OBSERVATIONAL PLAN

DRUG UTILISATION OF EDOXABAN
DSE-EDO-01-14-EU

VERSION NUMBER: FINAL VERSION 6.0
DATE OF VERSION: 08 JUN 2017

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STUDY INFORMATION

Protocol Number	DSE-EDO-01-14-EU, Version 6.0
Medicinal Product	Lixiana®
Product Reference	EMEA/H/C/002629
Procedure Number	EMA/H/C/002629/MEA/005
PASS Register Number	The study has not yet been registered
Active Ingredient	Edoxaban tosilate (Proposed ATC: B01AF03)
Study Title	Edoxaban prescription patterns in Europe: a retrospective drug utilisation chart review study
Date of Last Version of Protocol	08 JUN 2017
Research Question and Objectives	The aim of this Drug Utilisation Study (DUS) is to provide real-world data related to the current prescription patterns of edoxaban. Study objectives are as follows: • To characterize users of edoxaban; • To evaluate the pattern of use of edoxaban; • To evaluate the effectiveness of the edoxaban Educational Material as a tool for risk minimization.
Countries of Study	Germany, Italy, Belgium, Switzerland, the United Kingdom (UK), Spain, Portugal
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1. SIGNATURES

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
BMI	Body Mass Index
CA	Competent Authority
CDISC	Clinical Data Interchange Standard Consortium
CHF	Congestive Heart Failure
CI	Confidence Interval
CrCl	Creatinine Clearance
CRO	Contract Research Organisation
CSPV	Clinical Safety and Pharmacovigilance
DM	Data Management
DUS	Drug Utilisation Study
DS	Daiichi Sankyo
DSE	Daiichi Sankyo Europe GmbH
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
EDC	Electronical Data Capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FPI	First Patient In
GFR	Glomerular Filtration Rate
GP	General Practitioners
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices (GVP) (See section 10)
HCP	Health Care Professionals
ICF	Informed Consent Form
ICSR	Individual Case Safety Report
ID	Identification Number
IEC	Independent Ethics Committee
INR	International Normalised Ratio
ISPE	International Society for Pharmacoepidemiology
LPO	Last Patient Out

MAH	Marketing Authorisation Holder
NC	National Coordinator
NSAID	Nonsteroidal Anti-Inflammatory Drugs
NVAF	Non-valvular Arial Fibrillation
PE	Pulmonary Embolism
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System (software)
SDTM	Study Data Tabulation Model
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TIA	Transient Ischemic Attack
UK	United Kingdom
VTE	Venous Thromboembolism

3. RESPONSIBLE PARTIES

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3.1. List of Participating Centers and Countries

The following countries are planned to participate in the study: Germany, Italy, Switzerland, Belgium, the United Kingdom, Spain and Portugal.

A list of the principal investigators and all collaborating institutions and investigators is kept in a stand-alone document and can be made available upon request.

Table 1 - National Coordinators (Not applicable)

4. SUMMARY

Registry Title	Edoxaban prescription patterns in Europe: a retrospective drug utilisation chart review study
Protocol version identifier	DSE-EDO-01-14-EU, Version 6.0
Date of protocol version	08 Jun 2017
Marketing Authorisation Holder	Daiichi Sankyo Europe GmbH (DSE)
Main Authors	Dr Thomas Malzer, Clinical Safety and Pharmacovigilance (CSPV) Dr Petra Laeis, Head of Late Phase Clinical Operation and Real World Evidence & International Project Lead
Rationale and Background	Edoxaban is an orally administered anticoagulant that inhibits coagulation factor Xa. It is currently approved for use in adult patients with Non-Valvular Atrial Fibrillation (NVAF) with one or more risk factors, such as Congestive Heart Failure (CHF), hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or Transient Ischemic Attack (TIA) for prevention of stroke and systemic embolism. In addition, edoxaban is approved for the treatment of Venous Thromboembolism (VTE) including Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE), and prevention of recurrent VTE in adults. Clinical development programs have been undertaken to support marketing authorization submissions for edoxaban in those indications. However, as it is the case with any medicinal product, real-life use of edoxaban may differ from or extend beyond the patient population that has been studied in the phase 3 program or is included under the approved indication. One of the concerns in real-world use of medicinal practices is the off-label use. Daiichi Sankyo (DS) addressed this concern in the Risk Management Plan (RMP) in order to anticipate necessary risk minimization activities. The potential off-label use of edoxaban in unapproved indications was considered low, because of the availability of approved, indicated and well-established treatment alternatives. However, as it is the case with all other new anticoagulants a residual risk for off-label use might be considered in conditions (for which Edoxaban is not approved) that usually also require mid- or long-term anticoagulant treatment or in cases of poor compliance or contraindications for the patient. Standard routine risk minimisation activities include the communication of the information in the Summary of Product Characteristics (SmPC). In order to further optimise the correct use of the medicinal product by the physician, DSE is implementing additional risk minimisation activities, namely: • Prescriber guide as part of the educational programs to make prescribers fully aware of the approved indications and eligible patients for edoxaban, the dosing recommendations and management of safety concerns;

	• Patient alert card. Furthermore, the Drug Utilisation Study (DUS), described in this document aims to gain insight on how this new European medicinal product is going to be used in real practice. The DUS will help identify prescription patterns, the effectiveness of the educational programs and promptly detect potential safety concerns, so that pharmacovigilance planning and risk management for edoxaban could be effectively refined if necessary on an ongoing basis.

Research Question and Objectives	The aim of this DUS is to provide real-world data related to the current prescription patterns of edoxaban. Study objectives are as follows:
	• To characterize sites and physicians:
	  • Geographic location
	  • Profession or area of primary practice
	  • Patient volume
	• To characterize users of edoxaban
	  • According to demographic factors (e.g. age, gender, other);
	  • Patient comorbidity
	  • Patient subgroups for which there is missing information according to the RMP:
	  o Pregnant and/or breastfeeding women
	  o Paediatric patients
	  o Patients with hepatic impairment with coagulopathy and clinically relevant bleeding risk
	  o Patients with severe renal impairment (defined as having Creatinine Clearance [CrCl] < 30 ml/min or end-stage renal disease (CrCl < 15 ml/min or on dialysis)
	  o Patients with mechanical heart valves
	  • Patients being treated with dual antiplatelet therapy
	• To evaluate the pattern of use of edoxaban:
	  • Dose (including starting dose) and duration of treatment, including identification of long-term and chronic use, and dosing changes
	  • Use of concurrent/concomitant medications with special focus on medications potentially interacting with edoxaban or contraindicated especially those known to increase the risk of bleeding e.g., aspirin, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
	  • Detect the improbable event of use outside the labelled instructions, including use outside the indication[1]

1 According to SmPC, edoxaban is indicated in the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive

	(particularly indications for which alternative anticoagulants are indicated) and use in contraindicated situations. • History of past use of other anticoagulants • To evaluate the effectiveness of the edoxaban Educational Material as a tool for risk minimization. The specific objectives are: • To evaluate whether the Educational Material reached the target population (physicians prescribing edoxaban) as part of physician packet provided prior to drug supply • To assess clinical knowledge: awareness of the target population and the level of knowledge achieved by the educational intervention
Study Design	This is a multinational, multicentre study involving the retrospective chart review of edoxaban users' medical records. Nested in the study, a cross-sectional survey of all participating prescribing physicians will be performed starting from the date of the first data abstraction and repeated over the course of the study to evaluate the effectiveness of the physician educational program. Being retrospective, this study involves no intervention, and will not impact the usual medical care or affect the treatment of patients. Thus, the study will reflect real-world medical practice without the potential for prescriber response bias which may occur in prospective studies. The inception cohort is defined as patients initiating edoxaban during a 12-month period following the launch of the product in each country. An Electronical Data Capture System (EDC) will be used to collect study data. Data collection will be initiated following a study-defined index date, approximately 12 months after product launch. All study prescribers within a country will be assigned the same index date and will not be contacted prior to the index date. Initiation of prescriber-specific activities for selection of patient records meeting study selection criteria will commence on or following the index date. Data on drug utilisation will be censored on the index date. This approach will ensure that study procedures do not influence prescribing practices.
Setting	The study aims to include approximately 1200 medical records of patients who were treated at least once with one or more dose(s) of edoxaban. Country selection will take into account prescription volumes, the number of prescribers per capita, and favorable regulatory and ethical environment to conduct observational studies. It is foreseen that at least the following countries will be included: Germany, Italy, Switzerland, Belgium, the United Kingdom, Spain and Portugal. The sponsor may include additional European countries based on the actual use of edoxaban in initially-

heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA). Edoxaban is also indicated in the treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent VTE in adults.

