Summary Report of Benefit-Risk Assessment

LIXIANA FILM-COATED TABLET 15MG, 30MG AND 60MG

NEW DRUG APPLICATION

Active Ingredient(s)	Edoxaban Tosilate
Product Registrant	A. Menarini Singapore Pte Ltd
Product Registration Number	SIN16059P, SIN16060P and SIN16061P
Application Route	Abridged evaluation
Date of Approval	18 December 2020

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Table of Contents

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A INTRODUCTION

Lixiana is indicated for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, and the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as the prevention of recurrent DVT and PE in adults.

The active substance, edoxaban, is a selective, reversible inhibitor of free factor Xa and prothrombinase activity in the coagulation cascade, leading to reduced thrombin generation, prolonged clotting time and reduced risk of thrombus formation.

Lixiana is available as film coated tablets containing 15 mg, 30 mg and 60 mg of edoxaban (as tosilate). Other ingredients in the tablet core are mannitol, pregelatinised starch, crospovidone, hydroxypropylcellulose and magnesium stearate. Ingredients in the film coating include hypromellose, macrogol 8000, titanium dioxide, talc, carnauba wax, iron oxide yellow (15 mg and 60 mg tablets only) and iron oxide red (15 mg and 30 mg tablets only).

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, edoxaban tosilate, is manufactured at Daiichi Sankyo Chemical Pharma Co., Ltd, Fukushima, Japan. The drug product, Lixiana Film Coated Tablets, is manufactured at Daiichi Sankyo Europe GmbH, Pfaffenhofen, Germany.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used have been adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented for Daiichi Sankyo Chemical Pharma Co., Ltd is adequate to support the approved storage condition and re-test period. The packaging is double polyethylene bags within a high density polyethylene (HDPE) drum. The drug substance is approved for storage at 25°C with a re-test period of 60 months.

Drug product:

The tablet is manufactured using a wet granulation/compression approach, followed by film-coating. The process is considered to be a standard process.

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All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies are conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used have been adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted is adequate to support the approved shelf-life of 60 months when stored at or below 30ºC. The container closure system is a polyvinyl chloride/aluminium blister pack of 14 tablets per blister.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of edoxaban was based on 2 clinical studies, ENGAGE AF-TIMI 48 in patients with NVAF and Hokusai VTE in patients with DVT and PE.

The ENGAGE AF-TIMI 48 study was a Phase III, randomised, double-blind, double-dummy, parallel-group, multicentre, multi-national study comparing edoxaban with warfarin in adult patients with NVAF with a $CHADS_2$ index score ≥2. Subjects were randomised in a 1:1:1 ratio to receive daily doses of either edoxaban 60 mg, edoxaban 30 mg or warfarin (dose adjusted to maintain INR between 2.0 and 3.0). In both edoxaban treatment groups, the study dose was halved for subjects with moderate renal impairment (creatinine clearance ≥ 30 to ≤50 mL/min), low body weight (≤ 60 kg) or on concomitant medication (verapamil, quinidine or dronedarone). The use of warfarin as an active comparator was considered acceptable as it is the standard of care for NVAF.

The efficacy analysis was conducted in the modified intent-to-treat (mITT) population, i.e. all randomised patients who received at least 1 dose of the randomised study drug. The primary efficacy endpoint was the composite of stroke and systemic embolic events (SEE). Secondary endpoints were the composite of stroke/SEE and CV mortality, major adverse cardiovascular event (MACE, i.e. composite of non-fatal MI, non-fatal stroke, non-fatal SEE, and death) due to CV cause or bleeding, and the composite of stroke, SEE and all-cause mortality. The primary efficacy endpoint (time to the first occurrence) was first compared concurrently for non-inferiority between each of the 2 edoxaban groups and warfarin groups in the mITT population during the on-treatment period at a non-inferiority margin of 1.38 (hazard ratio), using a pairwise comparison significance level of $\alpha=0.05/2$ (where 2 is the number of comparisons for non-inferiority). The edoxaban 60 mg group was subsequently compared with warfarin for superiority (ITT population) if non-inferiority of the edoxaban 60 mg group with warfarin was established. Superiority testing followed the following hierarchical sequence – stroke/SEE, stroke/SEE/CV mortality, MACE, stroke/SEE/all-cause mortality at a significance level of 0.01.

A total of 21,105 subjects were randomised in the study and 21,026 received treatment – 7002 in the edoxaban 30 mg arm (dose-adjusted: 1774), 7012 in the edoxaban 60 mg arm (dose-adjusted: 1776) and 7012 in the warfarin arm (placebo dose-adjusted: 1780). The median duration of exposure was 916 days in the edoxaban 30 mg arm, 904 days in the edoxaban 60 mg arm and 904 days in the warfarin arm. In general, the patient demographics and baseline

characteristics were well-balanced between the treatment arms (for full doses and adjusted doses). Among the subjects who received the full dose of edoxaban, the median age was 70 years, the majority of subjects were male (~67%) and the median weight was 86 kg. In the subgroup of subjects who received adjusted doses, the median age was 77 years, the majority of subjects were female (54%) and the median weight was 65 kg. The majority of subjects had a $CHADS_2$ index score between 2 to 3.

Non-inferiority was demonstrated between both edoxaban groups and warfarin for the on-treatment period. The respective upper bounds of the 97.5% CI were below the non-inferiority margin of 1.38 – for the edoxaban 60 mg group, the hazard ratio (HR) was 0.79 (97.5% CI:0.632, 0.985), while in the edoxaban 30 mg group, the HR was 1.07 (97%CI: 0.874,1.314). The primary efficacy results stratified by treatment regimen (dose adjusted and full dose) demonstrated a consistent trend in the reported events for edoxaban 60 mg (30 mg dose adjusted) and edoxaban 30 mg (15 mg dose adjusted). Superiority of edoxaban 60 mg (30 mg dose adjusted) over warfarin was tested as non-inferiority had been shown for both treatment groups. However, superiority was not demonstrated for stroke/SEE (p=0.0807). Therefore, further testing of superiority for the secondary endpoints were not conducted.

