PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrLIXIANA®

Edoxaban Tablets (as edoxaban tosylate monohydrate)

15 mg, 30 mg and 60 mg film-coated tablets

Anticoagulant

SERVIER CANADA INC.
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Canada

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LIXIANA®

Edoxaban Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet 15 mg, 30 mg and 60 mg	Carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, iron oxide red (30 mg tablets and 15 mg tablets), iron oxide yellow (60 mg tablets and 15 mg tablets), magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized starch, talc, titanium dioxide

INDICATIONS AND CLINICAL USE

LIXIANA (edoxaban) is indicated for:

- Prevention of stroke and systemic embolic events in patients with atrial fibrillation, in whom anticoagulation is appropriate.

- Treatment of venous thromboembolism (VTE) (deep vein thrombosis [DVT], pulmonary embolism [PE]) and the prevention of recurrent DVT and PE.

Geriatrics (≥ 65 years of age):
Clinical studies in stroke prevention in patients with atrial fibrillation (SPAF), treatment of VTE and prevention of recurrent DVT and PE, included patients ≥ 65 years of age (see WARNINGS AND PRECAUTIONS- Table 1, DOSAGE AND ADMINISTRATION, and CLINICAL TRIALS).

Pediatrics < 18 years of age:
The safety and efficacy of LIXIANA in children under the age of 18 years have not yet been established. Therefore, use of LIXIANA is not recommended in these patients.

CONTRAINDICATIONS

The use of LIXIANA is contraindicated in the following conditions:

- Clinically significant active bleeding, including gastrointestinal bleeding

- Lesions or conditions at increased risk of clinically significant bleeding, e.g., recent cerebral infarction (hemorrhagic or ischemic), active peptic ulcer disease with recent bleeding, patients with spontaneous or acquired impairment of hemostasis

- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see ACTION AND CLINICAL PHARMACOLOGY, Hepatic Impairment)

- Concomitant treatment with any other anticoagulant, including
    - unfractionated heparin (UFH), except at doses used to maintain a patent central venous or arterial catheter,
    - low molecular weight heparins (LMWH), such as enoxaparin and dalteparin,
    - heparin derivatives, such as fondaparinux, and
    - oral anticoagulants, such as warfarin, dabigatran, apixaban, rivaroxaban except under circumstances of switching therapy to or from LIXIANA.

- Pregnancy (See WARNING AND PRECAUTIONS-Special Populations, Pregnant Women)

- Nursing Women (See WARNING AND PRECAUTIONS-Special Populations, Pregnant Women)

- Hypersensitivity to edoxaban or to any ingredients of the formulation. For a complete listing of ingredients see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

PREMATURE DISCONTINUATION OF ANY ORAL ANTICOAGULANT, INCLUDING LIXIANA, INCREASES THE RISK OF THROMBOTIC EVENTS.

To reduce this risk, consider coverage with another anticoagulant if LIXIANA is discontinued for a reason other than pathological bleeding or completion of a course of therapy (see DOSAGE AND ADMINISTRATION)**.**

The following Warnings and Precautions are listed in alphabetical order.

Bleeding

LIXIANA increases the risk of bleeding and can cause serious, potentially fatal bleeding. Promptly evaluate any signs or symptoms of blood loss. Discontinue LIXIANA in patients with clinically significant active bleeding. LIXIANA, like other anticoagulants, must be used with caution in patients with any increased risk of bleeding. Patients at high risk of bleeding should not be prescribed LIXIANA (see CONTRAINDICATIONS).

Should severe bleeding occur, treatment with LIXIANA must be discontinued and the source of bleeding investigated promptly.

Close clinical surveillance (looking for signs of bleeding or anemia) is recommended throughout the treatment period, especially in the presence of multiple risk factors for bleeding (see Table 1 below).

Table 1 – Factors Which Increase Hemorrhagic Risk

Factors increasing edoxaban plasma levels*	Severe renal impairment (CrCl 15-29 mL/min) Moderate renal impairment (CrCl 30 – 50 mL/min)
	Concomitant systemic treatment with P-gp inhibitors
	Low body weight ≤ 60 kg
Pharmacodynamic interactions	Chronic use of NSAIDs
	Platelet aggregation inhibitors, including ASA, clopidogrel, prasugrel, ticagrelor
Diseases / procedures with special hemorrhagic risks	Congenital or acquired coagulation disorders
	Thrombocytopenia or functional platelet defects
	Active ulcerative gastrointestinal disease
	Recent gastrointestinal bleeding
	Recent intracranial hemorrhage or ischemia
	Recent brain, spinal or ophthalmological surgery
Others	Age > 75 years

* (see DOSAGE AND ADMINISTRATION) for dose reductions

Coadministration with Anticoagulants, Antiplatelets, and Thrombolytics
Concomitant use of drugs affecting hemostasis may increase the risk of bleeding. These include antiplatelet agents, such as aspirin (ASA), $P2Y_{12}$ platelet inhibitors, other antithrombotic agents, fibrinolytic therapy and chronic nonsteroidal anti-inflammatory drugs (NSAIDs). Long term concomitant treatment with LIXIANA and other anticoagulants is therefore not recommended due to increased risk of bleeding. Short term co-administration may be needed for patients transitioning to or from LIXIANA (see DOSAGE AND ADMINISTRATION).

Concomitant use of LIXIANA with unfractionated heparin (UFH) is not recommended except at doses used to maintain a patent central venous or arterial catheter.

In clinical studies with LIXIANA, concomitant use of low dose (≤ 100 mg/day) ASA or thienopyridines (clopidogrel), and NSAIDs resulted in increased rates of clinically relevant bleeding. Other platelet aggregation inhibitors such as prasugrel and ticagrelor, have not been studied with LIXIANA in any patient population, and are **not** recommended as concomitant therapy (see DRUG INTERACTIONS).

Cardiovascular

Valvular Disease
Safety and efficacy of LIXIANA have not been studied in patients with prosthetic (mechanical or biological) heart valves or those with hemodynamically significant rheumatic heart disease, especially mitral stenosis. Therefore LIXIANA is not recommended in these patients. Of note, the ENGAGE AF-TIMI 48 study that evaluated LIXIANA in SPAF, has included patients with other valvular heart disease (e.g. aortic stenosis, aortic and or mitral regurgitation) (see CLINICAL TRIALS).

Cardioversion
Patients can be maintained on LIXIANA while being cardioverted.

Hepatic/Biliary Impairment

Hepatic Impairment
Patients with significant liver disease (e.g., acute hepatitis, chronic active hepatitis, cirrhosis) were excluded from clinical trials of LIXIANA. Therefore, LIXIANA is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.

LIXIANA has not been studied in patients with severe hepatic impairment; therefore it is not recommended. LIXIANA should be used with caution in patients with mild to moderate hepatic impairment (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Monitoring and Laboratory Tests

A specific anticoagulant reversal agent for LIXIANA is not commercially available.

The pharmacodynamic effects measured by anti-factor Xa (FXa) assay are predictable and correlate with the dose and the concentration of LIXIANA. As a result of FXa inhibition, LIXIANA also prolongs clotting time in tests such as prothrombin time (PT), and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests at the expected therapeutic dose, however, are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of LIXIANA.

Although LIXIANA therapy will lead to an elevated INR, depending on the timing of the measurement, the INR is not a valid measure to assess the anticoagulant activity of LIXIANA (see DOSAGE AND ADMINISTRATION, Switching from LIXIANA to VKA, Considerations for INR Monitoring of VKA Activity during Concomitant LIXIANA Therapy). The INR is only calibrated and validated for vitamin K antagonists (VKA) and should not be used for any other anticoagulant, including LIXIANA.

Although there is no need to monitor anticoagulation effect of LIXIANA during routine clinical practice, in certain infrequent situations such as overdosage, acute bleeding, urgent surgery, in cases of suspected non-compliance, or in other unusual circumstances, assessment of the anticoagulant effect of LIXIANA may be appropriate. Accordingly, a calibrated quantitative anti-FXa assay may be useful to inform clinical decisions in these circumstances (See ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics, Table 10**)** for predicted steady-state peak and trough anti-FXa activity in different indications and for different doses of LIXIANA).

Renal

Renal Impairment

Plasma concentration of LIXIANA is increased with the degree of renal impairment. Therefore renal function: CrCL should be monitored at the beginning of the treatment in all patients and afterwards when clinically indicated. There are limited data in patients with severe renal impairment (CrCl<30 mL/min) or on dialysis as these patients were excluded from pivotal Phase III trials. Therefore, LIXIANA is not recommended in these patients. Patients who develop acute renal failure while on LIXIANA should discontinue such treatment (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Peri-Operative/ Procedural Considerations

As with any anticoagulant, patients on LIXIANA who undergo surgery or invasive procedures are at increased risk for bleeding. In these circumstances, temporary discontinuation of LIXIANA may be required.

Pre-Operative Phase

If an invasive procedure or surgical intervention is required, LIXIANA should be stopped at least 24 hours before the intervention, if possible, due to increased risk of bleeding, and based on clinical judgment of the physician. If the procedure cannot be delayed, the increased risk of bleeding should be assessed against the urgency of the intervention. Although there are limited data in patients at higher risk of bleeding or in major surgery where complete hemostasis may be required, consider stopping LIXIANA at least 48 hours before surgery, depending on clinical circumstances. LIXIANA should be restarted after surgery or interventional procedures as soon

as it has been determined that adequate hemostasis has been established.

Peri-Operative Spinal/Epidural Anesthesia, Lumbar Puncture
When neuraxial (epidural/spinal) anesthesia or spinal puncture is performed, patients treated with antithrombotics for prevention of thromboembolic complications are at risk for developing an epidural or spinal hematoma that may result in long-term neurological injury or permanent paralysis.

The risk of these events is even further increased by the use of indwelling catheters or the concomitant use of drugs affecting hemostasis. Accordingly, indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of LIXIANA. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, the administration of LIXIANA should be delayed for 24 hours.

Patients who have undergone epidural puncture and who are receiving LIXIANA should be frequently monitored for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel or bladder dysfunction). If neurological deficits are noted, urgent diagnosis and treatment is necessary.

The physician should consider the potential benefit versus the risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis and use LIXIANA only when the benefits clearly outweigh the possible risks. An epidural catheter should not be withdrawn earlier than 24 hours after the last administration of LIXIANA.

Post-Procedural Period
LIXIANA should be restarted following an invasive procedure or surgical intervention as soon as adequate hemostasis has been established and the clinical situation allows, in order to avoid unnecessary increased risk of thrombosis.

Orthopedic Surgery
LIXIANA is not recommended for the prevention of VTE in patients who have undergone elective total Knee or hip surgery, since the safety and efficacy of LIXIANA have not been established in these clinical situations.

Pulmonary

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 LIXIANA have not been established in these clinical situations.

Special Populations

Pregnant Women
No data are available on the use of LIXIANA in pregnant women. Based on animal data, use of

LIXIANA is contraindicated throughout pregnancy (see CONTRAINDICATIONS, and TOXICOLOGY- Reproductive Toxicology and Lactation).

If LIXIANA is to be used in women of childbearing potential, pregnancy should be avoided.

The safety and effectiveness of LIXIANA during labor and delivery have not been studied in clinical studies. The risk for pregnancy-related hemorrhage and/or emergent delivery is increased with the use of an anticoagulant that is not readily reversible.

Animal reproductive and development toxicity studies showed maternal and embryo-fetal toxicities in rats and rabbits at higher doses. Reproductive performance was unaffected in both rats and rabbits (see TOXICOLOGY).

Nursing Women
No data are available on the use of LIXIANA in nursing mothers. In a non-clinical study, LIXIANA was excreted in the breast milk of rats. LIXIANA should only be administrated after breastfeeding is discontinued (see TOXICOLOGY-Reproductive Toxicology and Lactation).

It is not known if LIXIANA or its metabolites are excreted in human milk. Because many drugs are excreted in human milk caution should be exercised and a decision made whether to discontinue breastfeeding or discontinue LIXIANA, taking into account the importance of the drug to the mother.

Pediatrics (< 18 years of age)
The safety and efficacy of LIXIANA in children under age 18 years have not been yet established. Therefore, use of LIXIANA is not recommended in these patients.

Geriatrics (> 65 years of age)
No change in dose is generally required based on age (see ACTION AND CLINICAL PHARMACOLOGY).

