause serious, potentially fatal bleeding. Lixiana, like other anticoagulants, is recommended to be used with caution in patients with increased risk of bleeding. Lixiana administration should be discontinued if severe haemorrhage occurs (see sections 4.8 and 4.9).

In the clinical studies mucosal bleedings (e.g. epistaxis, gastrointestinal, genitourinary) and anaemia were seen more frequently during long term edoxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8). Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

The anticoagulant effect of edoxaban cannot be reliably monitored with standard laboratory testing.
A specific anticoagulant reversal agent for edoxaban is not available (see section 4.9).

Haemodialysis does not significantly contribute to edoxaban clearance (see section 5.2).

Elderly

The co-administration of Lixiana with ASA in elderly patients should be used cautiously because of a potentially higher bleeding risk (see section 4.5).

Renal impairment

The plasma AUC for subjects with mild (CrCL > 50 - 80 mL/min), moderate (CrCL 30 - 50 mL/min) and severe (CrCL < 30 mL/min but not undergoing dialysis) renal impairment was increased by 32%, 74%, and 72%, respectively, relative to subjects with normal renal function (see section 4.2 for dose reduction).

In patients with end stage renal disease or on dialysis, Lixiana is not recommended (see sections 4.2 and 5.2).

Renal function in NVAF
A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin (see section 5.1). Therefore, edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk.

Assessment of renal function: CrCL should be monitored at the beginning of the treatment in all patients and afterwards when clinically indicated (see section 4.2).

Hepatic impairment
Lixiana is not recommended in patients with severe hepatic impairment (see sections 4.2 and 5.2).

Lixiana should be used with caution in patients with mild or moderate hepatic impairment (see section 4.2).

Patients with elevated liver enzymes (ALT/AST > 2 x ULN) or total bilirubin ≥ 1.5 x ULN were excluded in clinical trials. Therefore Lixiana should be used with caution in this population (see sections 4.2 and 5.2). Prior to initiating Lixiana, liver function testing should be performed.
Periodic hepatic monitoring is recommended for patients on Lixiana treatment beyond 1 year.

Discontinuation for surgery and other interventions
If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, Lixiana should be stopped as soon as possible and preferably at least 24 hours before the procedure.

In deciding whether a procedure should be delayed until 24 hours after the last dose of Lixiana, the increased risk of bleeding should be weighed against the urgency of the intervention. Lixiana should be restarted after the surgical or other procedures as soon as adequate haemostasis has been established, noting that the time to onset of the edoxaban anticoagulant therapeutic effect is 1 – 2 hours. If oral medicinal products cannot be taken during or after surgical intervention, consider administering a parenteral anticoagulant and then switch to oral once daily Lixiana (see section 4.2).

*Interaction with other medicinal products affecting haemostasis*Concomitant use of medicines affecting haemostasis may increase the risk of bleeding. These include acetylsalicylic acid (ASA), $P2Y_{12}$ platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), and chronic nonsteroidal anti-inflammatory drugs (NSAIDs) (see section 4.5).

Prosthetic heart valves and moderate to severe mitral stenosis
Edoxaban has not been studied in patients with mechanical heart valves, in patients during the first 3 months after implantation of a bioprosthetic heart valve, with or without atrial fibrillation, or in patients with moderate to severe mitral stenosis. Therefore, use of edoxaban is not recommended in these patients.

Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy
Lixiana is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of edoxaban have not been established in these clinical situations.

Patients with active cancer
Efficacy and safety of edoxaban in the treatment and/or prevention of VTE in patients with active cancer have not been established.

Patients with antiphospholipid syndrome
Direct acting Oral Anticoagulants (DOACs) including edoxaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Laboratory coagulation parameters
Although treatment with edoxaban does not require routine monitoring, the effect on anticoagulation can be estimated by a calibrated quantitative anti-Factor Xa assay which may help to inform clinical decisions in particular situations as, e.g. overdose and emergency surgery (see also section 5.2).

Edoxaban prolongs standard clotting tests such as prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT) as a result of FXa inhibition. Changes observed in these clotting tests at the expected therapeutic dose are, however, small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of edoxaban.

4.5 Interaction with other medicinal products and other forms of interaction

Edoxaban is predominantly absorbed in the upper gastrointestinal (GI) tract. Thus, medicines or disease conditions that increase gastric emptying and gut motility have the possibility of reducing edoxaban dissolution and absorption.

P-gp inhibitors
Edoxaban is a substrate for the efflux transporter P-gp. In pharmacokinetic (PK) studies, concomitant administration of edoxaban with the P-gp inhibitors: ciclosporin, dronedarone, erythromycin, ketoconazole, quinidine, or verapamil resulted in increased plasma concentrations of edoxaban. Concomitant use of edoxaban with ciclosporin, dronedarone, erythromycin, or ketoconazole requires dose reduction to 30 mg once daily. Concomitant use of edoxaban with quinidine, verapamil, or amiodarone does not require dose reduction based on clinical data (see section 4.2).
The use of edoxaban with other P-gp inhibitors including HIV protease inhibitors has not been studied.

Lixiana 30 mg once daily must be administered during concomitant use with the following P-gp inhibitors:

- *Ciclosporin:* Concurrent administration of a single dose of ciclosporin 500 mg with a single dose of edoxaban 60 mg increased edoxaban AUC and C_{max} by 73% and 74%, respectively.
- *Dronedarone:* Dronedarone 400 mg twice daily for 7 days with a single concomitant dose of edoxaban 60 mg on Day 5 increased edoxaban AUC and C_{max} by 85% and 46%, respectively.
- *Erythromycin:* Erythromycin 500 mg four times daily for 8 days with a single concomitant dose of edoxaban 60 mg on Day 7 increased the edoxaban AUC and C_{max} by 85% and 68%, respectively.
- *Ketoconazole:* Ketoconazole 400 mg once daily for 7 days with a single concomitant dose of edoxaban 60 mg on Day 4, increased edoxaban AUC and C_{max} by 87% and 89%, respectively.

Lixiana 60 mg once daily is recommended during concomitant use with the following P-gp inhibitors:

- *Quinidine:* Quinidine 300 mg once daily on Days 1 and 4 and three times daily on Days 2 and 3, with a single concomitant dose of edoxaban 60 mg on Day 3, increased edoxaban AUC over 24 hours by 77% and C_{max} by 85%, respectively.
- *Verapamil:* Verapamil 240 mg once daily for 11 days with a single concomitant dose of edoxaban 60 mg on Day 10 increased the edoxaban AUC and C_{max} by approximately 53%.