Summary of Key Efficacy Results (Study ENGAGE AF-TIMI 48)

	Warfarin (N=7012)	**Edoxaban 30mg (15mg Dose Adjusted) (N = 7002)**	**Edoxaban 60mg (30mg Dose Adjusted) (N = 7012)**
Primary endpoint – First stroke and systemic embolic events (SEE)			
On-Treatment Period (mITT) – Non-inferiority analysis			
No. of events	232	253	182
Event Rate (%/yr)	1.50	1.61	1.18
Comparison with warfarin			
HR	-	1.07	0.79
97.5% CI	-	0.874,1.314	0.632,0.985
p-value	-	0.0055	<0.0001
Overall Study Period (mITT)			
No. of events	336	382	292
Event Rate (%/yr)	1.80	2.04	1.55
Comparison with warfarin			
HR	-	1.13	0.86
97.5% CI	-	0.955,1.336	0.719,1.029
p-value	-	0.0074	<0.0001
Overall Study Period (ITT) – Superiority analysis			
No. of events	337	383	296
Event Rate (%/yr)	1.80	2.04	1.57
Comparison with warfarin			
HR	-	1.13	0.87
97.5% CI	-	0.957,1.337	0.728,1.040
95% CI		0.977, 1.310	0.744, 1.017
p-value	-	0.0980	0.0807
Secondary efficacy endpoints (ITT – Overall Study Period)			
Stroke, SEE and CV Mortality			
No. of events	831	796	728
Event Rate (%/yr)	4.43	4.23	3.85
Comparison with warfarin			
HR	-	0.95	0.87
97.5% CI	-	0.866, 1.052	0.786,0.959
p-value	-	0.3447	0.0053

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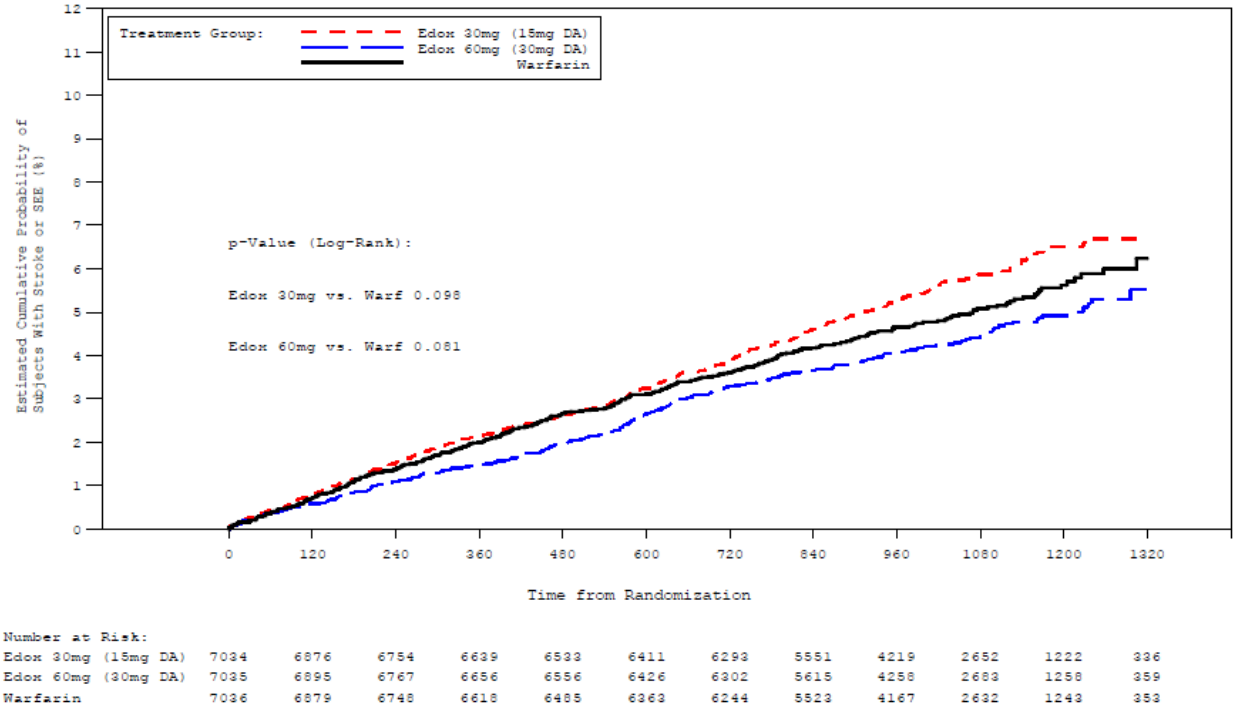
	Warfarin (N=7012)	Edoxaban 30mg (15mg Dose Adjusted) (N = 7002)	Edoxaban 60mg (30mg Dose Adjusted) (N = 7012)
MACE			
No. of events	926	913	827
Event Rate (%/yr)	4.98	4.90	4.41
Comparison with warfarin			
HR	-	0.98	0.89
97.5% CI	-	0.898,1.078	0.806,0.972
p-value	-	0.7195	0.0109
Stroke, SEE and All-cause Mortality			
No. of events	1046	985	949
Event Rate (%/yr)	5.57	5.23	5.01
Comparison with warfarin			
HR	-	0.94	0.90
97.5% CI	-	0.860,1.023	0.823,0.981
p-value	-	0.1496	0.0168