	selected countries and to ensure selection reflects geographic representation among European countries. Following the identification of the countries, an independent prescription data source will be used to identify a representative sample of the prescribers in each country. Based on these sources it is possible to retrieve general information on edoxaban number of prescribers per specialty and geographic region. Physicians participating in any interventional currently ongoing/planned study with edoxaban will not be eligible to participate in the DUS and the Educational Material Survey. **Countries and Sites:** At least 100 hospital- and office-based physicians (General Practitioners [GPs], internal medicine physicians and other specialists) in at least 7 Western European countries (Germany, Italy, Switzerland, Belgium, the United Kingdom, Spain and Portugal) are foreseen to participate in the study.
Inclusion/exclusion criteria	Inclusion criteria: All patients with at least one edoxaban prescription record in his/her medical record irrespective of their underlying health conditions or indication for edoxaban prescription and with a written informed consent form. Exclusion criteria: None
Variables	Site/ Physicians' characteristics To evaluate the diversity of sites the following information will be collected for each participating site using the site feasibility questionnaire: • Geographic location of physician site • Profession or area of primary practice (e.g., GPs, cardiologists, and other specialists) • Patient volume (i.e., number of patients and estimated number of patients using edoxaban). Edoxaban treated patient data The following data will be collected from manual chart review: • Demographics and medical history: o Birth (year/month) or age o Race/ethnicity (where permitted) o Height o Body weight o Smoking status o Alcohol consumption o Diagnosis o Risk factors and treatment (pharmacological or non-pharmacological) history pertaining to edoxaban treatment o Cardiovascular comorbidities (including valvular disease) and other relevant somatic comorbidities

- Relevant familial medical history;
- History of haemodialysis
- History of past use of other anticoagulants
- Pregnancy and lactation status at the time of prescription
- Time and type of any surgery (including orthopaedic surgery) during the treatment with edoxaban
- Presence of mechanical heart valves
- Pertinent lab tests upon availability including liver function test, CrCl test and/or Glomerular Filtration Rate (GFR) pertaining to possible hepatic or renal impairment.

- Drug utilisation:
  - Edoxaban prescription:
    - start and end date/ongoing treatment (including repeated prescriptions if any)
    - daily dose (30 mg, 60mg, other) at the beginning of the treatment and afterwards
    - reason for use
    - reason of discontinuation (if applicable)
  - Concomitant medications (including if patient is using dual antiplatelet therapy).

Health Care Professional (HCP) Educational Material knowledge assessments

- Survey administration variables
- Description of survey participants
- Assessment of knowledge of the key messages of the educational program.

Data Sources

DUS

This study is a retrospective chart review. The identified local site staff will review the medical charts of all patients that have been prescribed edoxaban, over the given time period and extract the desired data elements. The data will be entered pseudonymised into electronic Case Report Forms (eCRFs) via a secure web-based EDC system. In sites that do not have the capabilities to access the internet to enter data, a provision will be made to collect pseudonymised data recorded on paper CRFs and entered into the study database by the Sponsor or designee (e.g. Contract Research Organization, (CRO)) on behalf of the site staff.

To assess the representativeness of the sampled patient population, a screening log of all patients prescribed with edoxaban will be maintained by the site staff, including patient's age and gender, and whether the patient's chart data was included in the DUS or not. For patient charts that

were not captured in the DUS, the reasons for non-inclusion will be documented on the screening log.

Educational Material Evaluation Survey

At the prescribers' primary contact (index date), the physicians will be requested to express their preferences for a means of direct-to-physician contact (email or telephone) in order to complete the survey.

The identity and contact details of the participants will only be used for scheduling and carrying out the survey. The survey will assess the physician's level of awareness and understanding of the content of the educational material/SmPC. All information collected during the course of the survey will be kept strictly confidential.

Study Size

The medical records of at least 100-200 patients will be studied per country (sample would be representative dependent on country-specific volumes of edoxaban prescriptions) for 600 to 1,200 treated patients in total across the 7 targeted European countries.

For characterization of users including potential off-label use, we present the level of precision in different scenarios of available number of users of edoxaban for different prevalence of diseases and conditions. In general, the 95% level of confidence is adequate for a prevalence as low as 1% and 1,200 users of edoxaban.

The sample size has been estimated based on the distance from the assumed proportion of patients with off-label use to the limits of the corresponding 95% confidence Interval (CI). Table 2 presents the precision in the estimate of the proportion of the off label use of edoxaban out of the labelled indication for tentative proportions of 0.02, 0.03, 0.04, 0.05 (2%, 3%, 4%, 5%) and different sample sizes.

Table 2 - Precision of estimation for proportions of 0.02, 0.03. 0.04, 0.05 (2%3%, 4% 5%) of off label use and increasing sample size

Sample Size Scenario

	proportion = 0.02			proportion = 0.03			proportion = 0.04			proportion = 0.05		
sample size	½ CI	L95%	U95%	½ CI	L95%	U95%	½ CI	L95%	U95%	½ CI	L95%	U95%
200	0.019	0.001	0.039	0.024	0.006	0.054	0.027	0.013	0.067	0.030	0.020	0.080
400	0.014	0.006	0.034	0.017	0.013	0.047	0.019	0.021	0.059	0.021	0.029	0.071
600	0.011	0.009	0.031	0.014	0.016	0.044	0.016	0.024	0.056	0.017	0.033	0.067
800	0.010	0.010	0.030	0.012	0.018	0.042	0.014	0.026	0.054	0.015	0.035	0.065
1000	0.009	0.011	0.029	0.011	0.019	0.041	0.012	0.028	0.052	0.014	0.036	0.064
1200	0.008	0.012	0.028	0.010	0.020	0.040	0.011	0.029	0.051	0.012	0.038	0.062

Note: CI: 2-sided 95% Confidence Interval (CI); ½ CI: distance from proportion to lower/upper limit of the two-sided 95% CI (equals half of the width of the CI); L95%: lower limit of the 95% CI; U95%: upper limit of the 95% CI.

Table 2 shows that the width of the 95% CI decreases as sample size increases; samples greater than 500 patients enable the estimation of the proportion of off-label use with an acceptable degree of precision. Increasing the sample size beyond 600 patients shows additional (though

	small) effects on the width of the 95% CI. Therefore, the current aim of recruiting 1,200 patients will assure to receive reliable results. In addition, it is estimated that approximately 100 physicians will have to complete the survey to allow reasonable precision around estimates of the physician's awareness and understanding levels. No target thresholds for physicians reported awareness and understanding have been established in advance. However if it is assumed that 85% of physicians will demonstrate appropriate awareness and understanding of the survey. Given this, the lower bound of the 95% CI will be above 78% for a sample size of N=100.
Data Analysis	Details of the data analysis strategy will be fully described in a Statistical Analysis Plan (SAP). Briefly, descriptive statistics will be used to characterize prescriber and patient information. Summary statistics for continuous variables will include the number of observations, along with measures of location (means, medians) and variation (e.g., standard deviation, range). Categorical data will include counts and percentages. The 95% CIs will be reported where appropriate. Per country analyses will be performed where reasonable, as some subgroups might be too small to be looked at per country. The data may also be evaluated and presented for other meaningful subgroups of patients (e.g., by patients for which there is missing information). Among edoxaban users retrieved from the charts, the number and percentage of the following categories will be described: • All users (100%) • Patients categorized as inappropriate drug users as defined (but not restricted to) : (a) use in patients in which the product is contraindicated, (b) use in patients who are not under the indication label per SmPC (c) use involving a different dose (e.g. no dose reduction or dose reduction without reason), dosing regimen or route of administration or (d) use that demonstrates non-adherence to guidance in the label. • Body weight • Patients <18 years • Patients > 65 years • Pregnant women • Patients in any other disease groups, by specific disease type (renal, hepatic impairment) • Patients using concomitant drugs known to increase the risk of bleeding e.g., aspirin, NSAIDs. The number of patients who have been prescribed edoxaban inappropriately will be identified and characterized separately per country. Concerning the survey data, it will be reported as descriptive statistics for all the variables (survey administration variables, description of

	survey population, and assessment of knowledge of the key messages of the educational program). Data will be presented overall, by country and by key characteristics (e.g. specialty of physician, geographic location, etc.). The safety results will be described according to physicians' knowledge and awareness of the material.
Quality Control	This study will be conducted according to the rules of 'Good Pharmacoepidemiology Practice' (GPP) and the 'Guideline on Good Pharmacovigilance Practices (GVP) – Module VIII (Rev 1)' EMA/813938/2011 Rev 1. Representatives of the Sponsor's quality assurance unit/monitoring team and competent regulatory authorities must be permitted to inspect all study-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs and the patients' original medical records. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.
Milestones	Final protocol including questionnaires: within 3 months after marketing authorization in the European Union. Start of data collection (in waves depending on the launch): expected to start at 12 months after product launch or protocol approval whichever occurs the last, (mainly driven by regulatory approvals and edoxaban market uptake to have sufficient numbers of patients treated). End of data collection: approximately 12 months after start of abstraction in the respective countries. Final study report: 6 months after entire database lock. Final Report Planned for Q2 2019 (latest 6 months after data base lock)

5. AMENDMENTS AND UPDATES

This is the revised protocol according to the questions and comments received after review of the PRAC (see Table 3). In case of essential changes of the observational plan the investigators will be informed as well as the respective competent authorities and Independent Ethics Committees as required by local laws or regulations.