Amiodarone: Co-administration of amiodarone 400 mg once daily with edoxaban 60 mg once daily increased AUC by 40% and C_{max} by 66%. This was not considered clinically significant. In ENGAGE AF-TIMI 48 study in NVAF, efficacy and safety results were similar for subjects with and without concomitant amiodarone use.

P-gp inducers

Co-administration of edoxaban with the P-gp inducer rifampicin led to a decrease in mean edoxaban AUC and a shortened half-life, with possible decreases in its pharmacodynamic effects. The concomitant use of edoxaban with other P-gp inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to reduced edoxaban plasma concentrations. Edoxaban should be used with caution when co-administered with P-gp inducers.

P-gp substrates

Digoxin: Edoxaban 60 mg once daily on days 1 to 14 with coadministration of multiple daily doses of digoxin 0.25 mg twice daily (days 8 and 9) and 0.25 mg once daily (days 10 to 14) increased the C_{max} of edoxaban by 17%, with no significant effect on AUC or renal clearance at steady state. When the effects of edoxaban on digoxin PK were also examined, the C_{max} of digoxin increased by approximately 28% and AUC by 7%. This was not considered clinically relevant. No dose modification is necessary when Lixiana is administered with digoxin.

Anticoagulants, antiplatelets, NSAIDs and SSRIs/SNRIs

Anticoagulants: Co-administration of edoxaban with other anticoagulants is contraindicated due to increased risk of bleeding (see section 4.3).

Acetylsalicylic acid (ASA): Co-administration of ASA (100 mg or 325 mg) and edoxaban increased bleeding time relative to either medicine alone. Co-administration of high dose ASA (325 mg) increased the steady state C_{max} and AUC of edoxaban by 35% and 32%, respectively. The concomitant chronic use of high dose ASA (325 mg) with edoxaban is not recommended. Concomitant administration of higher doses than 100 mg ASA should only be performed under medical supervision.

In clinical studies concomitant use of ASA (low dose $\leq$ 100 mg/day), other antiplatelet agents, and thienopyridines was permitted and resulted in approximately a 2-fold increase in major bleeding in comparison with no concomitant use, although to a similar extent in the edoxaban and warfarin groups (see section 4.4). Co-administration of low dose ASA ($\leq$ 100 mg) did not affect the peak or total exposure of edoxaban either after single dose or at steady-state.
Edoxaban can be co-administered with low dose ASA ($\leq$ 100 mg/day).

Platelet inhibitors: In ENGAGE AF-TIMI 48 concomitant use of thienopyridines (e.g. clopidogrel) monotherapy was permitted and resulted in increased clinically relevant bleeding although with a lower risk of bleeding on edoxaban compared to warfarin (see section 4.4).

There is very limited experience on the use of edoxaban with dual antiplatelet therapy or fibrinolytic agents.

NSAIDs: Co-administration of naproxen and edoxaban increased bleeding time relative to either medicine alone. Naproxen had no effect on the C_{max} and AUC of edoxaban. In clinical studies, co-administration of NSAIDs resulted in increased clinically relevant bleeding. Chronic use of NSAIDs with edoxaban is not recommended.

SSRIs/SNRIs: As with other anticoagulants the possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets (see section 4.4).

Effect of edoxaban on other medicines

Edoxaban increased the C_{max} of concomitantly administered digoxin by 28%; however, the AUC was not affected. Edoxaban had no effect on the C_{max} and AUC of quinidine.

Edoxaban decreased the C_{max} and AUC of concomitantly administered verapamil by 14% and 16%, respectively.

4.6 Fertility, pregnancy and lactation

Woman of childbearing potential
Women of childbearing potential should avoid becoming pregnant during treatment with edoxaban.

Pregnancy
Safety and efficacy of edoxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that edoxaban passes the placenta, Lixiana is contraindicated during pregnancy (see section 4.3).

Breast-feeding
Safety and efficacy of edoxaban have not been established in breast-feeding women. Data from animals indicate that edoxaban is secreted into breast milk. Therefore Lixiana is contraindicated during breast-feeding (see section 4.3). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy.

Fertility
No specific studies with edoxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

4.7 Effects on ability to drive and use machines

Lixiana has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The safety of edoxaban has been evaluated in two Phase 3 studies including 21,105 patients with NVAF (ENGAGE AF-TIMI 48 study), and 8,292 patients with VTE (DVT and PE) (Hokusai-VTE study).

The average exposure to edoxaban 60 mg (including 30 mg dose reduced) was 2.5 years among 7,012 patients in ENGAGE AF-TIMI 48 and 251 days among 4,118 patients in Hokusai-VTE.
Adverse reactions were experienced by 2,256 (32.2%) of the patients treated with edoxaban 60 mg (30 mg dose reduced) in the ENGAGE AF-TIMI 48 study and 1,249 (30.3%) in the Hokusai-VTE study.

In both studies, the most common adverse reactions related to bleeding with edoxaban 60 mg based on adjudicated terms included cutaneous soft tissue haemorrhage (up to 5.9%) and epistaxis (up to 4.7%), while vaginal haemorrhage (9.0%) was the most common bleeding-related adverse reaction in Hokusai-VTE only.

Bleeding can occur at any site and may be severe and even fatal (see section 4.4).
Common other adverse reactions for edoxaban were anaemia, rash and abnormal liver function tests.

Tabulated list of adverse reactions
Table 3 provides the list of adverse reactions from the two pivotal Phase 3 studies in patients with VTE (DVT and PE) (Hokusai-VTE study) and AF (ENGAGE AF-TIMI 48 study) combined for both indications. The adverse reactions are classified by System Organ Class and frequency, using the following convention:
Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 3: List of adverse reactions for NVAF and VTE

System Organ Class	Frequency
Blood and lymphatic system disorders	
Anaemia	Common
Thrombocytopenia	Uncommon
Immune system disorders	
Hypersensitivity	Uncommon
Anaphylactic reaction	Rare
Allergic oedema	Rare
Nervous system disorders	
Dizziness	Common
Headache	Common
Intracranial haemorrhage (ICH)	Uncommon
Subarachnoid haemorrhage	Rare
Eye disorders	
Conjunctival/Scleral haemorrhage	Uncommon
Intraocular haemorrhage	Uncommon
Cardiac disorders	
Pericardial haemorrhage	Rare
Vascular disorders	
Other haemorrhage	Uncommon
Respiratory, thoracic and mediastinal disorders	
Epistaxis	Common
Haemoptysis	Uncommon
Gastrointestinal disorders	
Abdominal pain	Common
Lower GI haemorrhage	Common
Upper GI haemorrhage	Common
Oral/Pharyngeal haemorrhage	Common
Nausea	Common
Retroperitoneal haemorrhage	Rare
Hepatobiliary disorders	
Blood bilirubin increased	Common
Gammaglutamyltransferase increased	Common
Blood alkaline phosphatase increased	Uncommon
Transaminases increased	Uncommon
Aspartate aminotransferase increased	Uncommon
Skin and subcutaneous tissue disorders	
Cutaneous soft tissue haemorrhage	Common
Rash	Common
Pruritus	Common
Urticaria	Uncommon
Musculoskeletal and connective tissue disorders	
Intramuscular haemorrhage (no compartment syndrome)	Rare