HR: hazard ratio; CI: confidence interval; SEE: systemic embolic events; MACE: composite of non-fatal MI, non-fatal stroke, non-fatal SEE and death; mITT: modified intention to treat; ITT: intention to treat

Kaplan-Meier Curve: Time to First Occurrence of Stroke or SEE (ITT Analysis Set – Overall Study Period; Study ENGAGE AF-TIMI 48)



The subgroup analyses (stroke, ischemic stroke, haemorrhage stroke, fatal stroke, disabling stroke and SEE) demonstrated consistent benefit in terms of numerically fewer or comparable reported events in the subgroups investigated for edoxaban 60 mg compared to warfarin, for edoxaban 60 mg compared to warfarin. The benefit of edoxaban 60 mg over warfarin was observed to be consistent between the primary and secondary endpoints. However, more subjects in the edoxaban 30 mg group reported events compared to the warfarin arm. When stratified by key secondary components, the reported events of fatal and non-fatal myocardial infarction (MI) were higher for edoxaban 30 mg compared to warfarin. In general, the overall clinical effect of edoxaban 60 mg was numerically better compared to edoxaban 30 mg. The

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proposed dosing regimen of edoxaban 60 mg (30 mg dose adjusted) for prevention of stroke and systemic embolism in adults with NVAF was thus considered appropriate.

Subgroup Analyses of the Primary Endpoint (mITT Analysis Set – On-Treatment Period; Study ENGAGE AF-TIMI 48)

	Edoxaban 60mg (30mg Dose Adjusted) (N = 7012)		Warfarin (N = 7012)		Edoxaban 60mg (30mg Dose Adjusted)	
	No. of Events	Event Rate (%/yr)	No. of Events	Event Rate (%/yr)	HR (97.5% CI)	P-Value
Stroke	174	1.13	219	1.41	0.80 (0.655,0.975)	0.0273
Ischaemic Stroke	135	0.87	144	0.93	0.94 (0.746,1.193)	0.6258
Haemorrhagic Stroke	40	0.26	76	0.49	0.53 (0.362,0.778)	0.0012
Fatal Stroke	45	0.29	43	0.28	1.05 (0.694,1.602)	0.8038
Disabling Stroke	35	0.23	41	0.26	0.86 (0.548,1.349)	0.5107
SEE	8	0.05	13	0.08	0.62 (0.257,1.497)	0.2884

HR: hazard ratio; CI: confidence interval; SEE: systemic embolic events

A small subgroup of subjects with moderate (creatine clearance ≤50 mL/min) and severe renal impairment (creatinine clearance ≤30 mL/min) were evaluated in this study. Based on the supportive data from a phase 1 pharmacokinetic study (U120), it was observed that that geometric mean total exposure ($AUC_{0\text{-}inf}$) of edoxaban administered to subjects with mild, moderate and severe renal impairment increased by 32%, 74% and 72%, respectively, as compared to healthy subjects. The increase in exposure between moderate and severe renal impaired subjects were similar. From the limited dataset provided for the severe renal impaired subpopulation from the ENGAGE AF-TIMI 48 study, it was observed that the event rates for major bleeding and stroke/SEE were lower for edoxaban 60mg compared to warfarin, 6.76%/yr vs 9.29%/yr, respectively, for major bleeding; and 2.41%/yr vs 2.61%/yr, respectively, for stroke/SEE). A similar trend was observed in the moderate renal impaired subpopulation. The proposed dosing regimen of edoxaban to be used in patients with a creatinine clearance ≥15 mL/min was considered appropriate.

The Hokusai VTE study was a phase III randomised, double-blind, double-dummy parallel-group, multicentre, multi-national study comparing edoxaban with warfarin in adult patients with documented acute symptomatic DVT and/or PE. Subjects were randomised in a 1:1 ratio to receive either edoxaban 60mg or warfarin (dose adjusted to maintain INR between 2.0 to 3.0). In the edoxaban treatment group, the study dose was halved for subjects with moderate renal impairment (creatinine clearance ≥ 30 and ≤50ml/min), low body weight (≤ 60kg) or on concomitant medication (verapamil, quinidine, dronedarone, ketoconazole, itraconazole, erythromycin, azithromycin or clarithromycin). All subjects received an initial heparin-based therapy for a minimum of 5 days consisting either low molecular weight heparin or unfractionated heparin. Subjects received a maximum treatment duration of 12 months. The use of warfarin as an active comparator was considered acceptable as it is the standard of care.

The efficacy analysis was conducted in the mITT population, i.e. all randomised patients who received at least 1 dose of the randomised study drug. The primary efficacy endpoint was the composite of DVT, non-fatal PE and fatal PE (referred to as symptomatic recurrent venous thromboembolism). The secondary endpoint was the composite of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE and all-cause mortality. The primary efficacy endpoint was compared between edoxaban and warfarin in the mITT population in the overall

study period for non-inferiority at a significance level of α=0.05 with a non-inferiority margin of 1.5 (hazard ratio) – Edoxaban was subsequently compared with warfarin for superiority (mITT population) if non-inferiority between edoxaban and warfarin was established. Superiority testing was conducted for the secondary endpoint at a significance level of 0.01.

A total of 8292 subjects were randomised in the study and 8240 received treatment – 4118 in the edoxaban 60mg arm (dose-adjusted: 733) and 4122 in the warfarin arm. The median duration of treatment was ~266-267 days. The median age was 57 years (range 18 to 106 years), the majority of subjects were male (~57%), weighed above 60kg (~87%) and were White (~70%). A small proportion of subjects were randomised to receive edoxaban 30 mg (~17%). In general, the patient demographics and baseline disease characteristics were well-balanced between the treatment arms for edoxaban 60 mg (edoxaban 30 mg dose adjusted) vs warfarin.