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. Therefore, use of LIXIANA is not recommended in these patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

SPAF
In the pivotal double-blind randomized ENGAGE AF-TIMI 48 study, a total of 21,026 subjects with documented atrial fibrillation (AF) received at least one dose of LIXIANA 60 mg (N=7012), LIXIANA 30 mg (N=7002), or warfarin (N=7012). The duration of LIXIANA exposure was ≥360 days for 11,479 subjects and ≥720 days for 10,075 subjects. Median study drug exposure for the LIXIANA and warfarin treatment group was 2.5 years.

In the ENGAGE AF-TIMI 48 study, 2256 (32.2%) of the subjects treated with LIXIANA 60 mg (30 mg dose-reduced) experienced adverse reactions. Non-endpoint adverse events resulted in study drug discontinuation in 11.2% and 11.0% of the subjects in the LIXIANA 60 mg, and the warfarin treatment groups, respectively.

Treatment of VTE and Prevention of Recurrent DVT and PE

In the pivotal double-blind randomized HOKUSAI-VTE study, subjects with acute, symptomatic DVT involving the popliteal, femoral or iliac veins, or PE requiring anticoagulant therapy were treated with LIXIANA (N=4118) or warfarin (N=4122) after a heparin-based initial treatment of ≥5 days. These 8240 subjects comprised the safety population. The median time on treatment was 8.8 months in both groups. The duration of drug exposure for LIXIANA was ≤ 6 months for 1561 (37.9%) of subjects, > 6 months for 2557 (62.1%) of subjects and 12 months for 1661 (40.3%) of subjects.

In the HOKUSAI-VTE study, in total, 1249 (30.3%) of the subjects treated with LIXIANA 60 mg (30 mg dose-reduced) experienced adverse reactions. The frequency of non-endpoint adverse events resulting in permanent study drug discontinuation was 5.7% in the LIXIANA group and 5.4% in the warfarin group.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Bleeding Events

The most notable adverse reactions reported with LIXIANA were related to bleeding. Bleeding of any type of severity occurred at a rate of 14.2 % per year among subjects with AF treated with LIXIANA in the ENGAGE-AF TIMI 48 study and in 21.7 % in the HOKUSAI-VTE study. Bleeding can occur at any site and may be severe, life-threatening, and even fatal (see WARNINGS AND PRECAUTIONS).

In both studies, the most common adverse reactions related to bleeding with LIXIANA 60 mg (30 mg dose-reduced) group included cutaneous soft tissue hemorrhage (≤ 5.9%) and epistaxis (≤ 4.7%), while vaginal hemorrhage (9.0%) was the most common bleeding-related adverse reaction in HOKUSAI-VTE study only.

Since the patient populations treated with LIXIANA for different indications are not interchangeable, a summary description of major and total bleeding is provided by indication and pivotal trial below.

ENGAGE AF-TIMI 48 study

Table 2 - Adjudicated Bleeding Events in SPAF Patients, ENGAGE AF-TIMI 48 study

	LIXIANA 60mg (30mg dose-reduced) (N=7012)	Warfarin (N=7012)	LIXIANA 60mg (30mg dose-reduced) vs Warfarin	
Bleeding Category - First Event	**n (%/yr) [a]**	**n (%/yr) [a]**	**HR (95% CI)**	**p-value**
Major[b]	418 (2.75)	524 (3.43)	0.80 (0.707, 0.914)	0.0009
ICH[c]	61 (0.39)	132 (0.85)	0.47 (0.344, 0.631)	<0.0001
Gastrointestinal	232 (1.51)	190 (1.23)	1.23 (1.019, 1.496)	0.0311
Fatal	32 (0.21)	59 (0.38)	0.55 (0.355, 0.840)	0.0059
ICH[c]	24 (0.15)	42 (0.27)	0.58 (0.349, 0.951)	0.0312
Non-ICH	8 (0.05)	17 (0.11)	0.47 (0.204, 1.095)	0.0804
CRNM [d]	1214 (8.67)	1396 (10.15)	0.86 (0.795, 0.927)	0.0001
Any Confirmed Bleeds[e]	1865 (14.15)	2114 (16.40)	0.87 (0.816, 0.924)	<0.0001

Abbreviations: CI = Confidence Interval; ICH = Intracranial Hemorrhage; HR = Hazard Ratio versus Warfarin; yr = year; CRNM = Clinically Relevant Non-Major

Note: Adjudicated bleeding events include events during treatment or within 3 days of stopping study treatment.

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

[a]: The event rate (%/yr) is calculated as # of events/subject-year exposure.

[b]: A Major Bleeding event (the study primary safety endpoint) was defined as clinically overt bleeding that met one of the following criteria: fatal bleeding; symptomatic bleeding in a critical site such as retroperitoneal, intracranial, intraocular, intraspinal, intra-articular, pericardial, or intramuscular with compartment syndrome; a clinically overt bleeding event that caused a fall in hemoglobin of at least 2.0 g/dL (or a fall in hematocrit of at least 6.0% in the absence of hemoglobin data), when adjusted for transfusions (1 unit of transfusion = 1.0 g/dL drop in hemoglobin).

[c]: ICH includes primary hemorrhagic stroke, subarachnoid hemorrhage, epi/subdural hemorrhage, and ischemic stroke with major hemorrhagic conversion.

[d]: CRNM (Clinically Relevant Non-Major bleeding) was defined as an overt bleeding event that required medical attention, including those that may have resulted in diagnostic or therapeutic measures.

[e]: Any Confirmed Bleed includes those that the adjudicator defined as clinically overt.

The site of major bleeds was mostly in the gastrointestinal (GI) tract, followed by intracranial, and intra-ocular. There were more Major GI bleeds in the LIXIANA 60 mg (30 mg dose-reduced) group than the warfarin group (1.5% and 1.2% per year, respectively).

A higher proportion of LIXIANA treated patients reported anemia related events; 8.2% (578/7012) of the 60 mg patients (30 mg dose-reduced) as compared to 5.6 % (396/7012) of warfarin treated patients. Similarly, more anemia and anemia-related events were reported to be serious or severe for LIXIANA 60 mg (30 mg dose-reduced) group (1.4%) compared to the warfarin group (0.7%). The majority of the bleeding events occurring in LIXIANA 60 mg (30 mg dose-reduced) treated patients with either serious or severe anemia/anemia-related events were from the GI tract. A number of risk factors have been identified to increase the risk of bleeding which may result in post hemorrhagic anemia (see WARNINGS AND PRECAUTIONS- Table 1) and are associated with dose adjustments (see DOSAGE AND

ADMINISTRATION).

The percentage of subjects who discontinued study drug due to Investigator-reported bleeding events was 3.9% and 4.1%, respectively, for the LIXIANA 60 mg (30 mg dose-reduced) and the warfarin treatment groups.

HOKUSAI-VTE study

Table 3 - Adjudicated Bleeding Events in VTE Patients, HOKUSAI-VTE Study

Adjudicated Bleeding	LIXIANA 60mg (30mg dose-reduced) N=4118	Warfarin N=4122	LIXIANA vs. Warfarin	
			HR (95% CI)	p-value
Major/CRNM Bleeding, n (%)	349 (8.5)	423 (10.3)	0.81 (0.705, 0.936) [a]	0.0040 [a]
ICH, n (%)	5 (0.1)	18 (0.4)	-	-
Gastrointestinal, n (%)	98 (2.4)	94 (2.3)	-	-
Major Bleeding, n (%) [b]	56 (1.4)	66 (1.6)	0.84 (0.592, 1.205) [a]	0.3521 [a]
ICH, n (%)	5 (0.1)	18 (0.4)	-	-
Fatal ICH, n (%)	0 (0)	6 (0.1)	-	-
Gastrointestinal, n (%)	27 (0.7)	18 (0.4)	-	-
All Bleeding, n (%)	895 (21.7)	1056 (25.6)	0.82 (0.750, 0.896)	<0.0001

Abbreviations: CI = Confidence Interval, CRNM = Clinically Relevant Non-Major, HR = Hazard Ratio vs. Warfarin, ICH: intracranial hemorrhage; N = number of subjects in analysis set, n = number of subjects meeting event criteria.

Note: Adjudicated bleeding events include events during treatment or within 3 days of stopping study treatment.

[a] The HR and two-sided CI are based on the Cox proportional hazards regression model including treatment and the following randomization 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 LIXIANA/LIXIANA placebo dose at randomization (yes, no), p-value α =0.01 [two-sided].

[b] A Major Bleeding event was defined as clinically overt bleeding that met one of the following criteria: associated with a fall in hemoglobin level of 2.0 g/dL or more, or leading to transfusion of two or more units of packed red cells or whole blood; occurring in a critical site or organ: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; contributing to death.

The percentage of subjects who discontinued study drug due to Investigator-reported bleeding events was 1.4% in both groups.

Most Common Adverse Drug Reaction

The most common non-bleeding treatment-emergent adverse reactions reported in the ENGAGE AF-TIMI 48 Study for LIXIANA 60 mg (30 mg dose-reduced) group versus warfarin were rash (4.2% vs 4.1%), and abnormal liver function tests (4.8% vs. 4.6%), respectively. Results are presented below in Table 4.

Table 4 - Common Adverse Drug Reactions observed in ≥ 1% of LIXIANA-treated Patients in ENGAGE AF-TIMI 48 Study

	LIXIANA 60 mg (30 mg Dose -Reduced) N = 7012 n (%)[a]	Warfarin N = 7012 n (%)[a]
Respiratory, Thoracic and Mediastinal Disorders		
Epistaxis	392 (2.6)	359 (2.4)
Gastrointestinal Disorders		
Lower GI haemorrhage	411 (2.7)	264 (1.7)
Upper GI haemorrhage	187 (1.2)	144 (0.9)
Skin and Subcutaneous Tissue Disorders		
Cutaneous soft tissue haemorrhage	577 (3.8)	947 (6.6)
Renal and Urinary Disorders		
Macroscopic hematuria/urethral	293 (1.9)	255 (1.7)
Blood and Lymphatic System Disorders		
Anaemia	368 (5.2)	242 (3.5)
Skin and subcutaneous tissue disorders		
Rash	295 (4.2)	147 (4.1)
Investigations		
Liver function test abnormal	337 (4.8)	326 (4.6)

[a] Summary of adjudicated bleeding events by location (%/year).

The most common treatment-emergent adverse drug reactions in the HOKUSAI-VTE Study are presented below in Table 5.

Table 5 - Common Adverse Reactions observed in ≥ 1% of LIXIANA-treated Patients in HOKUSAI-VTE Study

	LIXIANA 60 mg (30 mg Dose-Reduced) N = 4118 n (%)[a]	**Warfarin N = 4122 n (%)[a]**
Respiratory, Thoracic And Mediastinal Disorders		
Epistaxis	195 (4.7)	237 (5.7)
Gastrointestinal Disorders		
Lower GI haemorrhage	141 (3.4)	126 (3.1)
Oral/Pharyngeal haemorrhage	138 (3.4)	162 (3.9)
General		
Puncture site haemorrhage	56 (1.4)	99 (2.4)
Skin and Subcutaneous Tissue Disorders		
Cutaneous soft tissue haemorrhage	245 (5.9)	414 (10.0)
Rash	147 (3.6)	151 (3.7)
Renal and Urinary Disorders		
Macroscopic hematuria/urethral	91 (2.2)	117 (2.8)
Reproductive System and Breast Disorders		
Vaginal haemorrhage	158 (9.0)	126 (7.1)
Blood and Lymphatic System Disorders		
Anaemia	72 (1.7)	55 (1.3)
Investigations		
Liver function test abnormal	322 (7.8)	322 (7.8)

[a] Summary of adjudicated bleeding events by location (%). For gender specific category (vaginal bleeding) the event rate is based on the gender specific subject numbers

Less Common Clinical Trial Adverse Drug Reactions (<1%) *(Not otherwise reported)*

ENGAGE AF-TIMI 48
Eye Disorders: Intraocular haemorrhage
Cardiac Disorders: Pericardial haemorrhage
Respiratory, Thoracic and Mediastinal Disorders: Haemoptysis, Interstitial Lung Disease
Gastrointestinal Disorders: Oral/Pharyngeal haemorrhage, Retroperitoneal haemorrhage
Musculoskeletal and Connective Tissue Disorders: Intramuscular (no compartment syndrome), Intra-articular haemorrhage
Reproductive System and Breast Disorders: Vaginal haemorrhage
Vascular: Other haemorrhage (including subconjunctival, ear, pleural)
General: Puncture site haemorrhage
Injury, Poisoning and Procedural Complications: Surgical site haemorrhage

Hokusai VTE
Eye Disorders: Conjunctival/Scleral haemorrhage, Intraocular haemorrhage
Cardiac Disorders: Pericardial haemorrhage
Respiratory, Thoracic and Mediastinal Disorders: Haemoptysis
Musculoskeletal and Connective Tissue Disorders: Intramuscular (no compartment syndrome), Intra-articular haemorrhage
Vascular: Other haemorrhage (including surgical site, pleural)
Injury, Poisoning and Procedural Complications: Subdural haemorrhage, Procedural haemorrhage

DRUG INTERACTIONS

Overview
In vitro studies indicate that edoxaban is a substrate of p-glycoprotein (P-gp) transporter; therefore its plasma concentration may increase in the presence of P-gp inhibitors such as cyclosporine, dronedarone, erythromycin, or ketoconazole (see Table 6). Edoxaban does not inhibit the major cytochrome P450 enzymes (CYP1A2, 2A6, 2B6, 2C8/9, 2C19, 2D6, 2E1, or 3A4) and does not induce CYP1A2, CYP3A4 or the P-gp transporter (MDR1). *In vitro* data also indicate that edoxaban does not inhibit the following transporters at clinically relevant concentrations: P-gp, the organic anion transporters OAT1 or OAT3; the organic cation transporters OCT1 or OCT2; or the organic ion transporting polypeptides OATP1B1 or OATP1B3.

Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 6 - Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
P-gp Inhibitors/Substrates			
Cyclosporine	CT	Concurrent administration of a single dose of cyclosporine 500 mg with a single dose of LIXIANA 60 mg increased LIXIANA AUC and C_{max} by 73% and 74%, respectively.	Concomitant use of LIXIANA with this drug requires dose reduction to 30 mg once daily.
Dronedarone	CT	Dronedarone 400 mg twice daily for 7days with a single concomitant dose of LIXIANA 60 mg on Day 5 increased LIXIANA AUC and C_{max} by 85% and 46%, respectively.	Concomitant use of LIXIANA with this drug requires dose reduction to 30 mg once daily.
Erythromycin	CT	Erythromycin 500 mg four times daily for 8 days with a single concomitant dose of LIXIANA 60 mg on Day 7 increased the LIXIANA AUC and C_{max} by 85% and 68%, respectively.	Concomitant use of LIXIANA with this drug requires dose reduction to 30 mg once daily.
Ketoconazole	CT	Ketoconazole 400 mg once daily for 7days with a single concomitant dose of LIXIANA 60 mg on Day 4, increased LIXIANA AUC and C_{max} by 87% and 89%, respectively.	Concomitant use of LIXIANA with this drug requires dose reduction to 30 mg once daily.
Quinidine	CT	Quinidine 300mg once daily on Days 1 and 4 and three times daily on Days 2 and 3, with a single concomitant dose of LIXIANA 60 mg on Day 3, increased LIXIANA AUC over 24 hours by 77% and C_{max} by 85% respectively. LIXIANA had no effect on the C_{max} and AUC of quinidine.	Concomitant use of LIXIANA with this drug requires dose reduction to 30 mg once daily.

Proper name	Ref	Effect	Clinical comment
Verapamil	CT	Verapamil 240 mg once daily for 11 days with a single concomitant dose of LIXIANA 60 mg on Day 10 increased the LIXIANA AUC and C_{max} by approximately 50%. LIXIANA decreased the C_{max} and AUC of concomitantly administered verapamil by 14% and 16%, respectively.	No dose adjustment is required. Use with caution in taking into account specific individual patient characteristic.
Amiodarone	CT	Amiodarone 400 mg once daily for 4 days with a single dose of LIXIANA 60 mg on Day 4 increased the LIXIANA AUC and Cmax approximately 40% and 66%, respectively, Amiodarone was not at steady state in this study.	No dose adjustment is required. Use with caution in taking into account specific individual patient characteristic.
CYP 3A4 and P-gp Inducers			
Rifampicin	CT	Rifampicin 600 mg once daily for 7 days with a single dose of LIXIANA 60 mg on Day 7 decreased the AUC of LIXIANA by 34% without an apparent effect on $C_{max.}$	Combined use with strong CYP3A4 and P-gp inducers (e.g. phenytoin, carbamazepine and phenobarbital) should generally be avoided, since efficacy of LIXIANA may be compromised.
P-gp Substrates			
Digoxin	CT	Multiple daily doses of digoxin 0.25 mg with co-administration of LIXIANA 60 mg one daily for Days 8-14 increased the C_{max} of LIXIANA by 17%, with no significant effect on AUC or renal clearance at steady-state. LIXIANA increased the C_{max} of concomitantly administered digoxin by 28%; however, the AUC was not affected.	No dose modification is necessary when LIXIANA is administered with digoxin.

Proper name	Ref	Effect	Clinical comment
CYP3A4 Inhibitors and Inducers	CT	Less than 10% of an orally administered LIXIANA dose is metabolised via CYP3A4 in subjects with normal renal function. Therefore, no interaction is anticipated with CYP3A4 inhibitors or inducers.	No dose modification is necessary for patients taking CYP inhibitors or inducers.
Proton-Pump Inhibitors (PPIs)			
Esomeprazole	CT	Esomeprazole 40 mg once daily for 5 days with a single concomitant dose of LIXIANA 60 mg on Day 5 had no effect on the AUC of LIXIANA but the C_{max} decreased by approximately 33%.	No dose modification is necessary when LIXIANA is administered with esomeprazole.
Anticoagulants	CT, T	A single subcutaneous dose of 1 mg/kg enoxaparin did not have an effect on the PK of a single oral dose of LIXIANA 60 mg when administered concomitantly or within 12 hours of each other.	Co-administration of LIXIANA with other anticoagulants is contraindicated due to increased risk of bleeding (see CONTRAINDICATION)
Platelet Inhibitors			
Acetylsalicylic acid (ASA)	CT	Co-administration of ASA (100 mg or 325 mg) and LIXIANA 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 LIXIANA by 35% and 32%, respectively. In clinical studies concomitant use of ASA (low dose ≤100 mg/day) was permitted and resulted in increased clinically relevant bleeding although with a lower risk of bleeding on LIXIANA compared to warfarin (see WARNINGS AND PRECAUTIONS).	LIXIANA can be co-administered with low-dose ASA (≤ 100 mg/day). Assess bleeding risk before co-administration, and use with caution, if deemed necessary.

Proper name	Ref	Effect	Clinical comment
Thienopyridines (e.g. Clopidogrel)	CT	In ENGAGE AF-TIMI 48 there was very limited experience on the use of LIXIANA with dual antiplatelet therapy or fibrinolytic agents.	Concomitant use of drugs affecting hemostasis may increase the risk of bleeding. Use with caution, if deemed necessary.
NSAIDs			
Naproxen	CT	Co-administration of naproxen and LIXIANA increased bleeding time relative to either medicine alone. Naproxen had no effect on the C_{max} and AUC of LIXIANA. In clinical studies, co-administration of NSAIDs resulted in increased clinically relevant bleeding.	Chronic use of NSAIDs with LIXIANA is not recommended. Short term use should be used with caution, if deemed necessary.
Other medications			
Atorvastatin	CT	Atorvastatin 80 mg once daily for 8 days with a single concomitant dose of LIXIANA 60 mg on Day 7 decreased the C_{max} or AUC of edoxaban by 15%.	Use with caution in taking into account specific individual patient characteristic.
HIV protease inhibitors, e.g. darunavir/ ritonavir, lopinavir/ritonavir	T	No specific drug-drug interaction has been performed with HIV protease inhibitors in combination with edoxaban. HIV protease inhibitors can inhibit P-gp (besides CYP3A) and potentially increase edoxaban exposure by 1.5 to 2-fold.	Used with caution, if deemed necessary.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions
LIXIANA can be taken with or without food.

Drug-Herb Interactions
Drug-herb interactions have not been established.

Drug-Laboratory Interactions
Drug-lab interactions have not been established.

Drug-Lifestyle Interactions
LIXIANA has no or negligible influence on the ability to drive and use machines.

DOSAGE AND ADMINISTRATION

Dosing Consideration

As for any non-vitamin K antagonist oral anticoagulant (NOAC) drug, before initiating LIXIANA, ensure that the patient understands and is prepared to accept adherence to NOAC therapy, as directed.

LIXIANA should be taken regularly, as prescribed, to ensure optimal effectiveness. All temporary discontinuations should be avoided, unless medically indicated.

Determine estimated creatinine clearance (eCrCl) in all patients before instituting LIXIANA, and monitor renal function during LIXIANA treatment, as clinically appropriate. Determination of renal function by eCrCL should occur at least once per year, and especially during circumstances when renal function may be expected to be compromised, ie, acute myocardial infarction (AMI), acute decompensated heart failure (AHF), increased use of diuretics, dehydration, hypovolemia, etc. Clinically relevant deterioration of renal function may require dosage adjustment or discontinuation of LIXIANA (see below, *Renal Impairment*).

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:

in males: $\frac{\text{(140-age) (years) x weight (kg) x 1.23}}{\text{serum creatinine (µmol/L)}}$ or, $\frac{\text{(140-age) (yrs) x weight (kg)}}{\text{72 x serum creatinine (mg/100 mL)}}$

in females: $\frac{\text{(140-age) (years) x weight (kg) x 1.04}}{\text{serum creatinine (µmol/L)}}$ or, $\frac{\text{(140-age) (yrs) x weight (kg) x 0.85}}{\text{72 x serum creatinine (mg/100 mL)}}$

Recommended Dose and Dosage Adjustment

SPAF
The usual recommended dose of LIXIANA is 60 mg once daily.

Treatment of VTE and Prevention of Recurrent DVT and PE
The recommended dose of LIXIANA is 60 mg once daily following initial use of a parenteral anticoagulant for 5-10 days.

The duration of therapy should be individualized after careful assessment of the treatment benefit against the risk of bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. surgery, trauma, immobilisation), while extended duration should be based on permanent risk factors or idiopathic DVT or PE.

Dose reductions for SPAF and VTE
The recommended dose of LIXIANA is 30 mg once daily in patients with one or more of the following clinical factors:

- Moderate renal impairment (creatinine clearance (CrCL) 30- 50 mL/min

- Low body weight ≤ 60 kg (132 lbs)
- Concomitant use of P-gp inhibitors except amiodarone and verapamil.

Table 7 - Summary Dosing in SPAF and VTE (DVT and PE)

Summary Guide for Dosing	
SPAF: Recommended dose	60 mg once daily
VTE: Recommended dose	60 mg once daily (following initial use of heparin)
Renal Impairment*:* Moderate (CrCL 30 - 50 mL/min) Low Body Weight: ≤ 60 kg, or P-gp Inhibitors except amiodarone and verapamil	30 mg once daily

Renal impairment

There are limited data in patients with severe renal impairment (CrCl<30 mL/min) or on dialysis as these patients were excluded from pivotal Phase III trials. Therefore, LIXIANA is not recommended in these patients (see WARNINGS AND PRECAUTIONS - Renal).

Table 8 - Summary Posology in Renal Impairment for SPAF and VTE

Renal Status	**Creatinine Clearance (CrCL) mL/min**	**LIXIANA Dose Once Daily**
Mild	50-80	60 mg
Moderate	30-50	30 mg
Severe Renal Disease or on Dialysis	<30	Not recommended (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

Hepatic impairment

In patients with mild to moderate hepatic impairment the recommended dose of LIXIANA is 60 mg once daily (see ACTION AND CLINICAL PHARMACOLOGY).

LIXIANA has not been studied in patients with severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY). Therefore, its use in these patients is not recommended.

LIXIANA is contraindicated in patients with hepatic disease associated with intrinsic coagulation abnormalities (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

Elderly Population
No dose reduction is generally required. Increasing age may be associated with declining renal function (see ACTION AND CLINICAL PHARMACOLOGY).

Switching to and from LIXIANA
Continued anticoagulant therapy is important in patients with SPAF and in the treatment of VTE. There may be situations that warrant a change in anticoagulation therapy.