Table 3 - Amendments and updates of the observational plan

No	Date	Section of study protocol	Amendment or update	Reason
1	24. Nov 2015	Full protocol	Amendment to V 1.0; new version 2.0	PRAC request
2	09 May 2016	Full protocol	Amendment to V 2.0; new version 3.0	PRAC request
3	05 August 2016	Full protocol	Amendment to V 3.0; new version 4.0	PRAC request
4	17 May 2017	Full protocol	Amendment to V 4.0; new version 5.0	Changes of - the participating countries list: France and the Netherlands excluded and Belgium, Spain and Portugal added; - the study milestones; - wording of section 11.2, Reporting of suspected ADRs by the Investigators
5	08 June 2017	Full protocol	Amendment to V 5.0; new version 6.0	Changes of - End of Data Collection per country: from “6 to 9 months” to “approximately 12 months”; - LPI milestone for all countries.

6. MILESTONES

The main milestones for the Drug Utilisation Study (DUS) will be:

Table 4 - Main study milestones

Start of data collection	Q3 2016
Interim report (planned)	Q3 2017
Planned end of data collection	Q4 2018
Final study report	Q2 2019 (latest 6 months after data base lock)

Recruitment will be performed in waves, as described in Table 5 (current planning dates – may be subject to change).

Table 5 - Milestones per country

Country	**First Patient In (FPI)**	**Last Patient In (LPI)**	**Wave**
Switzerland	Q3 2016	Q3 2017	I
Germany	Q3 2016	Q3 2017	I
United Kingdom	Q3 2016	Q3 2017	I
Belgium	Q3 2017	Q3 2018	II
Italy	Q3 2017	Q3 2018	II
Spain	Q3 2017	Q3 2018	II
Portugal	Q1 2018	Q4 2018	II

7. RATIONALE AND BACKGROUND

Edoxaban has been approved by the U.S. Food and Drug Administration FDA, the Swissmedic and by the European Medical Agency (EMA). In the EU it is approved for the following indications:

- Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack (TIA).
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

The approval is based on the following pivotal studies:

The **ENGAGE AF-TIMI 48** study (N=21105; mean $CHADS_2$ score = 2.8) compared edoxaban 60 mg once daily (high-dose regimen) and edoxaban 30 mg once daily (low dose regimen) with dose-adjusted warfarin (International Normalised Ratio [INR] 2.0–3.0) and found that both edoxaban regimens were non-inferior to warfarin in the prevention of stroke and systemic embolism in patients with NVAF. Both edoxaban regimens also provided significant reductions in the risk of haemorrhagic stroke, cardiovascular mortality, major bleeding and intracranial bleeding.[2]

The **Hokusai-VTE** study (N=8292) in patients with symptomatic VTE had a flexible treatment duration of 3–12 months and found that following initial heparin, edoxaban 60 mg once daily was non-inferior to dose-adjusted warfarin (INR 2.0–3.0) for the prevention of recurrent VTE, and also had a significantly lower risk for the composite of major or non-major clinically relevant bleedings (primary safety outcome).[3.]

Those clinical development programs have been undertaken to support marketing authorisation submissions for edoxaban in those indications. However, as is the case with any medicinal product, real-life use of edoxaban may differ from or extend beyond the patient population that has been studied in the phase 3 program or is included under the approved indication. One of the concerns in real-world use of medicinal practices is the off-label use. Daiichi Sankyo (DS) addressed this concern in the Risk Management Plan (RMP) in order to anticipate necessary risk minimization activities. The potential off-label use of edoxaban in unapproved indications was considered low, because of the availability of approved, indicated and well-established treatment alternatives. However, as it is the case with all other new anticoagulants a residual risk for off-label use might be considered in conditions (for which edoxaban is not approved) that usually also require mid- or long-term anticoagulant treatment or in cases of poor compliance or contraindications of the patient.

Standard routine risk minimisation activities include the communication of the information in the Summary of Product Characteristics (SmPC). In order to further optimise the correct use of the medicinal product by the physician, Daiichi Sankyo Europe GmbH (DSE) is implementing additional risk minimisation activities, namely, prescriber guide as part of the educational programs to make prescribers fully aware of

the approved indications and eligible patients for edoxaban, the dosing recommendations and management of safety concerns. In addition, Patient Alert Cards will be distributed.

The patient alert card is included in every edoxaban package in the European Union (EU).

Furthermore, the DUS, described in this document aims to gain insight on how this new European medicinal product is going to be used in real practice in order to identify prescription patterns, the effectiveness of the educational programs and promptly detect any safety concern, so that pharmacovigilance planning and risk management for edoxaban could be effectively refined, if necessary, on an ongoing basis.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Primary Objectives

The aim of this DUS is to provide real-world data related to the current prescription patterns of edoxaban. Study objectives are as follows:

To characterize sites and physicians:

- Geographic location of physician site
- Profession or area of primary practice (e.g., GPs, cardiologists, and other specialists
- Patient volume (i.e., number of patients and estimated number of patients using edoxaban).

To characterize users of edoxaban according to:

- Demographic factors (e.g. age, gender, other)
- Patient comorbidity
- Patient subgroups for which there is missing information according to the RMP:
  - Pregnant and/or breastfeeding women
  - Paediatric patients
  - Patients with hepatic impairment with coagulopathy and clinically relevant bleeding risk
  - Patients with severe renal impairment (defined as having Creatinine Clearance [CrCl] < 30 ml/min) or end stage renal disease (CrCl < 15 ml/min or on dialysis)
  - Patients with mechanical heart valves
- Patients being treated with dual antiplatelet therapy

To evaluate the pattern of use of edoxaban:

- Dose (including starting dose) and duration of treatment, including identification of long-term and chronic use, and changes
- Use of concurrent/concomitant medications with special focus on medications potentially interacting with edoxaban or contraindicated especially those known to increase the risk of bleeding e.g., aspirin, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
- Detect the improbable event of use outside the labelled instructions, including use outside the indication[1] (particularly indications for which alternative anticoagulants are indicated) and use in contraindicated situations.
- History of past use of other anticoagulants

To evaluate the effectiveness of the edoxaban Educational Material as a tool for risk minimization. The specific objectives are:

- To evaluate whether the Educational Material reached the target population (physicians prescribing edoxaban) as part of physician packet provided prior to drug supply
- To assess clinical knowledge: awareness of the target population and the level of knowledge achieved by the educational intervention

9. RESEARCH METHODS

9.1. Study Design

Multinational, multicentre study involving the retrospective chart review of edoxaban users' medical records. Nested in the study, a cross-sectional survey of all participating prescribing physicians will be performed starting from the date of the first data abstraction and repeated over the course of the study to evaluate the effectiveness of the physician educational program.

Being retrospective, this study involves no intervention, and will not impact the usual medical care or affect the treatment of patients. Thus, the study will reflect real-world medical practice without the potential for prescriber response bias which may occur in prospective studies. The inception cohort is defined as patients initiating edoxaban during a 12 month period following the launch of the product in each country.

The study design will allow the evaluation of the effectiveness of the risk minimisation activities targeting the minimisation of any potential off-label use as follows:

On the one hand, the surveys will assess physician' knowledge of the educational materials. But a survey methodology might not be the most appropriate approach for the evaluation of behavior, since surveys collect and analyse self-reported data from healthcare professionals and patients.