Non-inferiority was demonstrated between edoxaban and warfarin in the overall treatment period. The upper bound of the 95% CI was 1.128 and below the non-inferiority margin of 1.5 – the HR was 0.89 (95% CI 0.703,1.128), p < 0.0001. The primary efficacy (symptomatic recurrent VTE) results stratified by treatment regimen (dose adjusted and full dose) demonstrated consistent trends in the reported events between edoxaban and warfarin. Further stratification by the type of bleeding events (PE with/without DVT and DVT) showed that numerically fewer events were reported in both edoxaban treatment regimens (dose adjusted and full dose) compared to warfarin.

Summary of Key Efficacy Results (Study Hokusai VTE)

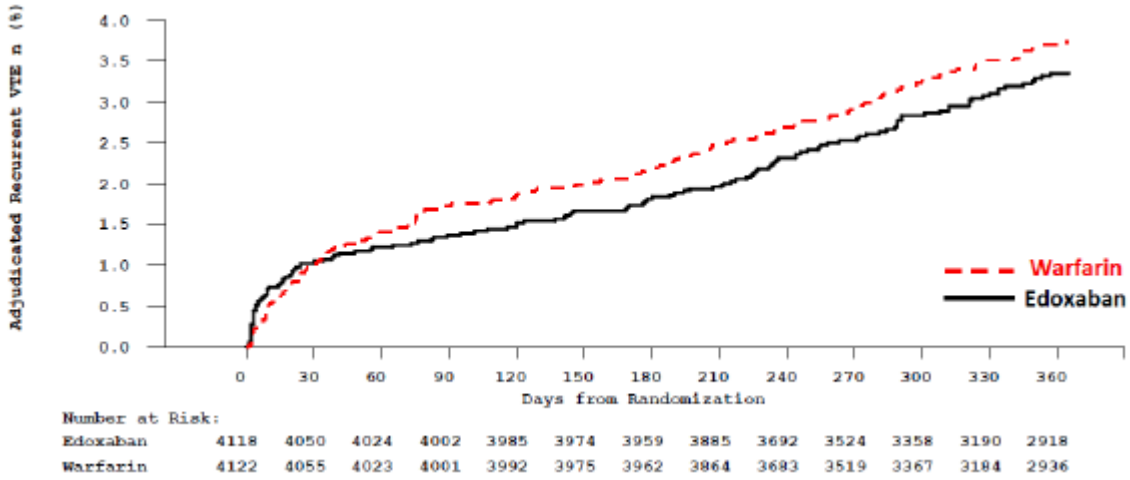
	Warfarin (N = 4112)	**Edoxaban 60 mg (30 mg Dose Adjusted) (N = 4118)**
Primary Endpoint - Symptomatic recurrent venous thromboembolism (mITT – Overall Study Period)		
All subjects with recurrent VTE, n (%)	130 (3.2)	146 (3.5)
HR Edoxaban vs Warfarin (95% CI)	0.89 (0.703,1.128)	
p-value (for non-inferiority)	<0.0001	
p-value (for superiority)	0.3362	
Type of first recurrent VTE, n (%)		
PE with/without DVT	73 (1.8)	83 (2.0)
DVT only	57 (1.4)	63 (1.5)
Secondary Efficacy Endpoint (mITT – Overall Study Period)		
All subjects with recurrent VTE or all-cause mortality, n (%)	122 (3.0)	106 (2.6)
HR Edoxaban vs Warfarin (95% CI)	1.00 (0.832,1.200)	
p-value	0.9933	
Type of initial recurrent VTE or all-cause mortality		
All-cause mortality	122 (3.0)	106 (2.6)
Non-fatal PE	49 (1.2)	59 (1.4)
DVT only	57 (1.4)	63 (1.5)

CI: confidence interval; mITT: modified intent-to-treat; VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis; HR: hazard ratio

From the Kaplan-Meier curve, a higher proportion of recurrent VTE events were reported for edoxaban compared to warfarin during the first 10 days of treatment received by subjects; 30 (0.7%) vs 22 (0.5%) respectively. However, with continual exposure, a decline in recurrent

events favouring edoxaban was thereafter observed. When stratified by PE with or without DVT, the incidence rates were observed to be comparable between the treatment groups.

Kaplan-Meier Curve: Cumulative Event Rate Estimates for Adjudicated Symptomatic Recurrent VTE (mITT Analysis Set – Overall Study Period; Study Hokusai VTE)



The subgroup analyses similarly demonstrated consistent benefit in the subgroups studied, including age, race and sex. Superiority of edoxaban over warfarin was tested as non-inferiority had been demonstrated. However, superiority was not demonstrated for recurrent VTE/all-cause mortality (p = 0.9933).

Subgroup Analyses of the Primary Endpoint (mITT Analysis Set –Overall Study Period; Study Hokusai VTE)

Subgroup	Edoxaban 60 mg (30 mg Dose Adjusted)			Warfarin			HR	P-value
	M	n	(%)	M	n	(%)	(95% CI)	
Age group								0.0586
<75 years	3558	116	3.3	3578	119	3.3	0.98 (0.760,1.267)	
>=75 years	560	14	2.5	544	27	5.0	0.52 (0.274,0.996)	
Gender								0.5810
Male	2360	82	3.5	2356	87	3.7	0.94 (0.694,1.268)	
Female	1758	48	2.7	1766	59	3.3	0.82 (0.558,1.195)	
Race								0.8264
Caucasian	2867	91	3.2	2895	98	3.4	0.94 (0.705,1.247)	
Black or African American	156	6	3.8	144	7	4.9	0.78 (0.265,2.308)	
Asian	866	27	3.1	861	34	3.9	0.79 (0.474,1.301)	