Table 9 – Recommendation For Switching To And From LIXIANA

Switching from:	**TO LIXIANA**
Vitamin K Antagonist (VKA)	Discontinue the VKA and start LIXIANA when the international normalised ratio (INR) is ≤ 2.5.
Oral anticoagulants other than VKA	Discontinue the non-VKA oral anticoagulant and start LIXIANA at the time of the next non-VKA dose (see CLINICAL TRIALS)
Subcutaneous anticoagulant	Discontinue subcutaneous anticoagulant and start LIXIANA at the time of the next scheduled subcutaneous anticoagulant dose.
Unfractionated heparin	Discontinue the infusion and start LIXIANA 4 hours later.
Switching from LIXIANA	**TO:**
	VKA oral option: Administer a LIXIANA dose of 30 mg (15 mg for patients on a reduced dose for one or more of the following: moderate to severe renal impairment (CrCL 15– 50 mL/min), low body weight, or use with P-gp inhibitors (except amiodarone and verapamil), together with an appropriate VKA dose. INR must be measured at least weekly and just prior to the daily dose of LIXIANA to minimize the influence of LIXIANA on INR measurements. Once a stable INR of ≥ 2.0 is achieved, LIXIANA must be discontinued.
	VKA 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 must be discontinued and the VKA continued.
	Oral anticoagulants other than VKA: Discontinue LIXIANA and start the non-VKA anticoagulant at the time of the next scheduled dose of LIXIANA.
	Parenteral anticoagulants: Discontinue LIXIANA and start the parenteral anticoagulant at the time of the next scheduled dose of LIXIANA.

Missed Dose
If a dose of LIXIANA is missed, the dose must be taken as soon as possible on the same day. The dose of LIXIANA must not be doubled to make up for a missed dose. Return to normal dosing schedule the next day.

OVERDOSAGE

Overdose with LIXIANA may lead to hemorrhage. Experience with overdose cases is very limited. In cases of overdose, depending on the clinical situation LIXIANA must be stopped or the next dose delayed, taking the half-life (t½) of LIXIANA (10-14 hours) into account.

In cases of bleeding, initiate appropriate measures such as packed red blood cells and/or hemostasis.

A specific reversal agent for LIXIANA is not available. Although not evaluated in patients, 3-factor or 4-factor prothrombin complex concentrate (PCC), activated prothrombin complex concentrates (aPCCs), or recombinant Factor VIIa could be considered for the reversal of the anticoagulant effect of LIXIANA.

4-factor prothrombin complex concentrate (PCC): In healthy subjects, the administration of 4-factor PCC at 50 IU/kg reversed the anticoagulant effect of LIXIANA within 30 minutes after completing the infusion.

3-factor PCC: In healthy volunteers, a 3-factor PCC restored thrombin generation but did not normalize PT.

In animal models PCC, aPCC, and recombinant Factor VIIa agents have reversed coagulation biomarkers and bleeding.

The following are not expected to reverse the anticoagulant effects of LIXIANA: protamine sulfate, vitamin K, and tranexamic acid.

Hemodialysis does not significantly contribute to LIXIANA clearance.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

Pharmacodynamics

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

Table 10 - Predicted edoxaban steady state exposure and anti-FXa activity

ENGAGE-AF	**Edoxaban Cmin (ng/mL)**	**Edoxaban Cmax (ng/mL)**	**Edoxaban Anti-FXa activity Min[a] (IU/mL)**	**Edoxaban Anti-FXa activity Max[b], (IU/mL)**
Median (2.5^{th} –97.5^{th} percentile)				
Edoxaban 60 mg full dose	27.3 (14.6 – 45.5)	217 (129 – 302)	0.65 (0.11 – 3.50)	3.96 (0.23 – 8.0)
Edoxaban dose reduced to 30 mg	21.0 (10.2 – 30.7)	143 (91.1 - 198)	0.53 (0.05 – 2.15)	2.88 (0.24 – 6.15)
HOKUSAI VTE	**Edoxaban Cmin (ng/mL)**	**Edoxaban Cmax (ng/mL)**	**Edoxaban Anti-Xa activity Min[c], (IU/mL)**	**Edoxaban Anti-Xa activity Max[d], (IU/mL)**
Median (2.5^{th} –97.5^{th} percentile)				
Edoxaban 60 mg full dose	15.2 (8.37 –31.1)	211 (135 – 296)	0.28 (0.10 – 2.73)	2.79 (0.21 – 5.67)
Edoxaban dose reduced to 30 mg	11.7 (4.55 – 23.5)	141 (91.9 – 190)	0.26 (0.10 – 1.66)	1.95 (0.19 – 4.98)

[a] In ENGAGE-AF Edoxaban Anti-Xa activity Min was assessed on day 29 pre-dose
[b] In ENGAGE-AF Edoxaban Anti-Xa activity Max was assessed on day 29 post-dose
[c] For HOKUSAI-VTE Edoxaban Anti-Xa activity Min was assessed over 3 months, pre-dose
[d] For HOKUSAI-VTE Edoxaban Anti-Xa activity Max was assessed over 3 months, post-dose

Effects on coagulation markers when switching from rivaroxaban, dabigatran, and apixaban to LIXIANA

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 LIXIANA 60 mg on Day 4. Following the switch to LIXIANA on Day 4, effects on PT, aPTT, and anti-FXa (rivaroxaban, or apixaban) were comparable to those seen when LIXIANA was dosed alone for 4 days. After switching to LIXIANA from dabigatran, aPTT values were comparable to those seen on dabigatran. Based on these data, the first dose of LIXIANA can be initiated at the next scheduled dose of the previous anticoagulant.

Variants of the Vitamin K epoxide reductase complex subunit 1(VKORC1) and CYP2C9 genes that are known to affect warfarin sensitivity had no effect on bleeding in patients treated with LIXIANA.

Effects on coagulation markers when switching from Warfarin to LIXIANA

In a double-blind study after a single 60 mg dose of edoxaban administered 24 h after the last warfarin dose, mean INR values increased from 2.25 (24 h time point) to peak levels of approximately 3.7. Mean INR values then decreased and attained levels close to the mean pre-dose value at approximately 12 h post dose (36 h).

Pharmacokinetics

Table 11 - Summary of Pharmacokinetic Parameters in Healthy Subjects (Single-Dose)

	C_{max}	$t_{½}$ (h)	$AUC_{0-\infty}$	Clearance	Volume of distribution
Single dose mean	309 ± 97 ng/mL	10 - 14	63.1±12.5 % (arithmetic mean ±SD)	21.8±3.03 L/h	107 ±19.9 L

Absorption

Edoxaban is absorbed with peak plasma concentrations attained within 1-2 hours. The absolute bioavailability is 62%. Food increases peak exposure to varying degrees, but has minimal effect on total exposure. LIXIANA 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. It is predominantly absorbed in the upper GI tract. Thus, drugs or disease conditions that increase the stomach pH or increase gastric emptying and gut motility have the possibility of reducing edoxaban dissolution and absorption. However, co-administration of proton pump inhibitors (esomeprazole) did not impact edoxaban exposure (see DRUG INTERACTIONS).

Distribution

Disposition is biphasic. The mean volume of distribution is 107 ±19.9 L (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.

Metabolism
Unchanged edoxaban is the predominant form in plasma. There is minimal metabolism (<10%) via hydrolysis (mediated by carboxylesterase 1), conjugation or oxidation by CYP3A4. The predominant metabolite (M-4), formed by hydrolysis is active and reaches < 10% of the exposure of the parent compound in healthy subjects. Exposure to the other metabolites is < 5%.

Excretion
In healthy subjects, edoxaban is cleared both through metabolism and as unchanged drug in urine and feces. Renal clearance (11 L/hour) of unchanged drug contributes approximately 50% to total clearance (22 L/hour) with the remaining 50% non-renal clearance occurring through metabolism and biliary secretion. The t½ 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.

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

Special Populations and Conditions

Geriatrics
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 subjects ≥ 75 years of age in the ENGAGE AF-TIMI 48 study.

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

Race
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.

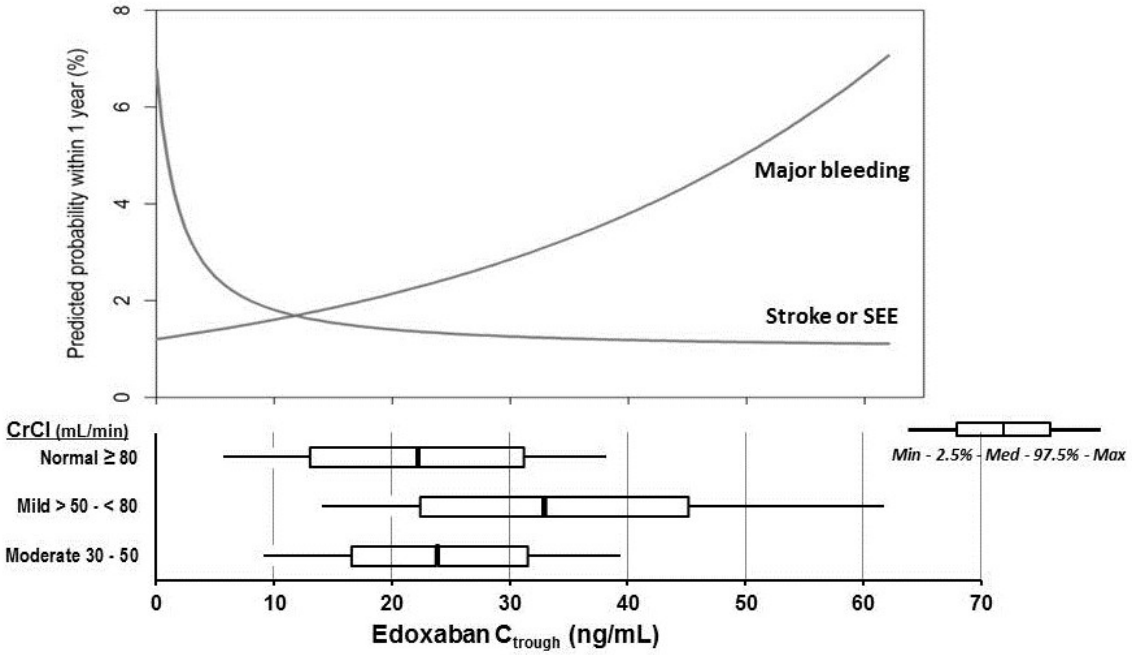
Hepatic Insufficiency
Patients with mild or moderate hepatic impairment (classified as Child Pugh A or Child Pugh B) exhibited comparable pharmacokinetics and pharmacodynamics to their matched healthy control group. LIXIANA has not been studied in patients with severe hepatic impairment (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency
50% of unchanged edoxaban is eliminated by the kidney and the plasma AUCs for subjects with mild (50-80 mL/min), moderate (30-50 mL/min) and severe (<30 mL/min but not undergoing dialysis) renal impairment were increased by 32%, 74%, and 72%, respectively, relative to subjects with normal renal function. 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.

Predicated efficacy and safety responses in patients with different renal function based on modeling and simulation is shown in figure below. Figure 1 describes the modeled relationship between drug exposure and outcomes.The two curves represent the average predicted probability of a stroke/SEE or major bleeding event given an average ENGAGE AF patient, i.e. using the mean age (72 years), and weighted with the probability of risk factors for stroke/SEE (prior stroke/TIA versus no prior stroke/TIA) or major bleeding (concomitant use aspirin/antiplatelet agent (ASA) or no concomitant use of ASA). The exposure response modelling predicts minimal differences in efficacy within the range of LIXIANA concentrations noted in the renal function groups, but predicts a significant increase in major bleeding over this same range. The therapeutic implications of using these data in monitoring patients on edoxaban have not been established in clinical trials.

Figure 1 - Predicted Efficacy and Safety Response for average AF Patient



Note: Edoxaban trough concentrations were predicted using population PK modelling; concentrations immediately before outcomes were not available.
Horizontal bars represent model predicted Ctrough in normal renal function (edoxaban dose 60 mg), mild renal impairment (edoxaban dose 60 mg) and moderate renal impairment (edoxaban dose 30 mg).

Hemodialysis
A 4 hour hemodialysis session reduced total LIXIANA exposures by less than 7%.