System Organ Class	Frequency
Intra-articular haemorrhage	Rare
Renal and urinary disorders	
Macroscopic haematuria/urethral haemorrhage	Common
Reproductive system and breast disorders	
Vaginal haemorrhage[1]	Common
General disorders and administration site conditions	
Puncture site haemorrhage	Common
Investigations	
Liver function test abnormal	Common
Injury, poisoning and procedural complications	
Surgical site haemorrhage	Uncommon
Subdural haemorrhage	Rare
Procedural haemorrhage	Rare

[1] Reporting rates are based on the female population in clinical trials. Vaginal bleeds were reported commonly in women under the age of 50 years, while it was uncommon in women over the age of 50 years.

Description of selected adverse reactions

Due to the pharmacological mode of action, the use of Lixiana may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 Management of bleeding). In the clinical studies mucosal bleedings (e.g. epistaxis, gastrointestinal, genitourinary) and anaemia were seen more frequently during long term edoxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see Haemorrhagic risk in section 4.4). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock.

Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for Lixiana. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

4.9 Overdose

Overdose with edoxaban may lead to haemorrhage. Experience with overdose cases is very limited.

A specific antidote antagonising the pharmacodynamic effect of edoxaban is not available.

Early administration of activated charcoal may be considered in case of edoxaban overdose to reduce absorption. This recommendation is based on standard treatment of drug overdose and data available with similar compounds, as the use of activated charcoal to reduce absorption of edoxaban has not been specifically studied in the edoxaban clinical programme.

Management of bleeding

Should a bleeding complication arise in a patient receiving edoxaban, the next edoxaban administration should be delayed or treatment should be discontinued as appropriate. Edoxaban has a half-life of approximately 10 to 14 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression

(e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

For life-threatening bleeding that cannot be controlled with the measures such as transfusion or haemostasis, the administration of a 4-factor prothrombin complex concentrate (PCC) at 50 iU/kg has been shown to reverse the effects of Lixiana 30 minutes after completing the infusion.

Recombinant factor VIIa (r-FVIIa) can also be considered. However, there is limited clinical experience with the use of this product in individuals receiving edoxaban.

Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings.

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of edoxaban.

There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving edoxaban. There is neither scientific rationale for benefit nor experience with the use of systemic haemostatics (desmopressin, aprotinin) in individuals receiving edoxaban. Due to the high plasma protein binding edoxaban is not expected to be dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antithrombotic agents, ATC code: B01AF03

Mechanism of action

Edoxaban is a highly selective, direct and reversible inhibitor of factor Xa, the serine protease located in the final common pathway of the coagulation cascade. Edoxaban inhibits free factor Xa, and prothrombinase activity. Inhibition of factor Xa in the coagulation cascade reduces thrombin generation, prolongs clotting time and reduces the risk of thrombus formation.

Pharmacodynamic effects

Edoxaban produces rapid onset of pharmacodynamic effects within 1 - 2 hours, which corresponds with peak edoxaban exposure (C_{max}). The pharmacodynamic effects measured by anti-factor Xa assay are predictable and correlate with the dose and the concentration of edoxaban. As a result of FXa inhibition, edoxaban also prolongs clotting time in tests such as prothrombin time (PT), and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests are expected at the therapeutic dose, however, these changes are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of edoxaban.

Effects of coagulation markers when switching from rivaroxaban, dabigatran, or apixaban to edoxaban

In clinical pharmacology studies, healthy subjects received rivaroxaban 20 mg once daily, dabigatran 150 mg twice daily, or apixaban 5 mg twice daily, followed by a single dose of edoxaban 60 mg on Day 4. The effect on prothrombin time (PT) and other coagulation biomarkers (e.g. anti-FXa, aPTT) was measured. Following the switch to edoxaban on Day 4 the PT was equivalent to Day 3 of rivaroxaban and apixaban. For dabigatran higher aPTT activity was observed after edoxaban administration with prior dabigatran treatment compared to that after treatment with edoxaban alone. This is considered to be due to the carry-over effect of dabigatran treatment, however, this did not lead to a prolongation of bleeding time.

Based on these data, when switching from these anticoagulants to edoxaban, the first dose of edoxaban can be initiated at the time of the next scheduled dose of the previous anticoagulant (see section 4.2).

Clinical efficacy and safety

Prevention of stroke and systemic embolism

The edoxaban clinical programme for atrial fibrillation was designed to demonstrate the efficacy and safety of two dose groups of edoxaban compared to warfarin for the prevention of stroke and systemic embolism in subjects with nonvalvular atrial fibrillation and at moderate to high risk of stroke and systemic embolic events (SEE).

In the pivotal ENGAGE AF-TIMI 48 study (an event-driven, Phase 3, multi-centre, randomised, double-blind double-dummy parallel-group study), 21,105 subjects, with a mean $CHADS_2$ score of 2.8, were randomised to either edoxaban 30 mg once daily treatment group, or edoxaban 60 mg once daily treatment group or warfarin. Subjects in both edoxaban treatment groups had their dose halved if one or more of the following clinical factors were present: moderate renal impairment (CrCL 30 – 50 mL/min), low body weight (≤ 60 kg) or concomitant use of specific P-gp inhibitors (verapamil, quinidine, dronedarone).

The primary efficacy endpoint was the composite of stroke and SEE. Secondary efficacy endpoints included: Composite of stroke, SEE, and cardiovascular (CV) mortality; major adverse cardiovascular event (MACE), which is the composite of non-fatal MI, non-fatal stroke, non-fatal SEE, and death due to CV cause or bleeding; composite of stroke, SEE, and all-cause mortality.

The median study drug exposure for both the edoxaban 60 mg and 30 mg treatment groups was 2.5 years. The median study follow-up for both the edoxaban 60 mg and 30 mg treatment groups was 2.8 years. The median subject-year exposure was 15,471, and 15,840 for the 60 mg and 30 mg treatment groups, respectively; and the median subject-year follow-up was 19,191 and 19,216 for the 60 mg and 30 mg treatment groups, respectively.