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Subgroup	Edoxaban 60 mg (30 mg Dose Adjusted)			Warfarin			HR	P-value
	M	n	(%)	M	n	(%)	(95% CI)	
American Indian or Alaska Native	0	0	0.0	0	0	0.0	- (-,-)	
Native Hawaiian or other Pacific Islander	0	0	0.0	0	0	0.0	- (-,-)	
Other	220	6	2.7	211	7	3.3	0.85 (0.289,2.510)	
Presenting diagnosis								0.1772
PE with/without DVT	1650	47	2.8	1669	65	3.9	0.73 (0.502,1.062)	
DVT Only	2468	83	3.4	2453	81	3.3	1.02 (0.750,1.384)	
Need for edoxaban 30 mg dose at randomisation								0.4217
Yes	733	22	3.0	719	30	4.2	0.73 (0.420,1.262)	
No	3385	108	3.2	3403	116	3.4	0.93 (0.718,1.213)	
Fragile subject population								0.0408
Yes	715	18	2.5	706	34	4.8	0.53 (0.296, 0.932)	
No	3403	112	3.3	3416	112	3.3	1.00 (0.773, 1.304)	
Medical history: Cancer								0.1581
History of cancer	268	8	3.0	273	16	5.9	0.50 (0.212,1.177)	
No history of cancer	3850	122	3.2	3849	130	3.4	0.94 (0.734,1.202)	
Centres with %Time in Therapeutic Range (TTR) (INR 2.0-3.0)								0.1581
< 60%	1199	38	3.2	1271	45	3.5	0.89 (0.574, 1.364)	
≥ 60%	2876	89	3.1	2845	101	3.6	0.87 (0.653, 1.153)	
< 25th percentile	713	28	3.9	748	27	3.6	1.09 (0.641, 1.848)	
≥25th to < 50th percentile	1329	35	2.6	1291	44	3.4	0.77 (0.496, 1.205)	
≥ 50th to < 75th percentile	1115	41	3.7	1180	42	3.6	1.05 (0.681, 1.610)	
> 75th percentile	918	23	2.5	897	33	3.7	0.66 (0.384, 1.129)	
Initial Heparin Duration (days)								0.9818
< Median (7 days)	1792	57	3.2	1300	51	3.9	0.82 (0.566, 1.193)	

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Subgroup	Edoxaban 60 mg (30 mg Dose Adjusted)			Warfarin			HR	P-value
	M	n	(%)	M	n	(%)	(95% CI)	
≥ Median (7 days)	2326	73	3.1	2822	95	3.4	0.93 (0.688, 1.266)	
≤ 5	870	34	3.9	583	24	4.1	0.97 (0.580,1.614)	
6	922	23	2.5	717	27	3.8	0.67 (0.385, 1.160)	
7	726	18	2.5	749	25	3.3	0.75 (0.411, 1.375)	
8-9	885	34	3.8	1011	40	4.0	0.98 (0.618, 1.546)	
≥1 0	715	21	2.9	1062	30	2.8	0.98 (0.563, 1.714)	

CI: confidence interval; PE: pulmonary embolism; DVT: deep vein thrombosis; HR: hazard ratio; M: number of subjects in each subgroup

The benefit of edoxaban over warfarin was consistent between the primary and secondary endpoints. The reported incidence of symptomatic recurrent VTE events (primary endpoint) were lower in the edoxaban group compared to warfarin; 130 (3.2%) vs 146 (3.5%) respectively. There was a similar trend, favouring edoxaban, reported for secondary endpoints non-fatal PE and DVT (non-fatal PE: 49 (1.2%) vs 59 (1.4%); DVT: 57 (1.4%) vs 63 (1.5%), respectively). There was a higher incidence of all-cause mortality for edoxaban compared to warfarin, 122 (3.0%) vs 106 (2.6%) respectively. However, the numerical imbalance between the treatment groups might be attributed to other factors such as non-VTE related deaths, specifically those related to infections.

There were too few subjects with severe renal impairment (creatinine clearance ≥15 mL/min to ≤30 mL/min) to allow for meaningful evaluation of the data in this subpopulation. However, based on study ENGAGE AF-TIMI 48, study U120 and population pharmacokinetic modelling, the efficacy and safety in the NVAF population could be reasonably extrapolated to the VTE population in subjects with severe renal impairment.

In both studies ENGAGE AF-TIMI 48 and Hokusai VTE, subjects on concomitant medication received half a dose of edoxaban (e.g. 30 mg dose adjustment). Concomitant administration with edoxaban included quinidine. Based on pharmacokinetic studies, it was observed that the effect of concomitantly administered quinidine on the exposure and C_{max} of edoxaban 60 mg increased by 77% and 85%, respectively. Considering that with the adjusted dose of edoxaban investigated in the pivotal studies, there were no reported events of stroke/SEE in study ENGAGE AF-TIMI 48 and 1 event of recurrent VTE reported in a subject receiving quinidine and/or verapamil in study Hokusai VTE, a dose adjustment of edoxaban to 30 mg would be appropriate in these patients.

Overall, the results of study ENGAGE AF-TIMI 48 and Hokusai VTE for the proposed dosing regimen of edoxaban 60 mg (30 mg dose adjusted) were consistent in meeting the primary and secondary efficacy endpoints and demonstrated robustness. The results adequately supported the efficacy of edoxaban for prevention of stroke and systemic embolism with NVAF and treatment of DVT and PE and prevention of recurrent DVT and PE in adults.

