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Summary of the risk management plan (RMP) for Lixiana (edoxaban)

This is a summary of the risk management plan (RMP) for Lixiana, which details the measures to be taken in order to ensure that Lixiana is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Lixiana, which can be found on Lixiana's EPAR page.

Overview of disease epidemiology

Lixiana is a medicine used to prevent stroke and blood clots in patients with atrial fibrillation, and to treat and prevent venous thromboembolism (deep vein thrombosis and pulmonary embolism).

Atrial fibrillation is a condition where the heart beats irregularly and often rapidly. Patients are at risk of developing blood clots that block blood vessels in the brain, causing a stroke, or in other organs (systemic embolism). About 2.8% of people are thought to be affected by atrial fibrillation. Most of these people are between 65 and 85 years old, and more men than women have the condition. The risk of having atrial fibrillation is increased by a number of other conditions, such as high blood pressure, an overactive thyroid gland, obesity, diabetes, and kidney disease.

Venous thromboembolism is a condition where the blood forms a clot in the veins, most often in the deep veins of the leg (deep vein thrombosis, DVT) giving rise to pain and swelling. Dislodged clots that travel to the lungs, blocking their blood supply, are known as pulmonary embolism, a serious and potentially fatal condition. Venous thromboembolism becomes more common with increasing age, particularly over 40 years. The risk may be increased by prolonged immobilisation, pregnancy, use of female hormones (oral contraceptives, hormone replacement therapy), cancer, some cancer treatments, obesity, and smoking.

Summary of treatment benefits

Lixiana is an anticoagulant (a medicine that stops blood clotting) containing the active substance edoxaban. It has been shown to be as effective as the standard anticoagulant warfarin in preventing stroke and systemic embolism in patients with atrial fibrillation. The effects were studied in one main study, which involved over 21,000 patients for an average of 2.5 years. The main measure of effectiveness was the rate of stroke or systemic embolism among the patients each year. A first systemic embolism or stroke occurred in 182 patients given standard doses of Lixiana and in 232 of those given warfarin, corresponding to annual rates for these events of around 1.2% and 1.5% respectively. When another recommended definition of the type of stroke was used, embolism or stroke due to blood clots was seen in 143 patients given Lixiana (0.9%) and 157 given warfarin (1%). There was a trend for better results in patients with reduced kidney function than those whose kidney function was very good.

In the treatment and prevention of blood clots in patients with DVT or pulmonary embolism, Lixiana was also found to be as effective as warfarin in a study involving over 8,200 patients. The main measure of effectiveness was the number of patients who had another episode of DVT or pulmonary embolism during the study period. Further episodes were seen in 130 of 4,118 patients given edoxaban (3.2%) and in 146 of 4,122 given warfarin (3.5%).

Unknowns relating to treatment benefits

In the Lixiana clinical trial programme, there was limited or no experience of use in children, pregnant and breastfeeding patients, those with kidney or liver impairment, or in patients whose atrial fibrillation was due to disease of the heart valves.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Bleeding (including bleeding due to use with other medicines that increase bleeding risk, or failure to reduce doses where recommended)	Bleeding is a well-established risk of anticoagulant treatment. Bleeding is common in patients given Lixiana (affecting up to 1 in 10 people) and may occur from or under the skin, from the nose, bowel, mouth or throat, or vagina (mostly in premenopausal women who experienced heavier monthly periods), in the stomach or following an injury; blood in urine and anaemia are also common. Other types of bleeding including from the eyes, from a surgical wound after an operation, in the brain and in spit when coughing are uncommon (affecting up to 1 in 100 people). Rarely (in up to 1 in 1000 people), there is bleeding in the muscles, joints, abdomen, heart and skull and as a consequence of a surgical procedure. Some patients are at a higher risk of bleeding than others, especially when taking certain medicines that themselves increase the risk of bleeding (e.g., aspirin, NSAIDs, or other antiplatelet medicines). In addition, some patients are at greater risk of bleeding because they may be exposed to relatively higher levels of the medicine in the body (because of low body weight, moderately or severely reduced kidney function, or through taking medicines known as strong P-gp inhibitors which slow the	Patients and prescribers are provided with a patient alert card and prescriber's guide respectively, explaining the need to be alert for symptoms of bleeding and for patients to seek appropriate medical attention promptly in order to minimise the impact of bleeding events. The risk of bleeding can be reduced by appropriate dose adjustment in patients with low body weight (less than 60 kg) or reduced kidney function, or in patients taking certain medicines (some P-gp inhibitors), as described in the product information. Use of the reduced dose in these patients leads to similar blood concentrations of edoxaban (and therefore a similar risk of bleeding) as in patients who do not need dose reduction.