In the warfarin group, the median TTR (time in therapeutic range, INR 2.0 to 3.0) was 68.4%.

The main analysis of efficacy was aimed to show the non-inferiority of edoxaban versus warfarin on first stroke or SEE that occurred during treatment or within 3 days from the last dose taken in the modified intention-to-treat (mITT) population. Edoxaban 60 mg was non-inferior to warfarin for the primary efficacy endpoint of stroke or SEE (upper limit of the 97.5% CI of the HR was below the pre-specified non-inferiority margin of 1.38) (Table 4).

Table 4: Strokes and Systemic Embolic Events in the **ENGAGE AF–TIMI 48 Study (mITT, on-treatment)**

Primary Endpoint	**Edoxaban 60 mg (30 mg Dose Reduced) (N = 7,012)**	**Warfarin (N = 7,012)**
First Stroke/SEE[a]		
n	182	232
Event Rate (%/yr)[b]	1.18	1.50
HR (97.5% CI)	0.79 (0.63, 0.99)	
p-value for non-inferiority[c]	<0.0001	
First Ischaemic Stroke		
n	135	144
Event Rate (%/yr)[b]	0.87	0.93
HR (95% CI)	0.94 (0.75, 1.19)	
First Haemorrhagic Stroke		
n	40	76
Event Rate (%/yr)[b]	0.26	0.49
HR (95% CI)	0.53 (0.36, 0.78)	
First SEE		
n (%/yr)[a]	8 (0.05)	13 (0.08)
HR (95% CI)	0.62 (0.26, 1.50)	

Abbreviations: HR = Hazard Ratio versus warfarin, CI = Confidence Interval, n = number of events, mITT = modified Intent To Treat, N = number of subjects in mITT population, SEE = Systemic Embolic Event, yr = year.

[a] A subject can be represented in multiple rows.
[b] The event rate (%/yr) is calculated as number of events/subject-year exposure.
[c] The two-sided p-value is based on the non-inferiority margin of 1.38.

During the overall study period in the ITT population (analysis set to show superiority), adjudicated stroke or SEE occurred in 296 subjects in the edoxaban 60 mg group (1.57% per year), and 337 subjects in the warfarin group (1.80% per year). Compared to warfarin-treated subjects, the HR in the edoxaban 60 mg group was 0.87 (99% CI: 0.71, 1.07, p = 0.08 for superiority).

In subgroup analyses, for subjects in the 60 mg treatment group who were dose reduced to 30 mg in the ENGAGE AF-TIMI 48 study (for body weight ≤ 60 kg, moderate renal impairment, or concomitant use of P-gp inhibitors), the event rate was: 2.29% per year for the primary endpoint, compared to the event rate of 2.66% per year for the matching subjects in the warfarin group [HR (95% CI): 0.86 (0.66, 1.13)].

The efficacy results for pre-specified major subgroups (with dose reduction as required), including age, body weight, gender, status of renal function, prior stroke or TIA, diabetes and P-gp inhibitors were generally consistent with the primary efficacy results for the overall population studied in the trial.

The Hazard Ratio (Edoxaban 60 mg vs. warfarin) for the primary endpoint in the centres with a lower average time of INR in the target range (INR TTR) for warfarin was 0.73 – 0.80 for the lowest 3 quartiles (INR TTR ≤ 57.7% to ≤ 73.9%). It was 1.07 in centres with the best control of warfarin therapy (4th quartile with > 73.9% of INR values in the therapeutic range).

There was a statistically significant interaction between the effect of edoxaban versus warfarin on the main study outcome (stroke/SEE) and renal function (p-value 0.0042; mITT, overall study period).

Table 5 shows ischaemic strokes/SEE by creatinine clearance category in NVAF patients in ENGAGE AF-TIMI 48. There is a decreasing event rate at increasing CrCL in both treatment groups.

Table 5: Number of Ischaemic Strokes/SEE by creatinine clearance category in ENGAGE AF-TIMI 48, mITT Analysis Set Overall Study

CrCL subgroup (mL/min)	Edoxaban 60 mg (N = 7,012)			Warfarin (N = 7,012)			
	n	Number of Events	Event rate (%/year)	n	Number of Events	Event rate (%/year)	HR (95% CI)
≥ 30 to ≤ 50	1,302	63	1.89	1,305	67	2.05	0.93 (0.66, 1.31)
> 50 to ≤ 70	2,093	85	1.51	2,106	95	1.70	0.88 (0.66, 1.18)
> 70 to ≤ 90	1,661	45	0.99	1,703	50	1.08	0.92 (0.61, 1.37)
> 90 to ≤ 110	927	27	1.08	960	26	0.98	1.10 (0.64, 1.89)
> 110 to ≤ 130	497	14	1.01	469	10	0.78	1.27 (0.57, 2.85)
> 130	462	10	0.78	418	3	0.25	--*

Abbreviations: N = number of subjects; mITT population overall study period; n = number of patients in subgroup
*HR not computed if number of events < 5 in one treatment group.

Within renal function subgroups, results for the secondary efficacy endpoints were consistent with those for the primary endpoint.

Superiority testing was performed on the ITT Overall Study Period.
Stroke and SEE occurred in fewer subjects in the edoxaban 60 mg treatment group than in the warfarin group (1.57% and 1.80% per year, respectively), with a HR of 0.87 (99% CI: 0.71, 1.07, p = 0.0807 for superiority).

The pre-specified composite endpoints for the comparison of the edoxaban 60 mg treatment group to warfarin for stroke, SEE, and CV mortality HR (99% CI) was 0.87 (0.76, 0.99), MACE 0.89 (0.78, 1.00), and stroke, SEE, and all-cause mortality 0.90 (0.80, 1.01).

The results for all-cause mortality (adjudicated deaths) in the ENGAGE AF-TIMI 48 study were 769 (3.99% per year) for subjects taking edoxaban 60 mg (30 mg dose reduced) as opposed to 836 (4.35% per year) for warfarin [HR (95% CI): 0.91 (0.83, 1.01)].
All-cause mortality (adjudicated deaths) per renal subgroups (edoxaban vs. warfarin): CrCL 30 to ≤ 50 mL/min [HR (95% CI): 0.81 (0.68, 0.97)]; CrCL > 50 to < 80 mL/min [HR (95% CI): 0.87 (0.75, 1.02)]; CrCL ≥ 80 mL/min [HR (95% CI): 1.15 (0.95, 1.40)].