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D ASSESSMENT OF CLINICAL SAFETY

The safety data supporting the use of edoxaban for the requested indications comprised a total of 29,020 subjects (18,010 for edoxaban and 11,010 for warfarin). In study ENGAGE AF-TIMI 48, there were a total of 21,026 subjects (14,014 for edoxaban and 7012 for warfarin) and in study Hokusai VTE, there were a total of 8240 subjects (4118 for edoxaban and 4122 for warfarin). The safety events from ENGAGE AF-TIMI 48 and Hokusai VTE, except bleeding events, were pooled for evaluation. Bleeding events in the studies were not pooled due to the differences in risks of bleeding between the two indications. The median duration of exposure was 2.5 years in study ENGAGE AF-TIMI 48 and 8.78 months in study Hokusai VTE.

Overview of bleeding events in study ENGAGE AF-TIMI 48

	Edoxaban 30mg (N = 7002)	Edoxaban 60mg (N = 7012)	Warfarin (N = 7012)
Bleeding Category – First Event (%/yr)			
Major	1.61	2.75	3.43
ICH	0.26	0.39	0.85
Non-ICH	1.36	2.36	2.60
Fatal	0.13	0.21	0.38
ICH	0.08	0.15	0.27
Non-ICH	0.06	0.05	0.11
Life Threatening	0.25	0.40	0.78
Treatment-related, n (%)			
All Bleeding	1174 (16.8)	1486 (21.2)	1761 (25.1)

In study ENGAGE AF-TIMI 48, a lower incidence of bleeding events was reported for edoxaban compared to warfarin (edoxaban 30 mg: 31.0%; edoxaban 60 mg: 36.5%; warfarin: 39.9%). This was similarly observed for treatment-related bleeding events (edoxaban 30 mg: 16.8%; edoxaban 60 mg: 21.2%; warfarin: 25.1%). When stratified by type of bleeding events, the reported incidences of all events (including major, fatal and life threatening) were observed to be lower for edoxaban compared to warfarin. Between edoxaban 60 mg and warfarin, frequently reported areas of major bleeding were gastrointestinal and intracerebral haemorrhage. The incidence of gastrointestinal bleed was higher for edoxaban 60 mg compared to warfarin (1.51%/yr vs 1.23%/yr, respectively), and this was mainly driven by upper gastrointestinal bleed (0.91%/yr vs 0.71%/yr, respectively). The package insert has included information on the risk of gastrointestinal bleeding under Special Warnings and Precautions for Use and contraindicated edoxaban use in patients with lesion or conditions that are considered to be a significant risk for major bleeding including current or recent gastrointestinal ulceration.

Overview of bleeding events in study Hokusai VTE

	Edoxban 60mg (N = 4118) n (%)	Warfarin (N = 4122) n (%)
Major Bleeding	56 (1.4)	66 (1.6)
Fatal	2 (<0.1)	10 (10.2)
All Bleeding	895 (21.7)	1056 (25.6)
Treatment-related bleeding events	563 (13.7)	711 (17.2)

In study Hokusai VTE, a lower incidence of bleeding events was reported for edoxaban 60 mg compared to warfarin, 20.1% vs 23.8%, respectively. This was similarly observed for treatment-related bleeding events with 13.7% in the edoxaban 60 mg arm and 17.3% in the warfarin arm. When stratified by major bleeding and clinically non-major bleeding events

(CRNM), reported incidences remained lower for edoxaban 60 mg compared to warfarin, 8.5% vs 10.3% respectively. The most frequently reported major/CRNM locations of bleeding events between edoxaban 60 mg and warfarin were gastrointestinal tract (2.4% vs 2.3%, respectively), vaginal (4.6% vs 3.2%, respectively), epistaxis (1.1% vs 0.9%, respectively) and macroscopic haematuria/urethral (1.8% vs 2.6%, respectively). The incidence of vaginal bleed was observed to be slightly higher for edoxaban 60 mg compared to warfarin.

Overview of non-bleeding adverse events in pooled ENGAGE AF-TIMI 48 and Hokusai VTE studies

Events	Edoxaban 30mg (N = 7002) n (%)	Edoxaban 60 mg (N = 11008) n (%)	Warfarin (N = 11010) n (%)
Treatment-emergent adverse events (AEs)	5696 (84.2)	8537 (77.6)	8630 (78.4)
Treatment-related AEs	712 (10.2)	1279 (11.6)	1609 (14.6)
Serious AEs (SAEs)	2635 (37.6)	3037 (27.6)	3225 (29.3)
Treatment-related SAEs	67 (1.0)	98 (0.9)	198 (1.8)
Discontinuations due to AEs	707 (10.1)	946 (8.6)	916 (8.3)
Deaths	731 (10.4)	882 (8.0)	952 (8.6)

AE: adverse event

A pooled safety analysis from ENGAGE AF-TIMI 48 and Hokusai VTE was provided for non-bleeding events. The overall reported incidences between edoxaban and warfarin were 84.2% for edoxaban 30 mg, 77.6% for edoxaban 60 mg and 78.4% for warfarin. Between edoxaban 60 mg and warfarin, the reported incidences were comparable. The incidence of treatment-related events was lower for edoxaban compared to warfarin (edoxaban 30 mg: 10.2%; edoxaban 60 mg: 11.6%; warfarin: 14.6%). The most frequently reported non-bleeding events between edoxaban 30 mg, edoxaban 60 mg and warfarin were urinary tract infection (10.4% vs 7.8% vs 8.1%, respectively), nasopharyngitis (9.3% vs 7.9% vs 7.8%, respectively), bronchitis (8.5% vs 6.3% vs 6.2%, respectively) and oedema peripheral (8.6% vs 6.7% vs 7.9%, respectively). In the majority of cases, the adverse events were of mild to moderate intensity. There were few treatment-related non-bleeding events with reported incidences of ≥ 0.5%. These events included anaemia, diarrhoea, hepatic enzyme increased, creatinine renal clearance decreased and international normalised ratio (INR) increased.