Genetic Polymorphism
Variants of the ABCB1 gene, which encodes P-gp, had no effect on LIXIANA pharmacokinetics in healthy subjects.

Low Body Weight
In a population pharmacokinetic analysis of the ENGAGE AF-TIMI 48 study, Cmax 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 SPAF and VTE indications), patients with body weight ≤ 60 kg had a 50% LIXIANA dose reduction and had consistent efficacy and safety outcomes with the overall results.

Table 12 - Summary of LIXIANA's Pharmacokinetic and Pharmacodynamics in sub-groups of interest in ENGAGE AF TIMI 48 Study

Edoxaban 60 mg (30 mg Dose-reduced)	**Edoxaban C_{trough} (ng/mL)**	**Edoxaban Anti-FXa activity Min[a] (IU/mL)**	**Edoxaban Anti-FXa activity Max[b] (IU/mL)**
	Median [2.5-97.5%]		
Edoxaban 60 mg full dose	27.3 [14.6 – 45.5]	0.65 (0.11, 3.56)	3.96 (0.22, 8.0)
Edoxaban dose reduced to 30 mg (due to single or multiple factors)	21.0 [10.2 – 30.7]	0.53 (0.05, 2.16)	2.88 (0.24, 6.20)
Renal function by CrCL at baseline			
30-50 mL/min*	23.7 [16.5 – 31.5]	0.56 (0.05, 2.12)	2.80 (0.24, 6.40)
>50-80 mL/min	32.8 [22.4 – 45.2]	0.74 (0.05, 3.32)	4.34 (0.23, 8.00)
>80 mL/min	22.1 [13.0 – 31.2]	0.51 (0.05, 3.92)	3.44 (0.19, 7.60)
Weight ≤60 Kg only*	19.6 [9.43 – 30.9]	0.43 (0.05, 2.52)	3.20 (0.31, 6.40)
Concomitant use of P-gp inhibitors only*	17.2 [9.24 – 32.4]	0.63 (0.05, 3.32)	3.28 (0.19, 8.00)
CrCL≤50 and P-gp	27.2 [15.7 – 36.7]	1.22 (0.24, 2.52)	3.52 (1.81, 6.52)
Weight ≤60 Kg and P-gp	22.4 [13.5 – 36.6]	0.66 (0.05, 2.52)	3.52 (0.24, 5.88)
North America	26.2 [14.1 – 45.0]	0.69 (0.11, 2.12)	3.44 (0.33, 7.96)
Age ≥75 years	28.2 [15.1 – 46.6]	0.68 (0.05, 2.56)	3.52 (0.28, 8.00)
Fragile patients**	26.1 [15.2 – 49.3]	0.63 (0.05, 2.16)	3.18 (0.24, 8.00)

*dose reduced to 30 mg
** Fragile patients defined as ≥80 years, weight ≤50 kg, CrCL ≤50 ml/min and or history of fall

[a] In ENGAGE-AF Edoxaban Anti-Xa activity Min was assessed on day 29 pre-dose
[b] In ENGAGE –AF Edoxaban Anti-Xa activity Max was assessed on day 29 post-dose

STORAGE AND STABILITY

Store at controlled room temperature 15°C-30°C.

Keep in a safe place out of the reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

No special requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

LIXIANA is available for oral administration as a 60 mg, 30 mg, or 15 mg round shaped, film-coated tablet, debossed with product identification markings.

The inactive ingredients are: carnauba wax, crospovidone, hydroxypropyl cellulose, magnesium stearate, mannitol, pregelatinized starch, talc.

The color coatings contain hypromellose, iron oxide red (30 mg tablets and 15 mg tablets), iron oxide yellow (60 mg tablets and 15 mg tablets), polyethylene glycol 8000, talc, titanium dioxide.

60 mg Tablets:
Film-coated, yellow, round-shaped, debossed with “DSC L60”.

Each 60 mg tablet contains 80.82 mg edoxaban tosylate monohydrate equivalent to 60 mg of edoxaban.

30 mg Tablets:
Film-coated, pink, round-shaped, debossed with “DSC L30”.

Each 30 mg tablet contains 40.41 mg edoxaban tosylate monohydrate equivalent to 30 mg of edoxaban.

15 mg Tablets:
Film-coated, orange round-shaped, debossed with “DSC L15”.

Each 15 tablet contains 20.2 mg edoxaban tosylate monohydrate equivalent to 15 mg of edoxaban.

LIXIANA tablets are supplied in HDPE bottles containing 7, 30, 90 or 500 tablets each and PVC/AL blisters with 7 or 10 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

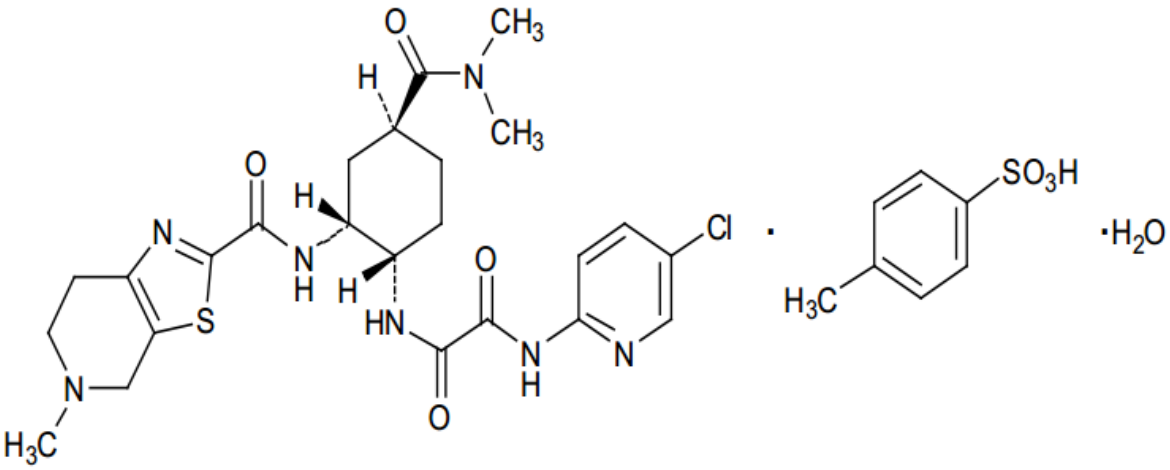
Drug Substance

Proper name: edoxaban tosylate monohydrate

Chemical name: *N*-(5-Chloropyridin-2-yl)-*N*′-[(1*S*,2*R*,4*S*)-4-(*N*,*N*-dimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydro[1,3]thiazolo[5,4-*c*]pyridine-2-carboxamido)cyclohexyl] oxamide mono (4-methylbenzenesulfonate) monohydrate

Molecular formula and molecular mass: $C_{24}H_{30}ClN_7O_4S \cdot C_7H_8O_3S \cdot H_2O$, 738.27 g/mol

Structural formula:



Physicochemical properties:

It is a white to pale yellowish-white crystalline powder. The solubility of edoxaban tosylate (pKa 6.7) decreases with increasing pH. It is slightly soluble in water, pH 3 to5 buffer, very slightly soluble at pH 6 to 7; and practically insoluble at pH 8 to 9.

CLINICAL TRIALS

Prevention of stroke and systemic embolism in patients with Atrial Fibrillation (SPAF): The ENGAGE- AF TIMI 48 Study

Trial Design and Study Demographics

The LIXIANA clinical programme for atrial fibrillation was designed to demonstrate the efficacy and safety of two dose regimens of LIXIANA compared to warfarin for the prevention of stroke and systemic embolism events (SEE) in subjects with nonvalvular atrial fibrillation and at moderate to high risk of stroke and 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 (21,026 of whom received study drug), with a mean $CHADS_2$ score of 2.8, were randomised to receive either LIXIANA 30 mg (15 mg dose-reduced) once daily, LIXIANA 60 mg (30 mg dose-reduced) once daily treatment group or warfarin. Subjects in both LIXIANA groups had their dose halved, if one or more of the following clinical factors, known to increase drug exposure, were present at randomisation or during the trial: moderate renal impairment (CrCL30 – 50 mL/min), low body weight (≤ 60 kg) or concomitant use of specific P-gp inhibitors (verapamil, quinidine, dronedarone). The most common reason for dose reduction was a CrCL ≤ 50 mL/min at randomization (19% of patients).

Table 13 - Summary of patient demographics for clinical trials in SPAF

Trial design	Dosage, route of administration and duration	Study subjects (n = number)[b]	Mean age (Range) years	Gender (M/F) %
Randomized, double-blind, double dummy, parallel group, active controlled	LIXIANA[a]: 30 mg QD PO	n = 7002	70.6 (27 – 95)	61.2/38.8
	LIXIANA[a]: 60 mg QD PO	n = 7012	70.6 (25 – 96)	62.1/37.9
	Warfarin: QD PO Dose adjusted to maintain INR between 2.0 and 3.0	n = 7012	70.5 (27 – 95)	62.5/37.5
	Median duration of treatment 2.5 years	Total = 21,026		

AF = atrial fibrillation, QD = once daily

[a] Dose reduction (30 mg to 15 mg QD; 60 mg to 30 mg QD) for moderate renal impairment, low body weight, or specified concomitant medications

[b] all treated patients receiving the drug or within 3 days from the last dose taken

Patients were well balanced with respect to demographic and baseline characteristics. The percentages of patients age ≥ 75 years and ≥ 80 years were approximately 40% and 17%, respectively. Concomitant diseases of patients in this study included hypertension (94%), congestive heart failure (58%), and prior stroke or transient ischemic attack (28%). At baseline, approximately 30% of patients were on aspirin and approximately 2% of patients were taking a thienopyridine.

Patients were excluded if they had a creatinine clearance <30 mL/min, significant liver disease, cancer, active bleeding, acute coronary syndrome or percutaneous coronary intervention (PCI) (within the previous 30 days). Patients with prosthetic heart valves, or those with hemodynamically significant rheumatic heart disease, especially mitral stenosis, were also excluded from the study, and thus were not evaluated. Of note, approximately 20% of patients had other valvular heart disease including aortic stenosis, aortic regurgitation, and/or mitral regurgitation. Patients with a history of mitral valve repair were not excluded from the study.

The primary efficacy endpoint was the composite of stroke and systemic embolic events (SEE) that occurred during treatment or within 3 days from the last dose taken (mITT-on treatment-See Table 14 for definition). Secondary efficacy endpoints included: Composite of stroke, SEE, and cardiovascular mortality (CV); 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 LIXIANA 60 mg and 30 mg treatment groups was 2.5 years. The median study follow-up for both the LIXIANA 60 mg and 30 mg treatment groups was 2.8 years.

Efficacy in SPAF

In the ENGAGE AF-TIMI 48 study both LIXIANA 30 mg and 60 mg group regimens were non-inferior to warfarin for the primary efficacy endpoint with the upper boundary of the 97.5% CI below the pre-specified non-inferiority margin of 1.38. However, the 30 mg regimen was numerically less effective than warfarin for the primary endpoint, and was also markedly inferior in reducing the rate of ischemic stroke (Table 14).