Therefore, real-world prescribers' behavior will be assessed by the collection of data from the patients' medical records.

9.2. Setting

The study aims to include approximately 1,200 medical records of consecutive patients who were treated at least once with one or more dose(s) of edoxaban.

9.2.1. Participating Sites

About 100 hospital- and office-based physicians (General Practitioners [GPs], internal medicine physicians and other specialists) in at least 7 Western European countries (Germany, Italy, Switzerland, the United Kingdom, Belgium, Spain and Portugal) are foreseen to participate in the study.

Country selection will take into account prescription volumes, the number of prescribers per capita, and favorable regulatory and ethical environment to conduct observational studies as well as the launch sequence of edoxaban in the different European countries. The sponsor may include additional European country(ies) based upon the actual use of edoxaban in initially-selected countries and to ensure selection reflects geographic representation among European countries.

Following the identification of the countries, an independent prescription data source (IMS Lifelink^{TM}) will be used to identify a representative sample of the prescribers in each country. Based on these sources it is possible to retrieve general information on edoxaban number of prescribers per specialty and geographic region.

At least 100 prescribers of edoxaban will be recruited in 7 European countries following each country-specific product launch and the distribution of the health care professional (HCP) Educational Material. These could include GPs, cardiologists, internal medicine specialists (and other specialists) from a variety of settings (e.g., office-based vs. hospital-based, urban vs. rural).

Physicians participating in interventional programs for edoxaban will not be eligible to participate in the study. By applying this approach both representativeness and comprehensiveness of the sample in terms of types of prescribers are ensured.

In the selected countries, available national prescription databases will be screened to identify geographic and edoxaban prescriber characteristics. Data from IMS LifeLink™ database for dispensing data in the community care setting, or another appropriate data source, will identify prescribers of edoxaban. This data source will be complementary to the full study and will be obtained prospectively on a quarterly basis, during the study period. On a national level for the targeted countries, the distribution of regional location of the sites as well as the distribution of the prescribers' specialty will be provided. Therefore, IMS LifeLink™ will be used to refine the a priori sampling strategy for the full study (using regional and specialty distribution of prescribers), and a posteriori to assess the representativeness of prescribers and patients included in the full study. This approach will contribute significantly to the enrolment of a more balanced population of edoxaban and alternative drugs prescribers at both the country and study level to cover broad indications. Potential sites for this DUS must meet the following criteria:

- Willing to provide a list of patients receiving edoxaban
- To allow/have access to patients' source data that are treated with edoxaban
- To be able to complete the study in the EDC system (only in exceptional cases paper CRFs are possible if no access to internet is provided)
- To be able to conduct the study adequately with respect to staff and time capacities.

9.2.2. Source Population

The current study aims to draw conclusions on the pattern of use of edoxaban. Therefore it aims to generalise its conclusions to all users that have been prescribed edoxaban since its launch in Europe.

Sites will be required to maintain a patient enrolment log of eligible patients at their treatment sites. This log will document how patients came to be included or excluded from the study, in order to assess the representativeness of the study population. The overall number of patients and sites may be adjusted during the study to meet enrolment goals, if needed. To the extent possible, consecutive patients meeting inclusion/exclusion criteria will be enrolled.

9.2.2.1. Inclusion criteria

Patients can be enrolled when they had at least one edoxaban prescription record in his/her medical record irrespective of the underlying health condition and with a written informed consent form.

9.2.2.2. Exclusion criteria

No exclusion criteria are defined.

9.2.3. Patient Groups

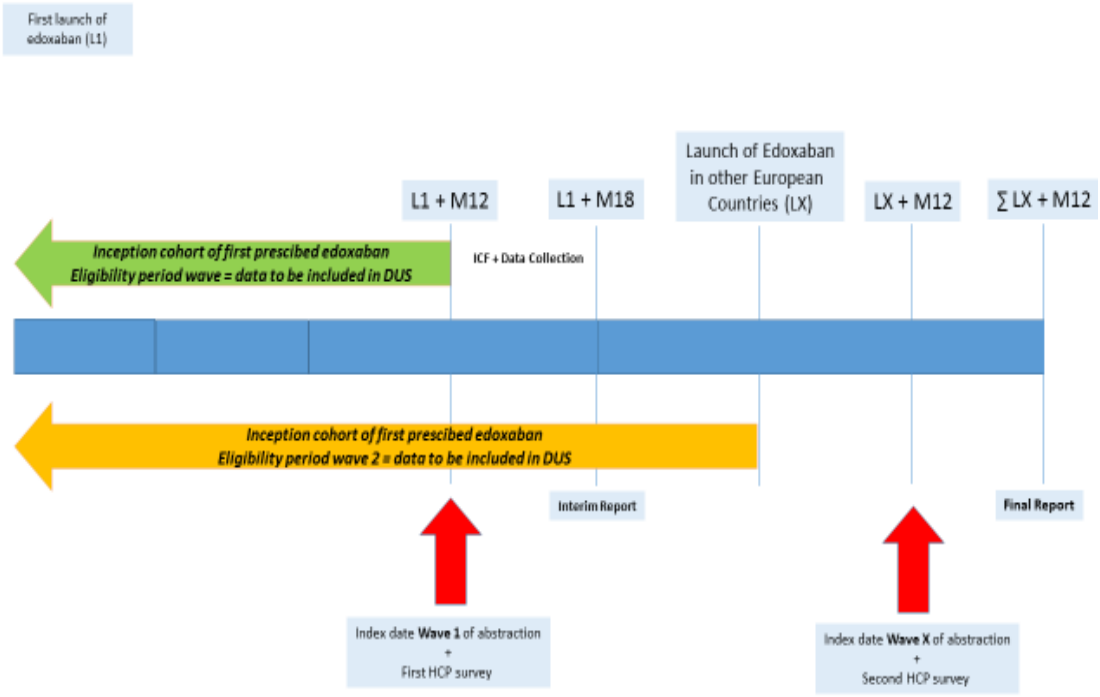
Not applicable

9.2.4. Schedule

The inception cohort is defined as patients initiating edoxaban during a 12-month period following the launch of the product in each country.

The eCRF will be used to collect study data. Data collection will be initiated following a study-defined index date, approximately 12 months after product launch (see study milestones; section 6). All study prescribers within a country will be assigned the same index date and will not be contacted prior to the index date. Initiation of prescriber-specific activities for selection of patient records meeting study selection criteria will commence on or following the index date. Data on drug utilisation will be censored on the index date. This approach will ensure that study procedures do not influence prescribing practices.

Figure 1 - Study flow chart per patient



Notes: DUS: Drug Utilisation Study. HCP: Health Care Professionals. ICF: Informed Consent Form. L1: Launch date in the first European country participating in the study; LX: Launch date in other European countries participating in the study. ΣLX: All medicinal products launched. M12: 12 months later. Final report planned latest 6 months after data base lock.
The launch of edoxaban in other European countries (LX) may also occur before the end of data collection for the first country.

9.2.5. Permanent discontinuation of Study Drug

Not applicable

9.2.6. Withdrawal of Consent from Registry Participation

Not applicable as data will be retrospectively retrieved from patients source data.

9.3. Variables

The following information will be entered in the CRF

I. **Site/ Physicians' characteristics**

To evaluate the diversity of sites the following information will be collected for each participating site from the site feasibility questionnaire:

- Geographic location of physician site;
- Profession or area of primary practice (e.g., GPs, cardiologists, and other specialists;
- Patient volume (i.e., number of patients and estimated number of patients using edoxaban).

II. **Edoxaban treated patient data**

1. **Demographics and medical history:**
   - Birth (year/month) or age
   - Race/ethnicity (where permitted)
   - Height
   - Body weight
   - Smoking status
   - Alcohol consumption
   - Diagnosis
   - Risk factors and treatment (pharmacological or non-pharmacological) history pertaining to edoxaban treatment
   - Cardiovascular comorbidities (including valvular disease) and other relevant somatic comorbidities
   - History of haemodialysis

- Relevant familial medical history
- History of past use of other anticoagulants
- Pregnancy and lactation status at the time of prescription
- Time and type of any surgery (including orthopaedic surgery) during the treatment with edoxaban
- Presence of mechanical heart valves
- Pertinent lab tests upon availability including liver function test, CrCl and/or Glomerular Filtration Rate (GFR) pertaining to possible hepatic or renal impairment.