Edoxaban 60 mg (30 mg dose reduced) resulted in a lower rate of cardiovascular mortality compared to warfarin [HR (95% CI): 0.86 (0.77, 0.97)].
Adjudicated efficacy cardiovascular mortality per renal subgroups (edoxaban vs. warfarin): CrCL 30 to ≤ 50 mL/min [HR (95% CI): 0.80 (0.65, 0.99)]; CrCL > 50 to < 80 mL/min [HR (95% CI): 0.75 (0.62, 0.90)]; CrCL ≥ 80 mL/min [HR (95% CI): 1.16 (0.92, 1.46)].

Safety in patients with NVAF in ENGAGE AF-TIMI 48

The primary safety endpoint was major bleeding.

There was a significant risk reduction in favour of the edoxaban 60 mg treatment group compared with the warfarin group in major bleeding (2.75%, and 3.43% per year, respectively) [HR (95% CI): 0.80 (0.71, 0.91); p = 0.0009], ICH (0.39%, and 0.85% per year, respectively) [HR (95% CI): 0.47 (0.34, 0.63); p < 0.0001], and other types of bleeding (Table 6).

The reduction in fatal bleeds was also significant for the edoxaban 60 mg treatment group compared with the warfarin group (0.21%, and 0.38%) [HR (95% CI): 0.55 (0.36, 0.84); p = 0.0059 for superiority], primarily because of the reduction in fatal ICH bleeds [HR (95% CI): 0.58 (0.35, 0.95); p = 0.0312].

Table 6: Bleeding Events in ENGAGE AF-TIMI 48 Study - Safety Analysis On-Treatment

	Edoxaban 60 mg (30 mg Dose Reduced) (N = 7,012)	**Warfarin (N = 7,012)**
Major Bleeding		
n	418	524
Event rate (%/yr)[a]	2.75	3.43
HR (95% CI)	0.80 (0.71, 0.91)	
p-value	0.0009	
ICH[b]		
n	61	132
Event rate (%/yr)[a]	0.39	0.85
HR (95% CI)	0.47 (0.34, 0.63)	
Fatal Bleeding		
n	32	59
Event rate (%/yr)[a]	0.21	0.38
HR (95% CI)	0.55 (0.36, 0.84)	
CRNM Bleeding		
n	1,214	1,396
Event rate (%/yr)[a]	8.67	10.15
HR (95% CI)	0.86 (0.80, 0.93)	
Any Confirmed Bleeding[c]		
n	1,865	2,114
Event rate (%/yr)[a]	14.15	16.40
HR (95% CI)	0.87 (0.82, 0.92)	

Abbreviations: ICH = Intracranial Haemorrhage, HR = Hazard Ratio versus warfarin,
CI = Confidence Interval, CRNM = Clinically Relevant Non-Major,
n = number of subjects with events, N = number of subjects in Safety population, yr = year.

[a] The event rate (%/yr) is calculated as number of events/subject-year exposure.
[b] ICH includes primary haemorrhagic stroke, subarachnoid haemorrhage, epi-/subdural haemorrhage, and ischaemic stroke with major haemorrhagic conversion. All ICHs reported on the Adjudicated Cerebrovascular and Non-Intracranial bleed eCRF forms confirmed by the adjudicators are included in ICH counts.
[c] 'Any Confirmed Bleeding' includes those that the adjudicator defined as clinically overt.

Note: A subject can be included in multiple sub-categories if he/she had an event for those categories. The first event of each category is included in the analysis.

Tables 7, 8 and 9 show major, fatal and intracranial bleedings, respectively, by creatinine clearance category in NVAF patients in ENGAGE AF-TIMI 48. There is a decreasing event rate at increasing CrCL in both treatment groups.

Table 7: Number of Major Bleeding Events by creatinine clearance category in ENGAGE AF-TIMI 48, Safety Analysis On-Treatment[a]

CrCL subgroup (mL/min)	Edoxaban 60 mg (N = 7,012)			Warfarin (N = 7,012)			
	n	Number of Events	Event rate (%/year)	n	Number of Events	Event rate (%/year)	HR (95% CI)
≥ 30 to ≤ 50	1,302	96	3.91	1,305	128	5.23	0.75 (0.58, 0.98)
> 50 to ≤ 70	2,093	148	3.31	2,106	171	3.77	0.88 (0.71, 1.10)
> 70 to ≤ 90	1,661	108	2.88	1,703	119	3.08	0.93 (0.72, 1.21)
> 90 to ≤ 110	927	29	1.33	960	56	2.48	0.54 (0.34, 0.84)
> 110 to ≤ 130	497	20	1.70	469	24	2.14	0.79 (0.44, 1.42)
> 130	462	13	1.18	418	21	2.08	0.58 (0.29, 1.15)

Table 8: Number of Fatal Bleeding Events by creatinine clearance category in ENGAGE AF-TIMI 48, Safety Analysis On-Treatment[a]

CrCL subgroup (mL/min)	Edoxaban 60 mg (N = 7,012)			Warfarin (N = 7,012)			
	n	Number of Events	Event rate (%/year)	n	Number of Events	Event rate (%/year)	HR (95% CI)
≥ 30 to ≤ 50	1,302	9	0.36	1,305	18	0.72	0.51 (0.23, 1.14)
> 50 to ≤ 70	2,093	8	0.18	2,106	23	0.50	0.35 (0.16, 0.79)
> 70 to ≤ 90	1,661	10	0.26	1,703	9	0.23	1.14 (0.46, 2.82)
> 90 to ≤ 110	927	2	0.09	960	3	0.13	--[*]
> 110 to ≤ 130	497	1	0.08	469	5	0.44	--[*]
> 130	462	2	0.18	418	0	0.00	--[*]

Table 9: Number of Intracranial Bleeding Events by creatinine clearance category in ENGAGE AF-TIMI 48, Safety Analysis On-Treatment[a]

CrCL subgroup (mL/min)	Edoxaban 60 mg (N = 7,012)			Warfarin (N = 7,012)			
	n	Number of Events	Event rate (%/year)	n	Number of Events	Event rate (%/year)	HR (95% CI)
≥ 30 to ≤ 50	1,302	16	0.64	1,305	35	1.40	0.45 (0.25, 0.81)
> 50 to ≤ 70	2,093	19	0.42	2,106	51	1.10	0.38 (0.22, 0.64)
> 70 to ≤ 90	1,661	17	0.44	1,703	35	0.89	0.50 (0.28, 0.89)
> 90 to ≤ 110	927	5	0.23	960	6	0.26	0.87 (0.27, 2.86)
> 110 to ≤ 130	497	2	0.17	469	3	0.26	--[*]
> 130	462	1	0.09	418	1	0.10	--[*]

Abbreviations: N = number of subjects; mITT population overall study period; n = number of patients in subgroup
*HR not computed if number of events < 5 in one treatment group.
[a] On-Treatment: Time from first dose of study drug to last dose plus 3 days.