Risk	What is known	Preventability
	removal of edoxaban from the body).	

Important potential risks

Risk	What is known
Liver damage (hepatic dysfunction)	Abnormal liver function tests may occur during Lixiana treatment in up to 1 in 10 people and liver damage is considered to be a potential risk. However, experimental studies suggest that the potential for causing liver damage may be considered low. During studies to license Lixiana, there were similar numbers of liver events and laboratory test abnormalities reported in the edoxaban and the warfarin groups.
Reduced effect in subjects with good kidney function (high creatinine clearance)	While the benefit of edoxaban was considered positive overall in all patients with atrial fibrillation, there were indications that edoxaban may not work as well in patients with high creatinine clearance compared with patients managed well on warfarin. Creatinine clearance is a measure of how well the kidneys work, and is calculated from a blood test. An additional study will be conducted to further investigate this. Doctors will check patients' kidney function before the start of treatment with Lixiana and subsequently as necessary.

Missing information

Risk	What is known
Overdose	Overdose of Lixiana could lead to bleeding but information is limited. In the clinical study program, a total of 17 patients had at least one overdose of edoxaban. In one case, the overdose was associated with a minor bleed; there were no major bleeds. The importance of taking Lixiana as prescribed will be provided in the prescriber's guide and patient alert card.
Reversibility	Currently information on a suitable antidote to reverse the action of Lixiana is lacking. Further clinical studies are underway or planned to address this question.
Use in children	There is no information on the use of Lixiana in patients less than 18 years of age. Results from studies in young rats may mean that the exposure to edoxaban in children younger than 2 years may not be comparable to that of older children or adults. A plan for studies in children has been agreed, and includes a study of how the medicine acts and is distributed in the body in children as well as clinical studies in children with problems due to blood clots or children with underlying heart disease in need of preventive therapy for thrombotic events.
Use in patients with reduced liver function	Patients with severe liver impairment may be at high risk of bleeding due to altered ability of the blood to clot. It is not known what the effect of giving Lixiana to these patients would be and hence it is not recommended that the

Risk	What is known
(hepatic impairment)	medicine is used in these patients. Edoxaban's distribution in the body has been studied in 16 patients with mild or moderate liver impairment but not in those with severe liver impairment, and such patients were also not included in the large studies that provided evidence to license the medicine.
Pregnancy and breastfeeding	In the clinical trials there were very few pregnant women treated with Lixiana. Because edoxaban reduces the ability of the blood to clot, there is an increased risk of bleeding during pregnancy and delivery. In animal studies, there was increased bleeding in the pregnant animals but this was at doses higher than what would be used in humans.Studies in animals have shown that edoxaban is found in breast milk. Therefore in breastfeeding women, either edoxaban should be stopped or breastfeeding should be stopped, depending on how important Lixiana's treatment is for the mother.
Patients with severely reduced kidney function (renal impairment) or end-stage kidney disease or on dialysis	The distribution of the active substance edoxaban was studied in patients with end-stage kidney disease or on dialysis, and showed they had increased exposure to edoxaban. These patients would therefore be expected to be at higher risk of bleeding and stroke compared with patients with normal kidney function, and they were excluded from the large studies that provided evidence to license the medicine. In the absence of more information the use of Lixiana in patients with end-stage kidney disease or on dialysis is not recommended.
Patients with mechanical heart valves	Patients with replacement mechanical heart valves are at significantly increased risk of thromboembolic events, and they were excluded from the large phase 3 clinical studies. Therefore the benefits and risks of Lixiana in this group are not known and the use of the medicine in patients with mechanical heart valves is not recommended.
Combination with dual antiplatelet therapy	Lixiana has not been studied when combined with more than one antiplatelet medicine. In the studies where Lixiana was combined with a single antiplatelet medicine, the frequency of bleeding was increased and it is assumed that additional antiplatelet therapy would increase the bleeding risk further.
Off-label use	Lixiana is approved for patients with atrial fibrillation or venous thromboembolism (DVT or pulmonary embolism). Its safety and effectiveness for uses outside the approved indications (off-label use) is not known.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Lixiana can be found on Lixiana's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Lixiana's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