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

Table 14 - Efficacy Results from ENGAGE AF-TIMI 48 Study (mITT analysis set on-treatment)

Primary Endpoint	LIXIANA 30 mg (15 mg Dose-Reduced) (N=7002)	LIXIANA 60 mg (30 mg Dose-Reduced) (N = 7,012)	Warfarin (N= 7,012)
First Stroke or SEE[a]			
n (%/yr)[b]	253 (1.61)	182 (1.18)	232 (1.5)
HR (97.5% CI)	1.07 (0.874, 1.314)	0.79 (0.632, 0.985)	
p-value[c]	0.0055	<0.0001	
First Ischemic Stroke			
n (%/yr)[b]	226 (1.43)	135 (0.87)	144 (0.93)
HR (95% CI)	1.54 (1.253, 1.903)	0.94 (0.746, 1.193)	
First Haemorrhagic Stroke			
n (%/yr)[b]	18 (0.11)	40 (0.26)	76 (0.49)
HR (95% CI)	0.23 (0.139, 0.389)	0.53 (0.362, 0.778)	
First SEE			
n (%/yr)[a]	11 (0.07)	8 (0.05)	13 (0.08)
HR (95% CI)	0.83 (0.370, 1.850)	0.62 (0.257, 1.497)	

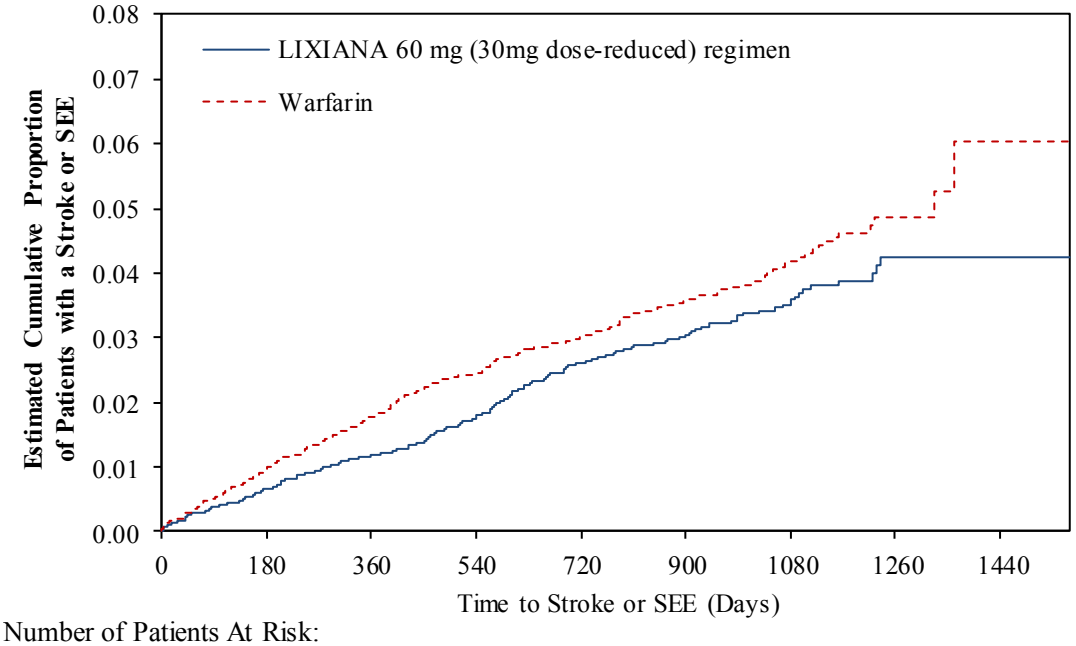
Abbreviations: HR= Hazard Ratio versus warfarin, CI= Confidence Interval, n = number of events, mITT = Modified Intent-to-treat, N = number of subjects in mITT population, SEE= Systemic Embolic Event, yr= year.

Note: The mITT population included only subjects who received at least one dose of drug; and the on- treatment period was the period during which the subject took study drug unless the patient had early drug discontinuation(s) in which case the on-treatment period included the 3 days following drug discontinuation(s).

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

Subjects who received LIXIANA 30 mg (dose reduced subjects in the 60 mg group) had an event rate of 1.79% per year for the primary endpoint, compared with an event rate of 2.21% per year for the matching dose reduced subjects in the warfarin group. Compared to warfarin-treated subjects, the HR in the LIXIANA 30 mg (dose reduced subjects in the 60 mg group) was 0.81 (95% CI: 0.58, 1.13).

Figure 2 - Kaplan-Meier Curve Estimate of Cumulative Event Rates for Primary Endpoint (first occurrence of stroke or SEE) (mITT analysis set - on Treatment Study Period) in the ENGAGE AF-TIMI 48 study



Number of Patients At Risk:

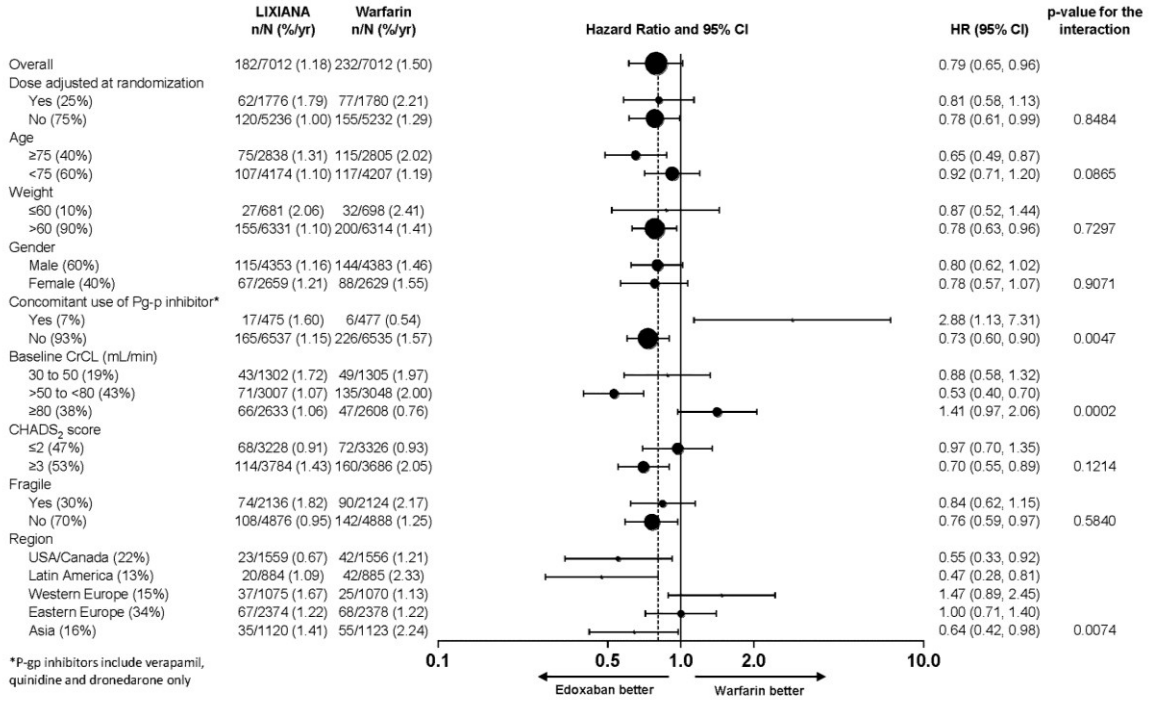
LIXIANA	7012	5699	5056	2213	46
Warfarin	7012	5724	5108	2186	55

The HR for the composite endpoints for the comparison of the LIXIANA 60 mg (30 mg dose-reduced) group and warfarin for stroke, SEE, and cardiovascular (CV) mortality was 0.87 (95% CI: 0.79, 0.96), MACE was 0.89 (95% CI: 0.81, 0.97), and stroke, SEE, and all-cause mortality was 0.90 (95% CI: 0.82, 0.98).

Results in subgroups of Interest

The efficacy results for pre-specified major subgroups (with dose reduction as required), including age, body weight, prior stroke or TIA, diabetes and P-gp inhibitors were generally consistent with the primary efficacy results for the overall population studies in the trial. However, there was a statistically significant interaction between the effect of edoxaban versus warfarin on the primary efficacy endpoint based on renal function (*HR was 1.41 in favor of warfarin for the subgroup with CrCL ≥ 80 mL/min*) and geographical regions (*HR was 1.47 in favor of warfarin for Western Europe*) (Figure 3).

Figure 3 - ENGAGE AF-TIMI 48 Study: Primary Efficacy Endpoint by Subgroups (mITT-on treatment)



Note: In the following patient groups, the edoxaban dosage was reduced to 30 mg: Weight ≤60 kg, CrCL 30 to 50 mL/min and concomitant use of P-gp inhibitors.
Fragile patients included patients who were ≥80 years, weight ≤50 kg, CrCL ≤50 ml/min and or history of fall.

An additional exploratory analysis was performed for the primary efficacy and safety endpoints by CrCl intervals of 20 mL/min. The observed percentage differences in efficacy in higher creatinine clearance groups between edoxaban and warfarin were numerically small, and notably, with overlapping confidence intervals. Tough the event rates of stroke/SEE in the edoxaban group were maintained in patients with CrCL between 70 and 130 mL/min, there was an unfavorable but non-significant effect of edoxaban compared to warfarin in patients with CrCL over 130 mL/min, for which there were fewer events (Figure 4). For major bleeding, the trend in favor of edoxaban 60 mg (30 mg dose-reduced) versus warfarin was preserved across the continuum of renal function (Figure 5).

Figure 4 - Stroke/SEE Event Rate by Baseline CrCl mITT Analysis Set, Overall Study Period-ENGAGE AF-TIMI 48 study

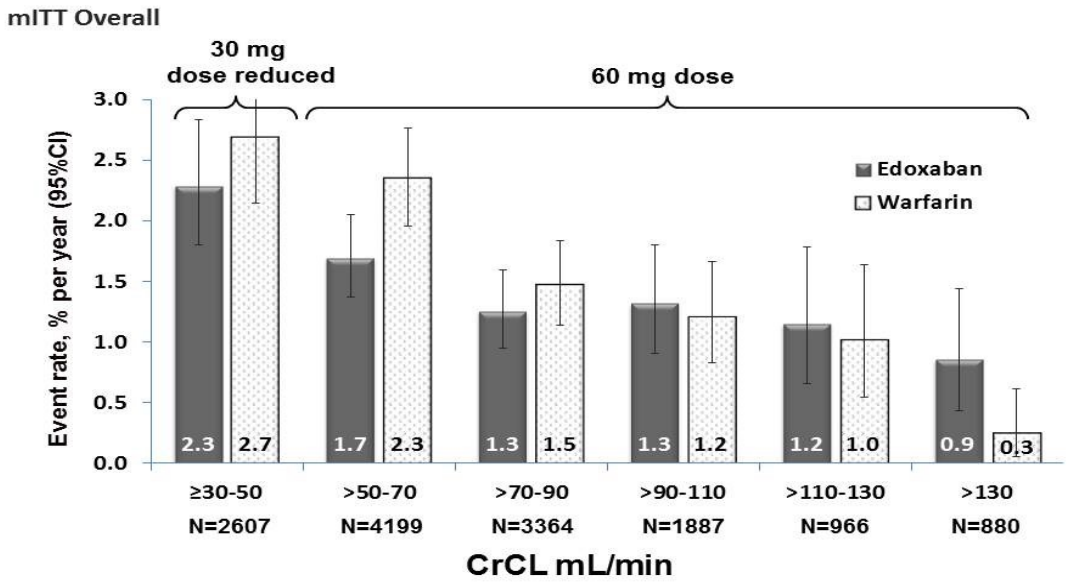
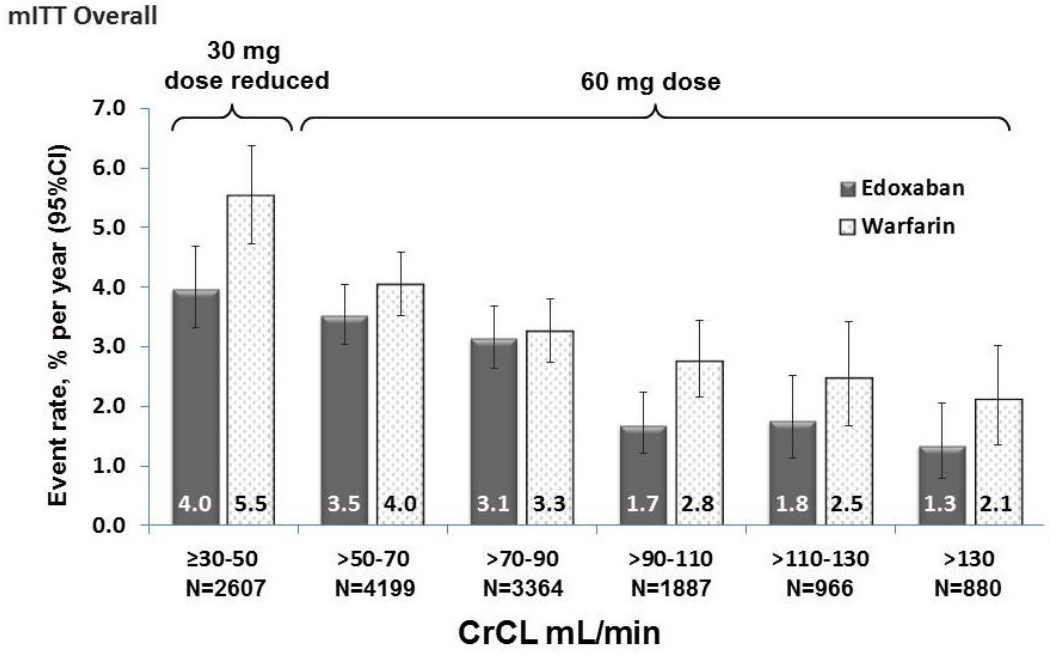


Figure 5 - Major Bleeds by Baseline CrCl Category in ENGAGE AF-TIMI 48 study



Transition to Other Anticoagulants

In the ENGAGE AF-TIMI 48 study, the transition schemes described in Table 9 (see DOSAGE AND ADMINISTRATION, *Switching to and from LIXIANA)* were effective when transitioning to VKA, Factor Xa and IIa inhibitors at the end of the study. The transition scheme included

LIXIANA at half dose for ≤14 days concurrently with VKA. The rate of Stroke and SEE during the 30 days following the last dose of blinded study drug was similar for those who transitioned off of LIXIANA and for those who transitioned off of warfarin. In the LIXIANA 60 mg group 7 of 4529 (0.2%) subjects had a stroke or SEE compared to 7 of 4506 (0.2%) subjects in the warfarin arm.