In subgroup analyses, for subjects in the 60 mg treatment group who were dose reduced to 30 mg in the ENGAGE AF-TIMI 48 study for body weight ≤ 60 kg, moderate renal impairment, or concomitant use of P-gp inhibitors, 104 (3.05% per year) of edoxaban 30 mg dose reduced subjects and 166 (4.85% per year) of warfarin dose reduced subjects had a major bleeding event [HR (95% CI): 0.63 (0.50, 0.81)].

In the ENGAGE AF-TIMI 48 study there was a significant improvement in Net Clinical Outcome (First Stroke, SEE, Major Bleed, or All-Cause Mortality; mITT population, overall study period) in favour of edoxaban, HR (95% CI): 0.89 (0.83, 0.96); p = 0.0024, when edoxaban 60 mg treatment group was compared to warfarin.

Treatment of DVT, treatment of PE and the prevention of recurrent DVT and PE (VTE)
The edoxaban clinical programme for VTE was designed to demonstrate the efficacy and safety of edoxaban in the treatment of DVT and PE, and the prevention of recurrent DVT and PE.

In the pivotal Hokusai-VTE study, 8,292 subjects were randomised to receive initial heparin therapy (enoxaparin or unfractionated heparin) followed by edoxaban 60 mg once daily or the comparator. In the comparator arm, subjects received initial heparin therapy concurrently with warfarin, titrated to a target INR of 2.0 to 3.0, followed by warfarin alone. The treatment duration was from 3 months up to 12 months, determined by the investigator based on the patient's clinical features.

The majority of edoxaban treated patients were Caucasians (69.6%) and Asians (21.0%), 3.8% were Black, 5.3% were categorised as Other race.

The duration of therapy was at least 3 months for 3,718 (91.6%) edoxaban subjects versus 3,727 (91.4%) of warfarin subjects; at least 6 months for 3,495 (86.1%) of edoxaban subjects versus 3,491 (85.6%) of warfarin subjects; and 12 months for 1,643 (40.5%) edoxaban subjects versus 1,659 (40.4%) of warfarin subjects.

The primary efficacy endpoint was the recurrence of symptomatic VTE, defined as the composite of recurrent symptomatic DVT, non-fatal symptomatic PE and fatal PE in subjects during the 12-month study period. Secondary efficacy outcomes included the composite clinical outcome of recurrent VTE and all-cause mortality.

Edoxaban 30 mg once daily was used for subjects with one or more of the following clinical factors: moderate renal impairment (CrCL 30 - 50 mL/min); body weight ≤ 60 kg; concomitant use of specific P-gp inhibitors.

In the Hokusai-VTE study (Table 10) edoxaban was demonstrated to be non-inferior to warfarin for the primary efficacy outcome, recurrent VTE, which occurred in 130 of 4,118 subjects (3.2%) in the edoxaban group versus 146 of 4,122 subjects (3.5%) in the warfarin group [HR (95% CI): 0.89 (0.70, 1.13); p < 0.0001 for non-inferiority]. In the warfarin group, the median TTR (time in therapeutic range, INR 2.0 to 3.0) was 65.6. For subjects presenting with PE (with or without DVT), 47 (2.8%) of edoxaban and 65 (3.9%) of warfarin subjects had a recurrent VTE [HR (95% CI): 0.73 (0.50, 1.06)].

Table 10: Efficacy Results from the Hokusai-VTE Study - mITT population, overall study period

Primary endpoint[a]	**Edoxaban 60 mg (30 mg Dose Reduced) (N = 4,118)**	**Warfarin (N = 4,122)**	**Edoxaban vs Warfarin HR (95% CI)[b] p-value[c]**
All subjects with symptomatic recurrent VTE[c], n (%)	130 (3.2)	146 (3.5)	0.89 (0.70, 1.13) p-value < 0.0001 (non-inferiority)
PE with or without DVT	73 (1.8)	83 (2.0)	
Fatal PE or Death where PE cannot be ruled out	24 (0.6)	24 (0.6)	
Non-fatal PE	49 (1.2)	59 (1.4)	
DVT only	57 (1.4)	63 (1.5)	

Abbreviations: CI = Confidence Interval; DVT = deep vein thrombosis; mITT = modified intent-to-treat; HR = Hazard Ratio vs. warfarin; n = number of subjects with events; N = number of subjects in mITT population; PE = pulmonary embolism; VTE = venous thromboembolic events.

[a] The primary efficacy endpoint is adjudicated symptomatic recurrent VTE (i.e., the composite endpoint of DVT, non-fatal PE, and fatal PE).
[a] The HR, two-sided CI are based on the Cox proportional hazards regression model including treatment and the following randomisation stratification factors as covariates: presenting diagnosis (PE with or without DVT, DVT only), baseline risk factors (temporary factors, all others), and the need for 30 mg edoxaban/edoxaban placebo dose at randomisation (yes/no).
[b] The p-value is for the pre-defined non-inferiority margin of 1.5.

For the subjects who were dose reduced to 30 mg (predominantly low body weight or renal function) 15 (2.1%) edoxaban and 22 (3.1%) of warfarin subjects had a recurrent VTE [HR (95% CI): 0.69 (0.36, 1.34)].

The secondary composite endpoint of recurrent VTE and all-cause mortality occurred in 138 subjects (3.4%) in the edoxaban group and 158 subjects (3.9%) in the warfarin group [HR (95% CI): 0.87 (0.70, 1.10)].

The results for all-cause mortality (adjudicated deaths) in Hokusai-VTE were 136 (3.3%) for subjects taking edoxaban 60 mg (30 mg dose reduced) as opposed to 130 (3.2%) for warfarin.

In a pre-specified subgroup analysis of PE subjects 447 (30.6%) and 483 (32.2%) of edoxaban and warfarin treated subjects, respectively, were identified as having PE and NT-proBNP $\geq$ 500 pg/mL. The primary efficacy outcome occurred in 14 (3.1%) and 30 (6.2%) of edoxaban and warfarin subjects, respectively [HR (95% CI): 0.50 (0.26, 0.94)].

The efficacy results for pre-specified major subgroups (with dose reduction as required), including age, body weight, gender and status of renal function were consistent with the primary efficacy results for the overall population studied in the trial.

Safety in patients with VTE (DVT and PE) in Hokusai-VTE

The primary safety endpoint was clinically relevant bleeding (major or clinically relevant non-major).