The incidence of non-bleeding serious adverse events (SAEs) were lower for edoxaban 60 mg compared to warfarin, but higher for edoxaban 30 mg compared to edoxaban 60 mg and warfarin; 37.6% with edoxaban 30 mg vs 27.6% with edoxaban 60 mg vs 29.3% with warfarin. For treatment-related SAEs, the reported incidences were lower for edoxaban compared to warfarin; 1.0% with edoxaban 30 mg vs 0.9% with edoxaban 60 mg vs 1.8% with warfarin. The most commonly reported non-bleeding SAEs between edoxaban 30 mg, edoxaban 60 mg and warfarin were pneumonia (2.5% vs 1.9% vs 1.9% respectively), atrial fibrillation (4.5% vs 2.4% vs 2.8% respectively), cardiac failure (3.6% vs 2.4% vs 2.7% respectively) and cardiac failure congestive (3.0% vs 2.0% vs 2.0% respectively). In general, the incidences of SAEs between edoxaban 60 mg and warfarin were similar.

Adverse events leading to discontinuation due to bleeding occurred in 2.6% subjects receiving edoxaban 30 mg, 3.9% subjects receiving edoxaban 60 mg and 4.1% subjects receiving warfarin in study ENGAGE AF-TIMI 48; and 1.4% subjects receiving edoxaban 60 mg and 1.4% subjects receiving warfarin in study Hokusai VTE. Adverse events leading to discontinuation due to non-bleeding occurred in 10.1% subjects receiving edoxaban 30 mg, 8.6% subjects receiving edoxaban 60 mg and 8.3% subjects receiving warfarin. In general, the

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reported incidence of adverse events leading to discontinuation were comparable between edoxaban 60 mg and warfarin.

Overall, there were 8.0% deaths reported with edoxaban 60 mg. The incidence was similar to warfarin (8.6%) and lower than that observed for edoxaban 30 mg (10.4%). The majority of deaths were considered to be related to cardiovascular causes.

Apart from the bleeding risk, hepatic events were identified as an adverse event of special interest associated with edoxaban. The incidences of liver enzyme and bilirubin abnormalities were generally similar between edoxaban (regardless of dose) compared to warfarin, in terms of concurrent increases in ALT or AST ≥ 3xULN and total bilirubin ≥2x ULN (0.4% vs 0.3%, respectively), concurrent increases in ALT or AST ≥3x ULN and total bilirubin ≥2x ULN and <2x ULN alkaline phosphatase (0.2% vs 0.2%, respectively) and concurrent ALT or AST ≥3x ULN and total bilirubin ≥ 2xULN and ≥2x ULN alkaline phosphatase (0.1% vs <0.1% respectively). However, investigator-reported hyperbilirubinaemia was slightly higher for edoxaban 60 mg than warfarin, 0.3% (33 events) vs 0.1% (16 events), respectively. To mitigate the potential risk of hepatic injury, the package insert advises caution in patients with elevated liver enzymes or total bilirubin and recommends liver function testing prior to initiation and periodic hepatic monitoring beyond 1 year.

Overall, edoxaban at the proposed dose of 60 mg (30 mg dose adjusted) was found to be generally well tolerated in the NVAF and VTE population. Edoxaban-related adverse events were generally comparable to warfarin.

E ASSESSMENT OF BENEFIT-RISK PROFILE

The current standard of care for NVAF and VTE includes treatment with warfarin or non-vitamin K oral anti-coagulations (e.g. dabigatran, rivaroxaban, apixaban). Commonly used therapies are known to be associated with bleeding risks including major bleeding. Therefore, new therapeutic options with an improved safety profile would be desirable.

In terms of efficacy, edoxaban (30 mg and 60 mg) demonstrated non-inferiority to warfarin in the patient population with NVAF. When further stratified by treatment regimen (dose adjusted and full dose), a consistent trend in the reported events were similarly observed for the primary endpoint. In general, between edoxaban 60 mg and warfarin, consistent benefits across primary and secondary endpoints were observed. Between edoxaban 30 mg and warfarin, the subgroup analysis of the primary endpoint including ischemic stroke and SEE revealed higher event rates in the edoxaban 30 mg group compared to warfarin. This trend was similar reported for key secondary components including fatal and non-fatal myocardial infarction evaluated. Overall, the clinical effect of edoxaban 60 mg (30 mg dose adjusted) appeared to be better compared to edoxaban 30 mg (15 mg dose adjusted).

A small subgroup of subjects with moderate (creatine clearance ≤50 mL/min) and severe renal impairment (creatinine clearance ≤30 mL/min) were additionally evaluated in the NVAF population. Based on the limited clinical dataset, it was observed that the event rates for major bleeding and stroke/SEE were lower for edoxaban 60mg compared to warfarin in the severe renal impaired subpopulation. A similar trend was observed in the moderate impaired subpopulation. The clinical data taken together with pharmacokinetic data supported the proposed dosing regimen of edoxaban in patients with creatinine clearance ≥15 mL/min.

Similarly, edoxaban 60 mg (30 mg dose adjusted) demonstrated non-inferiority to warfarin in the patient population with VTE. When stratified by treatment regimen (dose adjusted and full dose) and type of recurrent VTE (PE with/without DVT and DVT), consistent benefit in terms of numerically fewer reported events were observed in the edoxaban treatment regimens (dose adjusted and full dose) compared to warfarin. In general, across primary and secondary endpoints, edoxaban demonstrated favourable outcomes over warfarin. As there were too few subjects with severe renal impairment, a clinically meaningful evaluation of the data in this subpopulation could not be made. However, it can be reasonably assumed that extrapolation of efficacy and safety in the NVAF population would lead to similar outcomes as that in the VTE population.