2. Drug utilisation:

- Edoxaban prescription
  - start and end date/ongoing treatment (including repeated prescriptions if any)
  - daily dose (30 mg, 60mg, other) at the beginning of the treatment and afterwards
  - reason for use
  - reason of discontinuation (if applicable)
- Concomitant medications (including if patient is using dual antiplatelet therapy)

III. **HCP Educational Material knowledge assessments**

1. Survey administration variables:

- Number of physicians in sample, in total and by key characteristic;
- Number of physicians attempted to contact
- Number of physicians effectively contacted
- Number of contacted physicians who agreed to participate
- Of those agreed to participate, number who completed survey.

2. Description of survey participants

- Medical specialty
- Country
- Setting (type, geography)
- Experience with edoxaban (yes/no and if yes number of months)
- Receipt of educational material (yes/no) and time elapsed since its return.

3. **Assessment of knowledge of the key messages of the educational program:**
    - Frequency and distribution of response to each survey question
    - Percentage of respondents indicating correct and incorrect responses to each question
    - The success/failure rate of the survey (proportion of correct and incorrect answers) overall and by each section (group of related items)
    - Assessment of HCPs' opinion/satisfaction on the utility of educational material.

9.4. Data Sources

DUS

This study is a retrospective chart review. The participating site staff will review the medical charts of the specified number of patients that have been prescribed edoxaban, over the given time period and extract the desired data elements. The data will be entered pseudonymised into electronic Case Report Forms (eCRFs) by the prescribers via a secure web-based electronic data capture (EDC) system. In sites that do not have the capabilities to access the internet to enter data, a provision will be made to collect pseudonymised data recorded on paper CRFs and entered into the study database by the the Sponsor or designee (e.g., Contract Research Organization, CRO) on behalf of the site staff. Data quality will be enhanced through a range of data quality checks that automatically detect out-of-range or anomalous data. These checks will be programmed within the EDC system and system queries will be automatically raised and followed-up by the sponsor/CRO. The data will also be reviewed on an ongoing basis by the sponsor/CRO and manual queries raised as necessary. Further details on validity checks can be found in section 9.6 (Data Management).

Some limitations with regard to data completeness may occur in this study, mainly related to the type and completeness of the information captured in the patients' medical records. Measures to ensure the completion of the eCRF in a systematic, professional, and unbiased manner include:

- eCRF completion guidelines will provide consistent instructions on completion of the eCRF.
- All individuals performing data abstraction from medical records will be trained on appropriate data abstraction techniques in order to minimize possible discrepancies between interpretation of the information recorded by the prescriber in the medical records and the individual performing the review and abstraction of the data.
- Missing data will be followed up during remote monitoring contacts.

To assess the representativeness of the sampled patient population, a screening log of all patients prescribed with edoxaban will be maintained by the site staff, including patient's

age and gender, and whether the patient's chart data was included in the DUS or not. For patient charts that were not captured in the DUS, the reasons for non-inclusion will be documented on the screening log.

Educational Material Evaluation Survey

The survey will be administered either by phone or on line through a secure unique web link concomitantly at the time of the site initiation visit, thus minimizing the impact of any previous reading of the Educational Material by the physician. Six months later, the same Survey will be administered de novo.

The afore-described strategy, together with a comparative analysis of respondents and non-respondents' characteristics, is expected to minimize and detect any response bias or trend among the survey population.

The Educational Material will be distributed to all physicians prior to edoxaban availability and irrespectively from the participation in the DUS. However, investigators participating in the DUS may take part in the survey to assess the physicians' level of awareness and understanding of the content of the educational material/SmPC, including:

- Indications
- Dosing recommendations and dose reduction
- Populations at higher risk of bleeding
- Information on switching patients to or from edoxaban
- Perioperative management
- Temporary discontinuation
- Overdose
- Bleeding complications
- Coagulation testing

Physicians will not be individually assessed. Results will be reported in aggregate form only and not linked to any personal identifier. All information collected during the course of the survey will be kept strictly confidential.

9.5. Study Size

The medical records of approximately 200 patients will be studied per country (sample would be representative dependent on country-specific volumes of edoxaban prescriptions) to approximately 1,200 treated patients in total across the 6 targeted European countries.

For characterization of users including potential off-label use, we present the level of precision in different scenarios of available number of users of edoxaban for different prevalence of diseases/conditions. In general, the 95% level of confidence is adequate for a prevalence as low as 1% and 1,200 users of edoxaban.

The sample size has been estimated based on the precision of a percentage, that is, the width of the 95% confidence Interval (CI). Table 2 (see summary page 17) presents the precision in the estimate of the proportion of use of edoxaban out of the labelled indication for tentative proportions of 0.02, 0.03, 0.04, 0.05 (2%, 3%, 4%, 5%) and different sample sizes.

Table 6 - Precision of estimation for proportions of 0.02, 0.03, 0.04, 0.05 (2%, 3%, 4%, 5%) of off-label use and increasing sample size

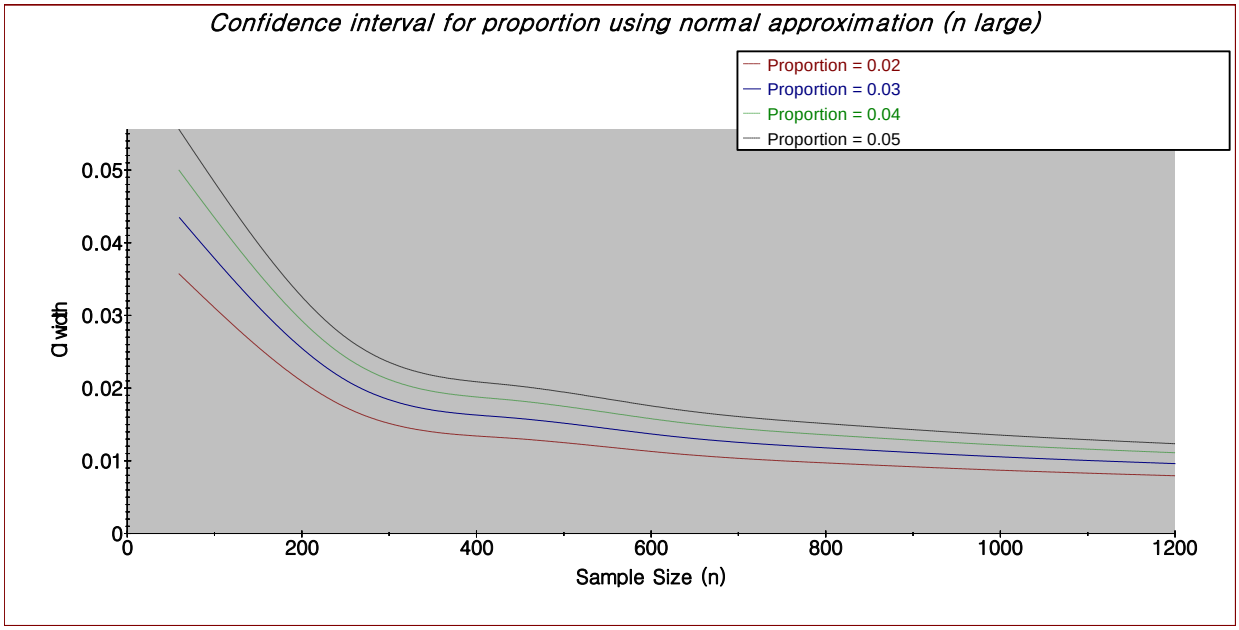
	Proportion											
	0.02			0.03			0.04			0.05		
Sample Size	½ CI	L95%	U95%	½ CI	L95%	U95%	½ CI	L95%	U95%	½ CI	L95%	U95%
200	0.019	0.001	0.039	0.024	0.006	0.054	0.027	0.013	0.067	0.030	0.020	0.080
400	0.014	0.006	0.034	0.017	0.013	0.047	0.019	0.021	0.059	0.021	0.029	0.071
600	0.011	0.009	0.031	0.014	0.016	0.044	0.016	0.024	0.056	0.017	0.033	0.067
800	0.010	0.010	0.030	0.012	0.018	0.042	0.014	0.026	0.054	0.015	0.035	0.065
1000	0.009	0.011	0.029	0.011	0.019	0.041	0.012	0.028	0.052	0.014	0.036	0.064
1200	0.008	0.012	0.028	0.010	0.020	0.040	0.011	0.029	0.051	0.012	0.038	0.062

Note: CI: 95% of Confidence Interval (CI); ½ CI: distance from proportion to lower/upper limit of the two-sided 95% CI (equals half of the width of the CI); L95%; L95%: lower limit of the 95% CI; U95%: upper limit of the 95% CI.