Table 11 summarises adjudicated bleeding events for the safety analysis set on-treatment period.
There was a significant risk reduction in favour of edoxaban compared with warfarin for the primary safety endpoint of clinically relevant bleeding, a composite of major bleeding or clinically relevant non-major bleeding (CRNM), which occurred in 349 of 4,118 subjects (8.5%) in the edoxaban group and in 423 of 4,122 subjects (10.3%) in the warfarin group [HR (95% CI): 0.81 (0.71, 0.94); p = 0.004 for superiority].

Table 11: Bleeding Events in Hokusai-VTE Study - Safety Analysis On-Treatment Period[a]

	Edoxaban 60 mg (30 mg Dose Reduced) (N = 4,118)	**Warfarin (N = 4,122)**
Clinically Relevant Bleeding (Major and CRNM)[b], n (%)		
n	349 (8.5)	423 (10.3)
HR (95% CI)	0.81 (0.71, 0.94)	
p-value	0.004 (for superiority)	
Major Bleeding n (%)		
n	56 (1.4)	66 (1.6)
HR (95% CI)	0.84 (0.59, 1.21)	
ICH fatal	0	6 (0.1)
ICH non-fatal	5 (0.1)	12 (0.3)
CRNM Bleeding		
n	298 (7.2)	368 (8.9)
HR (95% CI)	0.80 (0.68, 0.93)	
All Bleeding		
n	895 (21.7)	1,056 (25.6)
HR (95% CI)	0.82 (0.75, 0.90)	

Abbreviations: ICH = Intracranial Haemorrhage, HR = Hazard Ratio vs. warfarin; CI = Confidence Interval; N = number of subjects in safety population; n = number of events; CRNM = clinically relevant non-major

[a] On-Treatment Period: Time from first dose of study drug to last dose plus 3 days.
[b] Primary Safety Endpoint: Clinically relevant bleeding (composite of major and clinically relevant non-major bleeding).

In subgroup analyses, for subjects who were dose reduced to 30 mg in the Hokusai-VTE study for body weight ≤ 60 kg, moderate renal impairment, or concomitant use of P-gp inhibitors, 58 (7.9%) of edoxaban 30 mg dose reduced subjects and 92 (12.8%) of warfarin subjects had a major bleeding or CRNM event [HR (95%): 0.62 (0.44, 0.86)].

In the Hokusai-VTE study the Net Clinical Outcome (Recurrent VTE, Major Bleed, or All-Cause Mortality; mITT population, overall study period) HR (95% CI) was 1.00 (0.85, 1.18) when edoxaban was compared to warfarin.

Patients undergoing cardioversion

A multicentre, prospective, randomised, open-label study with blinded endpoint evaluation (ENSURE-AF) was conducted which randomised 2199 subjects (oral anticoagulant naïve and pre-treated) with non-valvular atrial fibrillation scheduled for cardioversion, to compare edoxaban 60 mg once daily with enoxaparin/warfarin to maintain a therapeutic INR of 2.0 to 3.0 (randomised 1:1), mean TTR on warfarin was 70.8%. A total of 2149 subjects were treated with either edoxaban (N = 1067) or enoxaparin/warfarin (N = 1082). Subjects in the edoxaban treatment group received 30 mg once daily if one or more of the following clinical factors were present: moderate renal impairment (CrCL 30 – 50 mL/min), low body weight (≤ 60 kg) or concomitant use of specific P-gp inhibitors. The majority of subjects in the edoxaban and warfarin groups had cardioversion performed (83.7% and 78.9%, respectively) or were auto-converted (6.6% and 8.6%, respectively). TEE-guided (within 3 days of initiation) or conventional cardioversion (at least 21 days of pre-treatment) was employed. Subjects were maintained on treatment for 28 days post cardioversion.

The primary efficacy outcome consisted of a composite of all stroke, SEE, MI and CV mortality. A total of 5 (0.5%, 95% CI 0.15% - 1.06%) events occurred in subjects in the edoxaban group (N = 1095) and 11 (1.0%, 95% CI 0.50% - 1.78%) events in the warfarin group (N = 1104); OR 0.46 (95% CI 0.12 - 1.43); ITT analysis set overall study period with mean duration of 66 days.

The primary safety outcome was a composite of major and CRNM bleeding. A total of 16 (1.5%, 95% CI 0.86% - 2.42%) events occurred in subjects in the edoxaban (N = 1067) group and 11 (1.0%, 95% CI 0.51% - 1.81%) events in the warfarin (N = 1082) group; OR 1.48 (95% CI 0.64 - 3.55); safety analysis set on-treatment period.

This exploratory study showed low rates of major and CRNM bleeding and thromboembolism in the two treatment groups in the setting of cardioversion.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with edoxaban in one or more subsets of the paediatric population in prevention of arterial thrombosis, treatment of thromboembolism and prevention of thromboembolism (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Edoxaban is absorbed with peak plasma concentrations within 1 - 2 hours. The absolute bioavailability is approximately 62%. Food increases peak exposure to a varying extent, but has minimal effect on total exposure. Edoxaban was administered with or without food in the ENGAGE AF-TIMI 48 and the Hokusai-VTE studies. Edoxaban is poorly soluble at pH of 6.0 or higher. Co-administration of proton-pump inhibitors had no relevant impact on edoxaban exposure.

Distribution

Disposition is biphasic. The volume of distribution is 107 (19.9) L mean (SD).
In vitro plasma protein binding is approximately 55%. There is no clinically relevant accumulation of edoxaban (accumulation ratio 1.14) with once daily dosing. Steady state concentrations are achieved within 3 days.

Biotransformation

Unchanged edoxaban is the predominant form in plasma. Edoxaban is metabolised via hydrolysis (mediated by carboxylesterase 1), conjugation or oxidation by CYP3A4/5 (< 10%). Edoxaban has three active metabolites, the predominant metabolite (M-4), formed by hydrolysis, is active and reaches less than 10% of the exposure of the parent compound in healthy subjects. Exposure to the other metabolites is less than 5%. Edoxaban is a substrate for the efflux transporter P-glycoprotein (P-gp), but not a substrate for uptake transporters such as organic anion transporter polypeptide OATP1B1, organic anion transporters OAT1 or OAT3 or organic cation transporter OCT2. Its active metabolite is a substrate for OATP1B1.

Elimination

In healthy subjects, the total clearance is estimated as 22 (± 3) L/hour; 50% is renally cleared (11 L/hour). Renal clearance accounts for approximately 35% of the administered dose. Metabolism and biliary/intestinal excretion account for the remaining clearance. The $t_{½}$ for oral administration is 10 - 14 hours.