Bleeding

Risk minimisation measure: Educational package including: • Prescriber's guide • Patient alert card • Healthcare professional and patient education
Objective and rationale: To educate patients and healthcare professionals on the risk of bleeding and on the signs and symptoms and the procedures related to the appropriate management to minimise its occurrence and severity, including avoidance of overdose and understanding those conditions/features where the dose of Lixiana needs to be reduced. Furthermore, patients and healthcare professionals are to be educated on the need for dose interruption for planned surgery and the need to continue required anticoagulation by other means.
Description: The educational materials to be provided to prescribing physicians and pharmacists will include information on: • The approved indications; • Overdose and the risk of bleeding, including dosing advice; • Management of haemorrhage (as part of the section on overdose); • Switching strategies, if switching to or from Lixiana; • Special situations requiring dose interruption or temporary switching to other anticoagulants; • Need for dose adjustment in patients weighing less than 60 kg, with moderate kidney impairment, or taking potent P-gp inhibitors; • Use of coagulation tests and their interpretation; • Guidance regarding surgery/invasive procedures and temporary discontinuation. The patient alert card will provide information on: • Risk of bleeding and importance of contacting a healthcare professionals in case of bleeding; • The need to carry the card with them at all times and present to any healthcare professionals who sees them; • The need to consult with a physician in case of any surgical procedure.

Missing information

Risk minimisation measure: Educational package including:

• Prescriber's guide • Healthcare professional education (use in populations where information is limited or missing)
Objective and rationale: To educate healthcare professionals about the indications of Lixiana and the limitations of data and the populations for which Lixiana is contraindicated or not recommended.
Description: The healthcare professional educational materials to be provided to prescribing physicians and pharmacists will include information on: • The approved indications; • Clear explanation of contraindications, including pregnancy and breastfeeding; • Understanding conditions where special attention is warranted, such as moderate kidney failure, mild or moderate liver impairment; • Need for dose adjustment in patients weighing less than 60 kg body weight, with moderate kidney impairment, or taking potent P-gp inhibitors.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	**Objectives**	**Safety concerns / efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
Drug utilization study: Monitor prescribing patterns and off-label use	Prescription patterns, extent and nature of off-label use in the EU.	Off-label use	Planned	Study design ongoing: Protocol for EMA comments within 3 months of marketing authorisation of edoxaban. Study execution and final report within 18 months post-EMA approval of protocol and minimum 1 year post-launch in at least 5 major EEA markets
PASS: Non-interventional study on Edoxaban treatment in routine clinical practice for	To collect real-world safety data on bleeding events including intracranial haemorrhage, drug-related adverse events such as liver adverse events,	Safety of edoxaban in clinical practice	Planned	Execution following approval of protocol by authorities. Submission of full study protocol within 3 months of