Table 2 shows that the width of the 95% CI decreases as sample size increases; samples greater than 500 patients enable the estimation of the proportion of off-label use with an acceptable degree of precision. Increasing the sample size beyond 600 patients shows additional (though small) effects on the width of the 95% CI. Therefore, the current aim of recruiting 1,200 patients will assure to receive reliable results.

A sample size of 600 patients for instance will allow the detection of a rate of 5% of off-label with a precision of 1.7%, that is, the estimated proportion will be comprised between 3.3% and 6.7%. A sample size of 1,200 patients will allow for an even higher precision, as a rate of 5% of off-label is detected with a precision of 1.2%, that is, the estimated proportion will be comprised between 3.8% and 6.2%.

Figure 2 - Confidence Interval (CI) for half of CI width



In addition, it is estimated that approximately 100 physicians will have to complete the survey to allow reasonable precision around estimates of the physician's awareness and understanding levels.

In order to achieve robust results from the various statistical validation methods, it is recommended to have at least 10 physicians per questionnaire item/observation. This rule has been adopted as the standard for psychometric (fit for purpose) validation with its origin within the classical test theory of principal component analysis.[4]

No target thresholds for physicians reported awareness and understanding have been established in advance. However if it is assumed that 85% of physicians will demonstrate appropriate awareness and understanding of the survey. Given this, the lower bound of the 95% CI will be above 78% for a sample size of N=100.[5]

9.6. Data Management (DM)

A data management plan (DMP) will be created that will describe all functions, processes, and specifications for data collection, cleaning and validation for the DUS.

High data quality standards will be maintained and processes and procedures utilised to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data.

9.6.1. Data Entry/Electronic Data Capture

Mixed data capture will apply: The pseudonymized data will be entered into electronic Case Report Forms (eCRFs) by the site staff via a secure web-based electronic data capture (EDC) system. In sites that do not have the capabilities to access the internet to enter data, a provision will be made to collect pseudonymised data recorded on paper

CRFs. Sites will be instructed to maintain completed paper CRFs in a secure environment prior to dispatch to the CRO.

The EDC system will be a secure web-based system using specific encryption mechanisms for exchanging data between the web browser of the user and the data server. All users of the EDC system (Investigators and site personnel as well as sponsor/CRO staff) will be able to access their account with a unique personalized username and password. Users will be assigned certain standardized user roles that will allow/restrict them to perform specific actions within the EDC application. An audit trail will record any actions within the eCRF such as session times, user who accessed the data, initial entry or changes made to the data (including reason for change or correction).

In case of eCRF data capture the sites will directly enter the data from their patients' medical records into the standardized English eCRFs. Each participating site will have access to its enrolled patient data only. All sites will be fully trained on using the online data capture system, and on the eCRF completion guidelines and other help files. All eCRFs should be completed by designated, trained personnel as appropriate. The eCRF is to be reviewed, electronically signed, and dated by the investigator.

The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous.

Edit checks within the eCRF may be checks tied to a certain field or edit checks across multiple fields.

Field checks may include the following:

- Checks on non-conformance (e.g., a non-existing date or a numeric field including text)
- Range checks on numeric fields (e.g., a field that has to be greater than x but lower than y)
- Checks on missing values (e.g., a predetermined required field)
- Checks on future dates

Edit checks across multiple fields may be any check firing on the condition of another field (or multiple fields) containing a certain value (or a range of values). These may be e.g. a relationship between a parent record and a sub-record or a comparison of different dates.

All edit checks will be listed in a Data Management document separate from the Observational Plan with a description of the check firing logic (including pseudo-code as necessary and any ranges defined, if applicable), the type of check and the query message text with reference to the applicable forms and items.

To ensure a high quality of data the Sponsor will take data snapshots at pre-defined time points and review the data for any potential data errors or discrepancies.

Ad hoc queries will be generated within the EDC system and followed up for resolution.

Paper CRFs completed by the sites will be collected by CRO staff and entered by trained CRO personnel into the EDC system. Queries will be posted on paper forms and sent to the sites for clarification.

The data from the project specific database will be exported into SAS data sets as per Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) definition for further validation and analysis.

9.6.2. Source Documents

The source documents are contained in the patient's medical record and data collected on the eCRFs must be traceable to these source documents. All original source documentation is expected to be stored at the site for the longest possible time required by local applicable regulations. The site will be instructed to notify the Sponsor before any destruction of medical records of study participants.

9.7. Data Analysis

All computations and generation of tables, listings and data for figures will be performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC, USA).

Assessing prescription patterns

Details of the data analysis strategy will be fully described in a Statistical Analysis Plan (SAP). Briefly, descriptive statistics will be used to characterize prescriber and patient information. Summary statistics for continuous variables will include the number of observations, along with measures of location (means, medians) and variation (e.g., standard deviation, range). Categorical data will include counts and percentages. The 95% CIs will be reported where appropriate. Per country analyses will be performed where reasonable, as some subgroups might be too small to be looked at per country. The data may also be evaluated and presented for other meaningful subgroups of patients (e.g., by patients for which there is missing information).

Among edoxaban users retrieved from the charts, the number and percentage of the following categories will be described:

- All users (100%)
- Patients categorized as inappropriate drug users as defined (but not restricted to) :

  (a) use in patients in which the product is contraindicated,

  (b) use in patients who are not under the indication label per SmPC

  (c) use involving a different dose (e.g. no dose reduction or dose reduction without reason), dosing regimen or route of administration or

  (d) use that demonstrates non-adherence to guidance in the label.
- Body weight
- Patients <18 years
- Patients > 65 years

- Pregnant women
- Patients in any other disease groups, by specific disease type (renal, hepatic impairment)
- Patients using concomitant drugs known to increase the risk of bleeding e.g., aspirin, NSAIDs.

The number of patients who have been prescribed edoxaban in a way that differs from what is described in the SmPC will be enrolled and characterized overall and by country.

The distribution of time on edoxaban for the categories outlined above will be calculated. Information on dose and discontinuations will be examined. Number of prescriptions of edoxaban per patient per year or number of prescription fills and refills since first prescription to index date will be characterised.

The history of use of other anticoagulants will be described for all edoxaban users and by patient's categories defined above.

Assessing clinical knowledge

The data will be reported as descriptive statistics for the variables already presented in section 9.3 (survey administration variables, description of survey population, and assessment of knowledge of the key messages of the educational program). Data will be presented overall, by country and by key characteristics (e.g. specialty of physician, geographic location, etc.).

Physicians who do not respond to the survey will be categorized into non-responders. Moreover, the responders and non-responders characteristics will be compared.

A comparison of responders and overall target population characteristics will also be performed.

9.8. Quality Control

This study will be conducted according to the rules of 'Good Pharmacoepidemiology Practice' (GPP) and the 'Guideline on Good Pharmacovigilance Practices (GVP) – Module VIII (Rev 1)' EMA/813938/2011 Rev 1. Related quality control mechanisms (e.g. data plausibility checks, monitoring of data) will be performed accordingly.

The physician will comply with the confidentiality policy as described in the site contract. The physician will comply with the observational plan and the requirements described in the contract. The physician is ultimately responsible for the conduct of all aspects of the study at the site and verifies by signature the integrity of all data transmitted to the sponsor.

During the site initiation visit, the monitor will provide training on the conduct of the study to the investigator, co-investigator(s), and all site staff involved in the study. In order to ensure the integrity of the data, sites will be monitored by a qualified monitor. A risk based monitoring approach will be conducted during the study to examine compliance with the protocol and adherence to the data collection procedures, to assess

the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study. This will include regular remote data monitoring and on site monitoring will be performed in 20% of the sites. During on-site monitoring, the monitor will verify 100% of informed consent documentation and perform source data verification against the patient's medical records in randomly selected patients (3 per site).

Data quality checks will be performed on an ongoing regular basis. Queries will be raised by the responsible CRO and shall be answered by the site in due course. The purpose is to ensure that the rights of the patients are protected, that the reported data are accurate and complete, and that the conduct of the study is in compliance with the observational plan and applicable regulatory requirements.

The monitor will close out each site after the last patient's final follow-up assessment is completed, all data have been entered and all outstanding monitoring issues have been resolved or addressed. All monitoring procedures will be described in a Clinical Operations Plan (COP). Monitor contact details for each participating site will be maintained in the Investigator Site File.