Linearity/non-linearity

Edoxaban displays approximately dose-proportional pharmacokinetics for doses of 15 mg to 60 mg in healthy subjects.

Special populations

Elderly

After taking renal function and body weight into account, age had no additional clinically significant effect on edoxaban pharmacokinetics in a population pharmacokinetic analysis of the pivotal Phase 3 study in NVAF (ENGAGE AF-TIMI 48).

Gender
After accounting for body weight, gender had no additional clinically significant effect on edoxaban pharmacokinetics in a population pharmacokinetic analysis of the Phase 3 study in NVAF (ENGAGE AF-TIMI 48).

Ethnic origin
In a population pharmacokinetic analysis of the ENGAGE AF-TIMI 48 study, peak and total exposure in Asian patients and non-Asian patients were comparable.

Renal impairment
The plasma AUCs for subjects with mild (CrCL > 50 - 80 mL/min), moderate (CrCL 30 - 50 mL/min) and severe (CrCL < 30 mL/min but not undergoing dialysis) renal impairment were increased by 32%, 74%, and 72%, respectively, relative to subjects with normal renal function. In patients with renal impairment the metabolite profile changes and a higher quantity of active metabolites are formed.
There is a linear correlation between edoxaban plasma concentration and anti-FXa activity regardless of renal function.
Subjects with ESRD undergoing peritoneal dialysis had 93% higher total exposure compared with healthy subjects.
Population PK modeling indicates that exposure approximately doubles in patients with severe renal impairment (CrCL 15 – 29 mL/min) relative to patients with normal renal function.

Anti-FXa activity by CrCL category
Table 12 below shows the edoxaban anti-Factor Xa activity by CrCL category for each indication.

Table 12: Edoxaban Anti-FXa activity by creatinine clearance

Edoxaban Dose	**CrCL (mL/min)**	**Edoxaban Anti-FXa activity post-dose (IU/mL)[1]**	**Edoxaban Anti-FXa activity pre-dose (IU/mL)[2]**
	Median [2.5 – 97.5% range]		
Prevention of stroke and systemic embolism: NVAF			
30 mg QD	≥ 30 to ≤ 50	2.92 [0.33 – 5.88]	0.53 [0.11 – 2.06]
60 mg QD*	> 50 to ≤ 70	4.52 [0.38 – 7.64]	0.83 [0.16 – 2.61]
	> 70 to ≤ 90	4.12 [0.19 – 7.55]	0.68 [0.05 – 2.33]
	> 90 to ≤ 110	3.82 [0.36 – 7.39]	0.60 [0.14 – 3.57]
	> 110 to ≤ 130	3.16 [0.28 – 6.71]	0.41 [0.15 – 1.51]
	> 130	2.76 [0.12 – 6.10]	0.45 [0.00 – 3.10]
Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTE)			
30 mg QD	≥ 30 to ≤ 50	2.21 [0.14 – 4.47]	0.22 [0.00 – 1.09]
60 mg QD*	> 50 to ≤ 70	3.42 [0.19 – 6.13]	0.34 [0.00 – 3.10]
	> 70 to ≤ 90	2.97 [0.24 – 5.82]	0.24 [0.00 – 1.77]
	> 90 to ≤ 110	2.82 [0.14 – 5.31]	0.20 [0.00 – 2.52]
	> 110 to ≤ 130	2.64 [0.13 – 5.57]	0.17 [0.00 – 1.86]
	> 130	2.39 [0.10 – 4.92]	0.13 [0.00 – 2.43]

*Dose reduction to 30 mg for low body weight ≤ 60 kg or specific concomitant P-glycoprotein (P-gp) inhibitors
[1] Post-dose is equivalent to C_{max} (post-dose samples were drawn 1 – 3 hours after edoxaban administration)
[2] Pre-dose is equivalent to C_{min}

Although treatment with edoxaban does not require routine monitoring, the effect on anticoagulation can be estimated by a calibrated quantitative anti-Factor Xa assay which may be useful in exceptional situations where knowledge of edoxaban exposure may help to inform clinical decisions, e.g. overdose and emergency surgery (see also section 4.4).

Haemodialysis
A 4 hour haemodialysis session reduced total edoxaban exposures by less than 9%.

Hepatic impairment
Patients with mild or moderate hepatic impairment exhibited comparable pharmacokinetics and pharmacodynamics to their matched healthy control group. Edoxaban has not been studied in patients with severe hepatic impairment (see section 4.2).

Body weight
In a population pharmacokinetic analysis of the ENGAGE AF-TIMI 48 study in NVAF, C_{max} and AUC in patients with median low body weight (55 kg) were increased by 40% and 13%, respectively, as compared

with patients with median high body weight (84 kg). In Phase 3 clinical studies (both NVAF and VTE indications) patients with body weight ≤ 60 kg had a 50% edoxaban dose reduction and had similar efficacy and less bleeding when compared to warfarin.

Pharmacokinetic/pharmacodynamic relationship(s)
PT, INR, aPTT and Anti-factor Xa correlate linearly with edoxaban concentrations.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, or phototoxicity.

Reproductive toxicology
Edoxaban showed vaginal haemorrhage at higher doses in rats and rabbits but had no effects in the reproductive performance of parent rats.

In rats, no effects on male or female fertility were seen.

In animal reproduction studies, rabbits showed increased incidence of gallbladder variations at a dosage of 200 mg/kg which is approximately 65 times the maximum recommended human dose (MRHD) of 60 mg/day based on total body surface area in mg/m^2. Increased post-implantation pregnancy losses occurred in rats at 300 mg/kg/day (approximately 49 times the MRHD) and in rabbits at 200 mg/kg/day (approximately 65 times the MRHD) respectively.

Edoxaban was excreted in the breast milk of lactating rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Mannitol (E421)
Pregelatinised starch
Crospovidone
Hydroxypropylcellulose
Magnesium stearate (E470b)

Film-coat:

Hypromellose (E464)
Macrogol 8000
Titanium dioxide (E171)
Talc
Carnauba wax
15 mg and 60 mg film-coated tablets: Iron oxide yellow (E172)
15 mg and 30 mg film-coated tablets: Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to outer box

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

15 mg film-coated tablets: PVC/Aluminium blisters. Cartons of 14 film-coated tablets
30 mg and 60 mg film-coated tablets: PVC/Aluminium blisters. Cartons of 28 film coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

15 mg film-coated tablets: 1C 104/59(NC)
30 mg film-coated tablets: 1C 105/59(NC)
60 mg film-coated tablets: 1C 106/59(NC)

9. MANUFACTURER

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10. DATE OF AUTHORISATION

2 December 2016

11. DATE OF REVISION OF THE TEXT

August 2019