The safety profile of edoxaban 60 mg (30 mg dose adjusted) was found to be generally well tolerated in NVAF and VTE subjects. The incidence of bleeding (major, fatal and life-threatening) and non-bleeding events were found to be lower or comparable for edoxaban 60 mg (30 mg dose adjusted) compared to warfarin. The identified risk of hepatic injury has been adequately addressed in the local package insert via provision of relevant warnings and precautions, as well as recommended periodic monitoring.

Overall, the benefit-risk profile of edoxaban based on the proposed dose of 60 mg (30 mg dose adjusted) indicated for prevention of stroke and systemic embolism with NVAF, treatment of DVT and PE and prevention of recurrent DVT and PE in adult patients was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of edoxaban indicated for prevention of stroke and systemic embolism with NVAF, treatment of DVT and PE and prevention of recurrent DVT and PE in adult patients was deemed favourable and approval of the product registration was granted on 18 December 2020.

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APPROVED PACKAGE INSERT AT REGISTRATION

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LIXIANA
PACKAGE INSERT

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

Lixiana 15 mg film-coated tablets:
Each film-coated tablet contains 15 mg edoxaban (as tosilate).

Lixiana 30 mg film-coated tablets:
Each film-coated tablet contains 30 mg edoxaban (as tosilate).

Lixiana 60 mg film-coated tablets:
Each 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.

Lixiana 15 mg film-coated tablets:
Orange, round-shaped film-coated tablets (6.7 mm diameter) debossed with “DSC L15”.

Lixiana 30 mg film-coated tablets:
Pink, round-shaped film-coated tablets (8.5 mm diameter) debossed with “DSC L30”.

Lixiana 60 mg film-coated tablets:
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: quinidine, 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	*Quinidine, 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.

Switching to Lixiana		
From	**To**	**Recommendation**
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).
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%.
		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.

Switching from Lixiana		
From	**To**	**Recommendation**
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 (i.e. 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: quinidine, 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 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 acetylsalicylic acid (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 quinidine, ciclosporin, dronedarone, erythromycin, or ketoconazole requires dose reduction to 30 mg once daily. Concomitant use of edoxaban with 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.
- *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.

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

- *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 ≤ 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 (≤ 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 (≤ 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 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

System Organ Class	Frequency
Musculoskeletal and connective tissue disorders	
Intramuscular haemorrhage (no compartment syndrome)	Rare
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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

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: Antithrombotic agents, direct factor xa inhibitor, 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 (4^{th} 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 and a trend towards decreasing efficacy with increasing creatinine clearance was also observed for edoxaban compared to well-managed warfarin.

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 (30 mg Dose Reduced) (N = 7,012)			Warfarin (N = 7,012)			
	n	Number of Events	Event rate (%/year)	n	Number of Events	Event rate (%/year)	HR (95% CI)
≥15 to ≤30**	450	22	3.36	450	15	2.50	1.37 (0.71, 2.66)
≥ 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.

** Subjects with CrCL <30 mL/min were excluded from the trial prior to randomization. These data are from subjects whose CrCL was <30 mL/min at baseline (as tested on randomization day) or fell below 30 mL/min at some point during the study (therefore these subjects may also be included/counted in other categories). The events reported for the CrCL ≥ 15 to ≤ 30 ml/min subgroup are those occurring only after a CrCL < 30 ml/min was observed.

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 (30 mg Dose Reduced) (N = 7,012)			Warfarin (N = 7,012)			
	n	Number of Events	Event rate (%/year)	n	Number of Events	Event rate (%/year)	HR (95% CI)
≥15 to ≤30[**]	450	22	7.65	450	22	7.45	1.04 (0.57, 1.89)
≥ 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 (30 mg Dose Reduced) (N = 7,012)			Warfarin (N = 7,012)			
	n	Number of Events	Event rate (%/year)	n	Number of Events	Event rate (%/year)	HR (95% CI)
≥15 to ≤30[**]	450	0	0	450	3	1.00	--[*]
≥ 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 (30 mg Dose Reduced) (N = 7,012)			Warfarin (N = 7,012)			
	n	Number of Events	Event rate (%/year)	n	Number of Events	Event rate (%/year)	HR (95% CI)
≥15 to ≤30[**]	450	2	0.67	450	5	1.67	--[*]
≥ 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.
** Subjects with CrCL <30 mL/min were excluded from the trial prior to randomization. These data are from subjects whose CrCL was < 30 mL/min at baseline (as tested on randomization day) or fell below 30 mL/min at some point during the study (therefore these subjects may also be included/counted in other categories). The events reported for the CrCL ≥ 15 to ≤ 30 ml/min subgroup are those occurring only after a CrCL < 30 ml/min was observed.
[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).

[b] 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).

[c] 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 ≥ 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.

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.

Pharmocokinetic/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

Excipients for all Lixiana film-coated tablets:

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

Film-coat
Hypromellose (E464)
Macrogol 8000
Titanium dioxide (E171)
Talc
Carnauba wax

Additional excipients for Lixiana 15 mg film-coated tablets:
Iron oxide yellow (E172)
Iron oxide red (E172)

Additional excipient for Lixiana 30 mg film-coated tablets:
Iron oxide red (E172)

Additional excipient for Lixiana 60 mg film-coated tablets:

Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Store below 30°C.

6.5 Nature and contents of container

PVC/Aluminium blisters of 14 film-coated tablets. Each carton contains 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. MANUFACTURER

Daiichi Sankyo Europe GmbH
Luitpoldstrasse 1
85276
Pfaffenhofen, Germany

Repacked by
Interthai Pharmaceutical Manufacturing Ltd.
1899 Phaholyothin road, Ladyao, Chatuchak, Bangkok 10900, Thailand

8. DATE OF REVISION OF THE TEXT

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