Safety in SPAF

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

Table 2 (See ADVERSE REACTIONS, Clinical Trial Adverse Reactions, Bleeding Events) summarises adjudicated bleeding events for the safety analysis set on-treatment period. Subjects in the LIXIANA 60 mg (30 mg dose-reduced) group experienced significantly lower bleeding events for all bleeding categories, (major Bleeding, CRNM, and any confirmed bleeding) compared with warfarin.

The rate of major bleeding was significantly less in the LIXIANA 60 mg (30 mg dose-reduced) group compared with the warfarin group (2.75%, and 3.43% per year, respectively) [HR (95% CI): 0.80 (0.71, 0.91)]; p=0.0009]. Similar benefits were observed in favor of the LIXIANA 60 mg (30 mg dose-reduced) group compared with the warfarin group for the subset of subjects experiencing ICH (0.39%, and 0.85%), respectively [HR (95% CI): 0.47 (0.34, 0.63); p<0.0001]. The rate in fatal bleeds was also significantly less in the LIXIANA 60 mg (30 mg dose-reduced) 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.

Subjects who received LIXIANA 30 mg (dose reduced subjects in the 60 mg group) had an event rate of 3.05% per year for major bleeding, compared with the event rate of 4.85% per year for the matching dose reduced subjects in the warfarin group. Compared to warfarin-treated subjects, the HR in the LIXIANA 30 mg (dose reduced subjects in the 60 mg group) was 0.63 (95% CI: 0.50, 0.81).

Subgroup analyses showed that LIXIANA 60 mg (30 mg dose-reduced) group had a lower event rate and an hazard ratio of less than 1 for major bleeding compared to the warfarin group for all subgroups, except for subjects with history of TIA only. In the subgroup of subjects with a high risk of bleeding, such as age ≥ 75 years, CrCL 30 to ≤ 50 and >50 to < 80 mL/min, and CHADS2 score ≥3, LIXIANA 60 mg (30 mg dose-reduced) group had an hazard ratio less than 1 for major bleeding compared with warfarin.

Treatment of VTE and the prevention of recurrent DVT and PE

The HOKUSAI VTE Study

Trial Design and Study Demographics

The LIXIANA clinical programme for venous thromboembolism (VTE) was designed to demonstrate the efficacy and safety of LIXIANA in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (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 for 5-10 days) followed by LIXIANA 60 mg once daily or the comparator. In the comparator arm, subjects received initial heparin therapy concurrently with warfarin, titrated to a target international normalized ratio (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. Patients were excluded if they required thrombectomy, insertion of a caval filter, use of a fibrinolytic agent, had a creatinine clearance <30 mL/min, significant liver disease, or active bleeding. 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 patients during the 12 months study period. Secondary efficacy outcomes included the composite clinical outcome of recurrent VTE and all-cause mortality.

Table 15 - Summary of patient demographics for clinical trials in VTE

Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range) years	Gender (M/F) %
Randomized, double-blind, matching placebo, parallel group, active controlled	LIXIANA 60 mg QD PO[a] Median duration of treatment = 267 days	n = 4118	55.7 (18 – 106)	57.3/42.7
	Warfarin QD PO[b] Median duration of treatment = 266 days	n = 4122	55.9 (18 – 95)	57.2/42.8
		Total = 8240		

VTE = venous thromboembolism, QD = once daily
[a] LIXIANA dose halved for subjects with moderate renal impairment [CrCL ≥ 30 and ≤ 50 mL/min], low body weight [≤ 60 kg], or on concomitant strong P-gp inhibitor [eg, verapamil, quinidine].
[b] Warfarin dose adjusted to maintain INR between 2.0 and 3.0, inclusive

Subjects in the LIXIANA 60 mg treatment group had their dose halved if one or more of the following were present: moderate renal impairment (CrCL30 - 50 mL/min); body weight ≤ 60 kg; concomitant use of specific P-gp inhibitors (verapamil and quinidine or the short-term concomitant administration of azithromycin, clarithromycin, erythromycin, oral itraconazole or oral ketoconazole).

Efficacy in VTE

In the HOKUSAI-VTE study (Table 16), LIXIANA was demonstrated to be non-inferior to warfarin for the primary efficacy outcome, recurrent VTE, which occurred in 130 of 4118 subjects (3.2%) in the LIXIANA group versus 146 of 4122 subjects (3.5%) in the warfarin group [HR (95% CI): 0.89 (0.70,1.13); p <0.0001 for non-inferiority to a pre-specified margin of 1.5]. In the warfarin group, the median TTR (time in therapeutic range, INR 2.0 to 3.0) was 63.5%. For subjects presenting with PE (with or without DVT), 47 (2.8%) LIXIANA and 65 (3.9%) of warfarin subjects had a recurrent VTE [HR (95% CI): 0.73 (0.50, 1.06)]. For subjects presenting with DVT, 83 (3.4 %) LIXIANA and 81 (3.3%) of warfarin subjects had a recurrent VTE [HR (95% CI): 1.02 (0.75, 1.38)].

For subjects who received the 30 mg dose (predominantly subjects with body weight ≤ 60 kg or moderate renal impairment) 22 (3.0%) LIXIANA and 30 (4.2%) of warfarin subjects had a recurrent VTE.

The composite endpoint of recurrent VTE and all-cause mortality occurred in 228 of subjects (5.5%) in the LIXIANA group and in 228 subjects (5.5%) in the warfarin group [HR: (95% CI):1.00 (0.83, 1.20)].

In the HOKUSAI-VTE study, the duration of drug exposure for LIXIANA 60 mg was ≤ 6 months for 1561 (37.9%) of patients, >6 months for 2557 (62.1%) of patients and 12 months for 1661 (40.3%) of patients.

Table 16 - Efficacy Results from the HOKUSAI-VTE Study (mITT Overall Study Period)

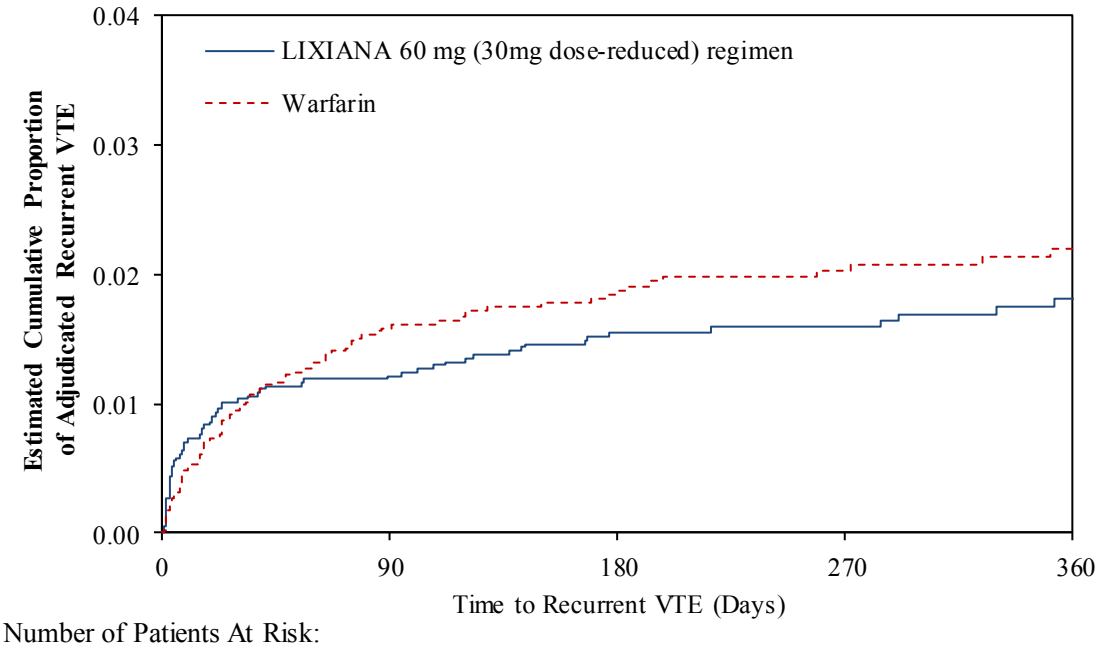
	LIXIANA 60 mg (30 mg Dose-Reduced) (N = 4118)	**Warfarin (N= 4122)**	**LIXIANA vs Warfarin HR (95% CI)**
All subjects with symptom recurrent VTE,[a] n (%)	130 (3.2)	146 (3.5)	0.89 (0.70, 1.13) p-value< 0.0001 (non-inferiority)
PE with or without DVT	73 (1.8)	83 (2.0)	
Fatal PE/Death where PE cannot be 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: mITT = modified intent-to-treat; HR= Hazard Ratio vs. warfarin; CI= Confidence Interval; N= number of subjects in mITT population; n= number of events

[a] Primary Efficacy Endpoint: Symptomatic recurrent VTE (i.e. the composite endpoint of DVT, non-fatal PE and fatal PE).

Note: The primary efficacy analysis was performed in the mITT Analysis Set, Overall Study Period - (all events occurring during the Overall Study Period are included regardless of study drug administration status).

Figure 6 - Kaplan-Meier Curve Estimate of cumulative event rates for the primary efficacy endpoint (mITT-on treatment) for the HOKUSAI study



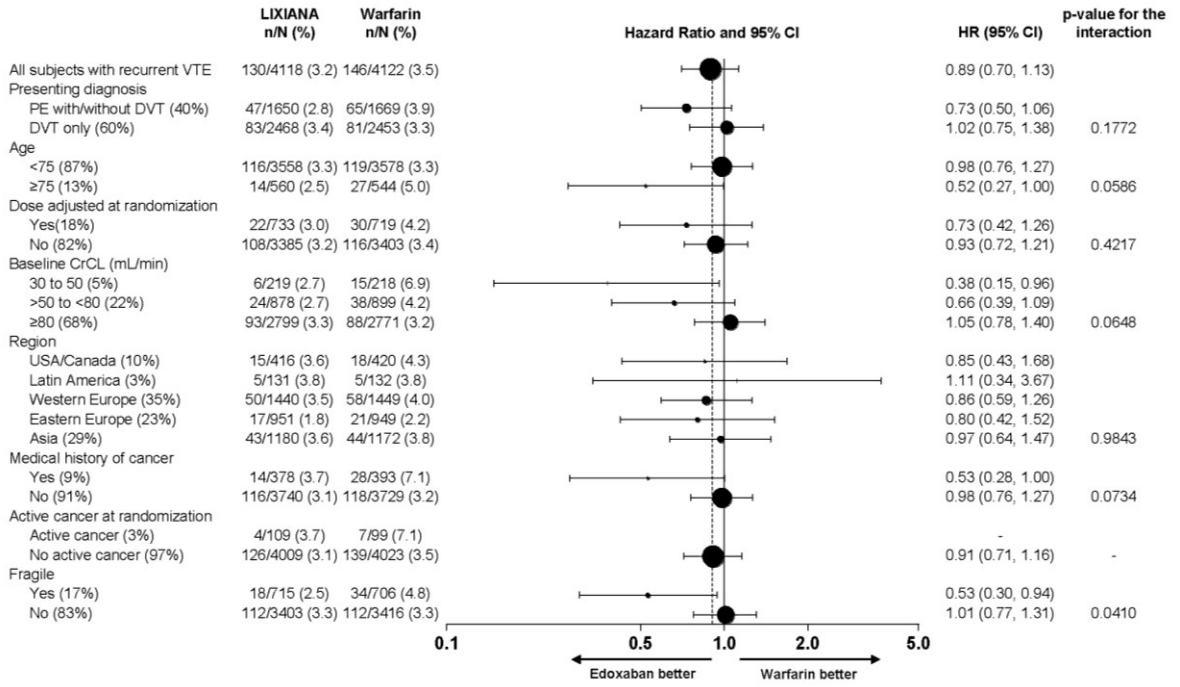
Number of Patients At Risk:

LIXIANA	4118	3724	3200	2029	1308
Warfarin	4122	3703	3170	2015	1306

Results in subgroups of Interest

The efficacy results for pre-specified major subgroups (with dose reduction as required), including age, body weight, and P-gp inhibitors were generally consistent with the primary efficacy results for the overall population studies in the trial (Figure 7).