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
patients with non-valvular atrial fibrillation (ETNA-AF-Europe)	cardiovascular and all-cause mortality in AF patients treated with edoxaban for up to 4 years.			positive CHMP opinion. Regular interim status reports, yearly data snapshots, pooled safety analysis after 1.5 years (combined with ETNA-VTE-Europe) Final Report: Q4 2021
Non-interventional study on Edoxaban treatment in routine clinical practice for patients with acute venous thromboembolism in Europe (ETNA-VTE-Europe)	The co-primary objective of this study is to collect real world safety data on bleeding events, drug-related adverse events such as liver adverse events, and mortality (VTE-related and all-cause) in VTE patients treated with edoxaban. Furthermore, safety analyses in pre-specified subpopulations such as patients with kidney impairment and patients with liver impairment will be performed. Primary objective is the analysis of the overall symptomatic VTE recurrence rate during an overall observational period of 18 months in unselected patients with acute VTE.	Safety of edoxaban in clinical practice VTE recurrence in clinical practice	Planned	Execution following approval of protocol by authorities. Submission of full study protocol within 3 months of positive CHMP opinion. Regular interim status reports, yearly data snapshots, pooled safety analysis after 1.5 years (combined with ETNA-AF-Europe) Final report approximately: Q2 2020
A Phase 2, randomized, double blind, vehicle-controlled multiple dose study to assess the safety,	To identify whether PRT064445 can reverse the effect of Factor Xa inhibitors	Reversibility of edoxaban effect in humans	Ongoing	To be confirmed

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
tolerability, pharmacokinetics, and pharmacodynamics of intravenously administered PRT064445 after dosing to steady state with edoxaban				
A Phase II randomized, sequential group, evaluation of ascending reversal doses of PER977 administered to subjects with steady state edoxaban dosing and re-anticoagulation with edoxaban following PER977 reversal	To identify whether PER977 can effectively reverse the effect of Factor IIa and Xa inhibitors.	Reversibility of edoxaban effect in humans	Ongoing. Clinical completion is anticipated in December 2014	CSR planned for July 2015
Prescriber Survey	Assess effectiveness of risk management system	Bleeding and missing information/off-label use	Planned	Execution will occur following approval of protocol and questionnaire by relevant regulatory authorities. The survey would be conducted approximately 1 year after launch, and depending on results may be repeated 1 year later in at least 5 European countries.
Planned for-	To develop a commercial	Measurement of	Planned	Commercially

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
registration study before filing for CE Marking of an anti-FXa assay in Q1 2016.	calibrated quantitative anti-FXa assay	edoxaban levels in humans		available assay planned to be available approximately Q2 2016
DU176b-A-U162: An open-label, multiple-dose pharmacokinetic and pharmacodynamic study of edoxaban in healthy subjects	The aim of this study is to correlate the observed anti-FXa levels, obtained in sodium-citrated plasma, to edoxaban-concentration data, obtained using lithium heparin as the anti-coagulant and analysed by liquid chromatography/ tandem mass spectrometry. In this study, other biomarkers of coagulation (e.g., thrombin generation and/or, intrinsic FX activity) will also be measured and analysed for correlation with the respective levels of anti-FXa activity.	To provide further technical validation of methods for anti-FXa assay.	Planned	Final CSR for submission is planned for Q2 2016
Evaluation of Lixiana (edoxaban) in patients with non-valvular atrial fibrillation and high creatinine clearance (short title: edoxaban in atrial fibrillation and high creatinine clearance)	To compare the exposure with an edoxaban 75 mg daily dose in patients with good kidney function (creatinine clearance over 100 mL/min) to that of an edoxaban 60 mg daily dose seen in the same patients treated for 12 months. The study will also look at: 1) distribution and action of these doses (pharmacokinetics/ pharmacodynamics) and anti-FXa assay evaluation	To investigate if improved protective effects against stroke could possibly be achieved by using a higher dose of edoxaban in patients with good kidney function	Planned	Final report for submission: approximately Q3 2018

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	2) The incidence of stroke/systemic embolism, and its components, ischaemic stroke, haemorrhagic stroke and systemic embolism as well as net clinical outcome 3) The incidence of major, intracranial, extracranial and clinically relevant bleeding (major and non-major)			

Studies which are a condition of the marketing authorisation

None of the above studies are conditions of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 06-2015.