Representatives of the Sponsor's quality assurance unit/monitoring team and competent regulatory authorities must be permitted to inspect all study-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs and the patients' original medical records. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

9.9. Limitations of the Research Methods

As this study aims at collecting real-world evidence, some limitations common to non-interventional studies apply. In addition to this, the following aspects need to be considered:

Although sites will be selected to promote representativeness for the respective country or region as much as possible, sites also need to have sufficient interest and capacities to participate in the registry.

Although eligible patients should be consecutively enrolled at a site, it needs to be considered, that patients need to give their informed consent for their medical records to be extracted. This might hamper consecutive enrolment at a site.

To allow for demonstrating representativeness of edoxaban patients included into the trial, an enrolment log will have to be filled by the sites, where all patients treated with edoxaban at the site at discretion of the physician need to be listed and the reason to participate or not to participate needs to be documented.

No explicit non-eligibility criteria are defined to avoid selection of patients and thus violation of the "real-life" principle.

However, as data collected in the study is part of routine medical practice and not collected for the purpose of the study, the extent of available information and the classification/description of medical data and procedures could vary.

Concerning the evaluation of effectiveness of the educational program, it could be noted that participation in a survey may not be representative of the target users given that participation is more likely amongst engaged healthcare professionals and/or more motivated or educated individuals.

10. PROTECTION OF HUMAN SUBJECTS

To ensure the quality and integrity of research, this study will be conducted under the Guidelines for Good Pharmacovigilance Practices (GVPs) and Good Pharmacoepidemiology Practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki and its amendments, and any applicable national guidelines.

10.1. Review by Ethics Committees/Competent Authorities (CAs)

Notification to or approval by IECs and CAs or other organizations will be performed as required by national regulations in the participating countries before commencement of enrolment at a study site.

10.2. Insurance and Liability

All treatments of patients included in this DUS are local standard of care and occur as part of the daily routine practice. The registry is non-interventional and does not foresee any change from treatment nor additional examinations apart from the standard of care. Insurance coverage will only be provided with regards to the product liability. A specific patient's insurance for DUS is not necessary (if not in contradiction with specific legal requirements in the country of conduct).

10.3. Patient Information, Informed Consent

Written Informed Consent will be obtained from all patients in informed consent forms (ICFs) in order to agree his/her patient source data are being transferred into an eCRF and are evaluated and analysed for scientific purposes.

10.4. Data Protection

The patients' privacy will be kept according to the requirements of Directive 95/46 EC and national legislation for data protection. Data will be collected in a pseudonymous way. A patient identification number (ID) assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting any study-related data.

Only authorised personnel as hospital/site staff, representatives of the sponsor and CRO, and CAs should have access to personalised patient data e.g. in original source documents (medical records). The patient will agree to this by signing a respective statement on the ICF.

10.5. Numbering and Identification of Patients

A patient ID will be assigned to each patient when reporting data in the eCRF or on the paper CRF. The patient ID will consist of the country code, followed by a three digit site number and the consecutive patient number (e.g. UK-001-001). Medical record number or other local reference identifiers are not collected.

At each site a patient ID list will be kept linking the ID to the patient's identity.

10.6. Assessments

The investigators or the data retriever will be instructed regarding the correct documentation of the required information to be captured for each patient in the eCRF. These data are available as part of the routine treatment.

11. MANAGEMENT AND REPORTING OF ADVERSE DRUG REACTIONS (ADR)

All adverse drug reactions that are judged by the investigator as related to edoxaban need to be reported according to the national requirements and local laws. The documentation and reporting follows the Guideline on Good Pharmacovigilance Practices (GVP Module VI).

11.1. Definitions

Adverse Drug Reaction (ADR)

A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reaction also includes adverse clinical consequences associated with use of the product outside the terms of the Summary of Product Characteristics or other conditions laid down for the marketing and use of the product (including prescribed doses higher than those recommended, overdoses or abuse).

Serious Adverse Drug Reaction

Serious adverse reaction means an adverse reaction which results in:

- Death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity, or
- Is a congenital anomaly/birth defect.

Life threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalisation or development of dependency or abuse.

11.2. Reporting of suspected ADRs by the Investigator

All Edoxaban related adverse drug reactions need to be reported by the site to the pharmacovigilance department of the sponsor as spontaneous ADR reports. The study specific ADR reporting form has to be sent to the respective Daiichi Sankyo affiliate in the country where the site is located and will then be forwarded to the sponsor (Daiichi Sankyo Europe GmbH, Clinical Safety & Pharmacovigilance Department, Zielstattstrasse 48, 81379 Munich, Germany). The sponsor will process all the ADR details in line with the requirements for spontaneous ADR reporting and in accordance with the Guideline on Good Pharmacovigilance Practices (GVP).

In addition, the investigator has to confirm in the eCRF whether or not an ADR has been reported.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Progress Reports

As already mentioned in section 11 Daiichi Sankyo will summarise relevant safety information or information with potential impact in the benefit-risk assessment (if any) in Periodic Safety Update Reports.

12.2. Annual/Interim Analyses and Reporting

The interim report will be prepared after the completion of data collection in the first wave countries. The interim report will be provided in the third Quarter 2017.

13. DOCUMENTATION AND ARCHIVING

The Sponsor is responsible for archiving study specific documentation (Observational plan, potential amendments, Final Report and Database) for at least ten years. Archived data may be held on electronic record, provided that a back-up exists and that hard copies can be obtained, if required.

The investigator is responsible for archiving the patient ID list, all signed ICFs and his/her contract for at least ten years and in accordance with local legislation.

Physicians are obliged to keep patient files according to national requirements.

14. LEGAL REQUIREMENTS

This DUS fulfils the requirements of the Directive 2001/83 EC, Module VIII of GVP, Directive 95/46 EC, the Declaration of Helsinki and will be conducted in accordance with the respective Standard Operating Procedures (SOP) of DSE.

14.1. Reimbursement

Compensation according to local regulations and to the time spent to inform patients and to document patient data will be paid two times a year if not specified otherwise in the site contract.

Investigator fees per patient:
will account for the time spent related to the study and is estimated to 7.5hours per patient. The fees are split to different study personals (investigators, study coordinators, study nurses) involved in the DUS. The number of hours was calculated taking into account:

- Repeated time by patient (information and consent discussion, extraction of patients data, data completed within the secured eCRF, edit checks and quality of data and regular monitoring
- Set up of the study (site initiation Visits, eCRF training, initial screening of potential eligible patients, Lixiana ® Survey questionnaires (2)).

The investigator fees will be calculated taking the Fair Market Value benchmarking priced within the industry in considerations.

14.2. Registration

In accordance with the 2010 EU pharmacovigilance legislation, information about this DUS will be entered into the publically available European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) E-Register of Studies. The study protocol will be entered into the register before the start of data collection. Updates to the study protocol in case of substantial amendments, progress reports where applicable, and the final study report will also be entered in the register.

15. FINAL REPORT

A final report will be presented by end of the second Quarter 2019, latest 6 months after data base lock. . The final report will encompass all planned analyses, including a description of the complete study population (in all countries), as described above and in the SAP.

16. PUBLICATION

In order to protect confidential information and/or the interests of DSE, all publications (manuscripts and congress presentations) or announcements originating from this research are governed the Sponsor.

17. PREMATURE TERMINATION OF THE NIS/REGISTRY

The physician may withdraw his/her participation in this registry at any time. In the case of a premature termination of the entire DUS by the sponsor, the project leader has to inform all participating sites, IECs, and CAs.

18. REFERENCES

[1] SmPCs Edoxaban

[2] Edoxaban versus Warfarin in Patients with Atrial Fibrillation
Giugliano RP, Ruff TC, Braunwald E, et.al. Edoxaban versus Warfarin in patients with Atrial Fibrillation: N Engl J Med 2013; 369:2093-2104

[3] Büller HR, Grosso MA, Mercuri M, et.al ; Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism: N Engl J Med 2013; 369:1406-15

[4] Hatcher, L (1994) A step –by Step Approach to Using the SAS System for Factor Analysis and structural Equation Modeling. Cary; NC: SAS Institute, INC

[5] Center for Drug Evaluation and Research. Risk Evaluation and Mitigation Strategy Assessments: Social Science Methodologies to Assess Goals Related to Knowledge. United States Food and Drug Administration: Department of Health and Human Services. Docket No: FDA–2012–N–0408, 2012.