Figure 7 - HOKUSAI-VTE Study: Primary Efficacy Endpoint by Subgroups (mITT-overall)



Note: Fragile patients included patients who were ≥ 75 years old and/or had body weight ≤ 50 kg and/or had CrCL ≥ 30 to ≤ 50 mL/min, each as determined at randomization

Safety in VTE

The principal safety endpoint was clinically relevant bleeding (major or clinically relevant non-major - CRNM) occurring during or within three days of interrupting or stopping study treatment. An additional endpoint included Major Adverse Cardiovascular Events - MACE (non-fatal MI, non-fatal stroke, non-fatal systemic embolic events, and cardiovascular death).

Table 3 (See ADVERSE REACTIONS, Clinical Trial Adverse Reactions, Bleeding Events) summarizes adjudicated bleeding events for the safety analysis set on-treatment period. LIXIANA was demonstrated to be superior to warfarin for the primary safety endpoint of clinically relevant bleeding, a composite of major bleeding or CRNM, which occurred in 349 of 4118 subjects (8.5%) in the LIXIANA group and in 423 of 4122 subjects (10.3%) in the warfarin group [HR (95% CI): 0.81 (0.71 to 0.94); p=0.004 for superiority].

The composite endpoint of MACE was 1.2% in the LIXIANA group and 1.0% in the warfarin group.

Subjects who received LIXIANA 30 mg (dose reduced subjects in the 60 mg group) had an event rate of 7.9% for clinically relevant bleeding, compared with the event rate of 12.8% for the matching dose reduced subjects in the warfarin group. Compared to warfarin-treated subjects, the hazard ratio (HR) in the LIXIANA 30 mg (dose reduced subjects in the 60 mg group) was 0.62 (95% CI: 0.44, 0.86).

Subgroup analyses of fragile subjects, elderly subjects, and subjects with a history of cancer demonstrated a favorable bleeding outcome with LIXIANA therapy. However, numerically higher rates of GI tract and vaginal bleeding events were noted in the LIXIANA group (See ADVERSE REACTIONS, Clinical Trial Adverse Reactions, Bleeding events).

DETAILED PHARMACOLOGY

QT/QTc Prolongation
In a randomised, double-blind, single dose, placebo- and active-controlled, four-period cross-over study, LIXIANA at 90 mg and 180 mg doses in healthy subjects (N=62) was not observed to affect the QTc interval, the QRS duration, the PR interval, or heart rate.

TOXICOLOGY

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

Repeat-Dose Toxicity
In the repeated-dose oral toxicity studies in rats, a small number of focal hemorrhagic lesions were observed in the pancreas, lung, and thymus of rats given edoxaban tosylate hydrate at ≥20 mg/kg/day. In repeated-dose oral toxicity studies in cynomolgus monkeys, hemorrhagic findings and anemia were noted in some animals given the drug at ≥15 mg/kg/day, leading to deteriorated animal condition or animal deaths with chronic dosing in a few monkeys.

These findings are thought to be related to the anticoagulant effect of edoxaban tosylate hydrate (its principal pharmacological action) which constitutes the only dose-limiting toxicity for this compound. Since the pharmacological activity of the drug for the cynomolgus monkey was comparable to that for humans, safety margins for hemorrhagic risk were estimated by comparison of exposures between cynomolgus monkeys and humans. The mean $AUC_{0\text{-}24h}$ values at NOAEL in the 52-week repeated dose oral toxicity study in cynomolgus monkeys were approximately 2.1 times higher than the exposures in human subjects given edoxaban at the maximum recommended clinical dose of 60 mg.

Carcinogenesis, Mutagenesis
Edoxaban was not carcinogenic when administered daily to mice and rats by oral gavage for ≤104 weeks. The highest dose tested (500 mg/kg/day) in male and female mice was 3 and 6 times, respectively, the human exposure (AUC) at the human dose of 60 mg/day, and the highest doses tested in male (600/400 mg/kg/day) and female (200 mg/kg/day) rats were 8 and 14 times, respectively, the human exposure at the human dose of 60 mg/day.

Genotoxicity
Based on the weight of evidence, edoxaban tosylate hydrate and its human-specific metabolite M-4 were not considered to pose any genotoxic risk to humans.

Reproductive Toxicology and Lactation

Edoxaban showed vaginal hemorrhage 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 [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 found in fetuses of pregnant rats and excreted in the breast milk of lactating rats.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

[Pr]LIXIANA®
Edoxaban Tablets (as edoxaban tosylate monohydrate)

Read this carefully before you start taking **LIXIANA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **LIXIANA**.

What is LIXIANA used for?

- To lower the risk of blood clots:
  - in the brain (stroke) and
  - in other blood vessels

  in people who have atrial fibrillation (a type of irregular heartbeat).
- To treat and prevent blood clots in the veins of the legs (deep vein thrombosis) or lungs (pulmonary embolism).

It is not known if LIXIANA is safe and effective in children.

How does LIXIANA work?
LIXIANA helps to reduce the risk of the formation of blood clots. LIXIANA blocks a protein called factor Xa. Factor Xa is involved in the natural formation of blood clots.

What are the ingredients in LIXIANA?
Medicinal ingredients: edoxaban tosylate monohydrate

Non-medicinal ingredients: carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, iron oxide red (30 mg tablets and 15 mg tablets), iron oxide yellow (60 mg tablets and 15 mg tablets), magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized starch, talc, titanium dioxide.

LIXIANA comes in the following dosage forms:
Tablets: 15mg, 30mg and 60mg

Do not use LIXIANA if:

- You are at risk of serious bleeding. This may be because you:
  - had recent bleeding in the brain.
  - have active ulcers that are bleeding or were recently bleeding.
- You have liver and blood-clotting problems.
- You are pregnant or breast-feeding.
- You are already being treated with a drug that stops your blood from clotting.

Examples include: warfarin, dabigatran, or apixaban.

- You are allergic to:
    - edoxaban (active ingredient of LIXIANA) or
    - any of the other ingredients in LIXIANA.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LIXIANA. Talk about any health conditions or problems you may have, including if you:

- are at risk of bleeding. This may be because you have or have had:
    - bleeding disorders.
    - an ulcer in your stomach or bowel.
    - bleeding in your brain, stomach or bowel.
    - very high blood pressure, not controlled by medical treatment.
    - an operation on your brain, spinal column or eye.
- take any drug that stops your blood from clotting.
- take aspirin, naproxen or ibuprofen (non-steroidal anti-inflammatory medications) on a regular basis.
- have liver or kidney problems.
- have a blockage in an artery in your lungs.
- have a catheter that stays in your bladder.
- have a body weight below 132 lbs (60 kg) .
- have a mechanical heart valve.
- have a heart problem as a result of rheumatic fever.
- had a recent injection into your spine such as an epidural.
- plan to become pregnant or if you are pregnant. It is not known if LIXIANA will harm your unborn baby. Tell your doctor right away if you become pregnant during treatment with LIXIANA.
- plan to breastfeed or if you are breastfeeding. It is not known if LIXIANA passes into your breast milk. You and your doctor should decide if you will take LIXIANA or breastfeed. You should not do both.
- plan to have any surgery or a dental procedure. Tell all of your healthcare professionals and dentists that you are taking LIXIANA. They should talk to the doctor who prescribed LIXIANA for you. This should be done before you have any surgery or dental procedure. You may need to stop and restart your treatment with LIXIANA.

Other warnings you should know about:

Risk of bleeding

- Taking LIXIANA may result in serious bleeding. You may bleed from your organs and

you may die.
- Do not stop taking LIXIANA without first talking to your doctor. This is important because blood clots may occur in the brain or in other blood vessels. This can cause death or severe disability.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with LIXIANA:
Taking LIXIANA with some other drugs may increase the risk of bleeding. Some of these drugs are:
- Cyclosporine, dronedarone, erythromycin, ketoconazole, quinidine, verapamil.
- Anticoagulants (medications to prevent blood clots).
- Aspirin and other nonsteroidal anti-inflammatory drugs such as naproxen.
- Drugs that block the action of platelets, such as clopidogrel.

How to take LIXIANA:
- You can take LIXIANA with or without food.
- Take LIXIANA exactly as prescribed by your doctor. Make sure to refill your prescription before you run out.
- **Do not stop taking LIXIANA without first talking with your doctor. Stopping LIXIANA may increase your risk of blood clots.**
- If you plan to have surgery, or a medical or a dental procedure, tell your doctor and dentist that you are taking LIXIANA. You may have to stop taking LIXIANA for a short time.
- Call your doctor right away if you fall or injure yourself, especially if you hit your head. Your doctor may need to examine you.

Usual dose:
- *To reduce the risk of blood clots in your brain (stroke) and other blood vessels*
    - 60 mg once a day

- *To treat and prevent blood clots in the veins of your legs or lungs*
    - 60 mg once a day.
    - You will receive LIXIANA after you have been given an injectable anticoagulant over 5-10 days.

- *Dose reductions*
    - The dose of LIXIANA is 30 mg once a day if you have one or more of the following:
        - Moderate kidney problems
        - Low body weight of 60 kg (132 lbs) or less
        - You take P-gp inhibitors (type of medication) except for amiodarone and

verapamil (types of P-gp inhibitor) while taking LIXIANA.

Overdose:

There are very few experiences of overdose with LIXIANA. Overdose with LIXIANA may lead to bleeding.

If you think you have taken too much LIXIANA, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of LIXIANA, take it as soon as you remember on the same day.
- Take your next dose at your usual time the next day.
- Do not take more than one dose of LIXIANA at the same time to make up for a missed dose.

What are possible side effects from using LIXIANA?

These are not all the possible side effects you may feel when taking LIXIANA. If you experience any side effects not listed here, contact your healthcare professional.

LIXIANA affects blood clotting. Most side effects are related to bleeding. LIXIANA can cause bleeding that is serious and may lead to death.

Patients treated with LIXIANA may experience the following side effects:

- Rash or itchy skin

Serious side effects and what to do about them				
Symptom / effect		**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
		Only if severe	**In all cases**	
COMMON	**Anemia**: fatigue, loss of energy, weakness, shortness of breath		✓	
	Bleeding from nose	✓		
	Bleeding in the stomach or bowel: dark stool (like tar), bright red blood in your toilet or on toilet tissue, vomiting blood		✓	
	Bleeding from mouth or gums	✓		
	Bruising and swelling		✓	
	Blood in urine:-pink or red urine		✓	
	Vaginal bleeding: Increase in or more frequent menstrual bleeding , unexpected vaginal bleeding		✓	
UN-COMMON	**Bleeding into the brain:** sudden, severe and unusual headache			✓
	Bleeding in eyes		✓	
	Coughing blood or blood stained sputum		✓	
	Bleeding from the surgical wound, an injury or other medical procedure		✓	
	Allergic reactions: rash, itching, hives, trouble breathing, throat tightening or constriction, swelling of the face, lips or tongue, sudden low blood pressure.			✓
RARE	**Bleeding into muscles:** sudden pain or swelling in your muscles		✓	
	Bleeding into a joint: stiff, sore, hot or painful joint		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:
- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store LIXIANA at room temperature between 15°C to 30°C.
- Keep in a safe place out of the reach and sight of children.

If you want more information about LIXIANA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php) or by calling the manufacturer, Servier Canada Inc. at: 1-800-363-6093.

This leaflet was prepared by:
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