APPENDIX 1. ENCEPP CHECKLIST

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Edoxaban prescription patterns in Europe: a retrospective drug utilisation chart review study

Study reference number:
DSE-EDO-01-14-EU

Section 1:	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	22
1.1.2 End of data collection[3]	☒	☐	☐	22
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	22

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	25
2.1.2 The objective(s) of the study?	☒	☐	☐	25-26
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	28
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Not applicable.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	27-28

[2] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[3] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☐	☒	
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

Descriptive analysis will be performed.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	28
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	29
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	30
4.2.4 Disease/indication?	☒	☐	☐	30
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	33

Comments:

Not Applicable.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	31
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	31

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Eligible patients are those prescribed edoxaban since its launch.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	☒	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

Not applicable.

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Not applicable.

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: 8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	30-32

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☒	
8.1.3 Covariates?	☒	☐	☐	33-36
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☒	☐	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☒	☐	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☒	☐	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

It is not know yet what information will effectively be available on the medical records.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	33-36

Comments:

Not applicable.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.2 Is the choice of statistical techniques described?	☒	☐	☐	33-36
10.3 Are descriptive analyses included?	☒	☐	☐	33-36
10.4 Are stratified analyses included?	☒	☐	☐	33-36
10.5 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

The Analysis Plan will be further developed in a specific Statistical Analysis Plan.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	33-36
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.3 Are methods of quality assurance described?	☒	☐	☐	38-39
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	39
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	38

Comments:

Not Applicable.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	39
12.1.2 Information biases?(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	39
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.3 Does the protocol address other limitations?	☒	☐	☐	38

Comments:

Not Applicable.

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	41
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	41

Comments:

Not Applicable.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	12

Comments:

Not Applicable.

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	45
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	49

Comments:

Not Applicable.

Name of the main author of the protocol: _____

Date: 18/05/2016

Signature: _____  _____

APPENDIX 2. LIXIANA® - SURVEY QUESTIONNAIRE

Thank you for participating in this voluntary survey to monitor the use of edoxaban in Europe. Please answer each question/statement as honestly as possible. You will not be individually assessed as results will be reported in aggregate form only and not linked to any personal identifier. All information collected during the course of the survey will be kept strictly confidential.

Part I – Edoxaban utilisation

1. Concerning the indications for which Lixiana is approved in the European Union, please indicate if the following sentences are true (T) or false (F):
    a. Lixiana is indicated in the prevention of stroke in adult patients with nonvavular atrial fibrillation with or without risks factors ___
    b. Lixiana is indicated in the prevention of systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more risk factors ___
    c. Lixiana is indicated in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults ___
    d. Lixiana is not indicated in the prevention of recurrent DVT and PE in adults ___
    e. Lixiana is indicated in the prevention of VTE in subjects undergoing orthopaedic surgery___
    f. Lixiana is indicated in the prevention of atherothrombotic events after acute coronary syndrome

2. Concerning the recommended dosing of Lixiana, please indicate if the following sentences are True (T) or false (F):
    a. In patients with mild to moderate hepatic impairment, the recommended daily dose is of 30mg___
    b. In patients with normal renal and hepatic function, the recommended daily dose is of 60mg___
    c. In patients with moderate to severe renal impairment as defined by a creatinine clearance between 15 and 50 mL/min, the recommended daily dose is of 30mg___
    d. Lixiana has to be taken outside of meals___
    e. The duration of treatment with Lixiana is well defined and independent of transient or permanent risk factors___
    f. Co-administration with cyclosporine does not require any adjustment in the dose of Lixiana___

3. Lixiana is contraindicated or not recommended in the following special patient populations (please select all that apply):

    a. Severe hepatic impairment
    b. Elevated liver enzymes ALT/AST 2x ULN
    c. Hepatic disease associated with coagulopathy and clinically relevant bleeding
    d. In co-administration with low dose ASA (≤ 100mg/day)
    e. Uncontrolled severe hypertension
    f. Patients with a body weight ≤ 60 Kg

4. When initiating treatment with Lixiana, an initial course of heparin for at least 5 days prior to treatment with Lixiana must be observed (please select the correct answer):

    a. In the treatment of patients with DVT and PE
    b. In the prevention of stroke and systemic embolism in patients with NVAF
    c. In both the treatment of DVT and PE patients, and prevention of stroke and systemic embolism in patients with NVAF

5. In the occurrence of a missed dose, the patient should be instructed to take it immediately even if it means to double the prescribed dose on the same day. Please indicate if the sentence is:

    a. True
    b. False
    c. I don’t know

6. When switching patients to Lixiana from non-Vitamin K antagonist oral anticoagulants, the non-VKA must be discontinued and Lixiana initiated at the time of the non-VKA next dose. Please indicate if the sentence is:

    a. True
    b. False
    c. I don’t know

7. When switching patients to Lixiana from Vitamin K antagonist anticoagulants, the INR must be ≤2.5 after discontinuing the VKA and before initiating Lixiana. Please indicate if the sentence is:

    a. True
    b. False
    c. I don’t know

8. When switching patients from Lixiana to warfarin, the initial dose of Lixiana remains the same during concomitant use. Please indicate if the sentence is:

    a. True
    b. False
    c. I don't know

9. When switching patients from Lixiana to warfarin, the INR should be measured 3 times (please selected the correct answer):

    a. Just after taking the daily dose of Lixiana
    b. Just prior to taking the daily dose of Lixiana
    c. One time just before the daily dose of Lixiana, a second time 1h after the daily dose of Lixiana and a third time 2 hours after the daily dose of Lixiana

10. When switching patients to Lixiana from parenteral anticoagulant therapy, or from parenteral anticoagulant therapy to Lixiana, the initial therapy must be always discontinued before initiating the second. Please indicate if the sentence is:

    a. True
    b. False
    c. I don't know

11. Lixiana must be initiated immediately after discontinuing the continuously administered parenteral anticoagulant therapy. Please indicate if the sentence is:

    a. True
    b. False
    c. I don't know

12. Concerning the perioperative management of patients under treatment with Lixiana (please select the correct answer):

    a. Lixiana does not need to be stopped before a surgical intervention or other invasive procedure
    b. Lixiana should be stopped at least 12 hours before a surgical intervention or other invasive procedure
    c. Lixiana should be stopped at least 24 hours before a surgical intervention or other invasive procedure
    d. I don't know

13. In case of overdose with Lixiana (please select the correct answer):

    a. The patient must be given an antidote during the first 2 hours

b. There is no antidote available, early administration of activated charcoal may be considered to reduce absorption
c. Haemodialysis must be considered
d. I don't know

14. In the management of bleeding complications treatment with Lixiana must be delayed or discontinued

a. True
b. False
c. I don't know

15. When taking Lixiana, routine coagulation tests include: INR, PT and aPTT. Please indicate if the sentence is:

a. True
b. False
c. I don't know

Part II – General questions

16. Are you aware of the Prescriber's Guide for Lixiana?

- Yes
- No

17. Have you received the Prescriber's Guide for Lixiana?

- Yes
- No

18. You received the Prescriber's Guide:

- Before prescribing Lixiana for the first time
- After prescribing Lixiana for the first time

19. Have you read the Prescriber's Guide?

- Yes, completely
- Yes, partially
- No

If not:

20. You have not read the Prescriber's Guide, please select the most relevant reason that applies.

    - You prefer other sources of information, such as the Summary of Product Information
    - The Guide was too time consuming
    - It is not the first time you prescribed an anticoagulant factor Xa inhibitor, so you did not think the Guide would add to your knowledge
    - Other (please specify)_____

If yes:

21. How often have you consulted the Prescriber's Guide thereafter?

    - Never
    - Once
    - 2-3 times
    - More than 3 times

22. You find the information in the Prescriber's Guide:

    - Not useful
    - Useful

23. Have you referred to other sources of information to aid you in prescribing and managing Lixiana?

    - No
    - Yes, please refer which ones:_____

24. Are you aware of the Patient Alert Card for Lixiana?

    - Yes
    - No

25. Have you referred all your patients to the Patient Alert Card, when you first prescribed them Lixiana?

    a. Yes, always
    b. Yes, most of the time
    c. No, not always
    d. No, I often forget

26. During follow-up consultations, do you confirm if the patient carries the Patient Card with them?

    a. Yes
    b. No

27. How regularly do you check your patients' knowledge on the content of the Patient Alert Card?

    a. Never
    b. In every consultation
    c. At specific occasions (please specify)_____