Summary of risk management plan for LIXIANA (edoxaban)

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Disclaimer

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of LIXIANA is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of LIXIANA in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Daiichi Sankyo (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of LIXIANA.

Summary of risk management plan for Lixiana (edoxaban)

This is a summary of the RMP for edoxaban. The RMP details important risks of edoxaban, how these risks can be minimised, and how additional information will be obtained about edoxaban's risks and uncertainties (missing information).

Edoxaban's SmPC and its package leaflet give essential information to healthcare professionals and patients on how edoxaban should be used.

Important new concerns or changes to the current ones will be included in updates of edoxaban's RMP.

I. The Medicine and What It Is Used For

Edoxaban is authorised for prevention of stroke and systemic embolism in adult patients with NVAF and treatment of VTE including DVT and PE, and prevention of recurrent VTE in adults (see the SmPC for the full indication). It contains the anhydrous free base of edoxaban tosylate as the active substance and it is given by oral administration.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of edoxaban, together with measures to minimise such risks and the proposed studies for learning more about edoxaban's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be as follows:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including by PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of Important Risks and Missing Information

Important risks of edoxaban are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be taken safely orally. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of edoxaban. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Lixiana (edoxaban tosilate) tablet for oral use

List of Important Risks and Missing Information	
Important identified risks	Bleeding or Bleeding due to: • Drug interaction in combination with other drugs known to increase the risk of bleeding eg, aspirin, NSAID • Inappropriate administration of the 60-mg dose /inadvertent overdose by use of the 60-mg dose, eg in combination with use of strong P-gp inhibitors; in patients with low body weight ≤60 kg; and in patients with moderate to severe renal impairment (CrCL 15–50 mL/min)
Important potential risks	• Hepatic dysfunction • Trend towards decreasing efficacy in NVAF subjects with high CrCL
Missing information	• Lack of reversal agent • Reproductive and development toxicity (Pregnancy and lactation) • Patients with hepatic impairment • Patients with severe renal impairment (CrCL <30 mL/min) or end-stage renal disease (CrCL <15 mL/min or on dialysis) • Patients with mechanical heart valves • Combination with dual antiplatelet therapy • Off-label use in Europe in populations or indications outside the approved indications per European SmPC

CrCL = creatinine clearance; NSAID = nonsteroidal anti-inflammatory drug; NVAF = nonvalvular atrial fibrillation; P-gp = P-glycoprotein; SmPC = Summary of Product Characteristics

II.B Summary of Important Risks

Bleeding or Bleeding Due to: • Drug interaction in combination with other drugs known to increase the risk of bleeding, eg, aspirin, NSAIDs • Inappropriate administration of the 60-mg dose /inadvertent overdose by use of the 60-mg dose, eg in combination with use of strong P-gp inhibitors; in patients with low body weight ≤60 kg; and in patients with moderate to severe renal impairment (CrCL 15–50 mL/min)	
Risk minimisation measures	• SmPC/PIL • Prescription-only medicine • Educational package including: – Prescriber Guide – Patient Alert Card
Additional pharmacovigilance activities	• None
Hepatic Dysfunction	
Risk minimisation measures	• SmPC/PIL • Prescription only medicine
Additional pharmacovigilance activities	• None
Trend Towards Decreasing Efficacy in NVAF Subjects with High Creatinine Clearance	
Risk minimisation measures	• SmPC • Prescription-only medicine
Additional pharmacovigilance activities	• None
Missing Information (including reversibility, pregnancy and lactation, hepatic impairment, renal impairment, mechanical heart valves, combination with antiplatelets and off-label use)	
Risk minimisation measures	• SmPC/PIL • Prescription-only medicine • Prescriber Guide
Additional pharmacovigilance activities	• Anticoagulant reversal programme • None

CrCL = creatinine clearance; NSAID = nonsteroidal anti-inflammatory drug; NVAF = nonvalvular atrial fibrillation; P-gp = P-glycoprotein; PIL = patient information leaflet; SmPC = Summary of Product Characteristics

II.C. Post-authorization Development Plan

II.C.1 Studies That Are Conditions of the Marketing Authorization

There are no studies that are conditions of the marketing authorisation or specific obligation of edoxaban.

II.C.2 Other Studies in Post-authorization Development Plan

Drug Utilisation Study (DSE-EDO-01-14-EU)

Purpose of the study: To assess off-label use in the EU. This study is completed.

Prescription Survey Study

Purpose of the study: To measure the effectiveness of the risk minimisation measures and educational programmes in European countries using edoxaban for its approved indications educational materials for HCP and patients. This study is completed.

PASS: ETNA-AF-Europe (DSE-EDO-04-14-EU)

Purpose of the study: To collect real-world safety data on bleeding events including intracranial haemorrhage, drug related adverse events such as liver adverse events, cardiovascular (CV) and all-cause mortality in AF patients treated with edoxaban up to 4 years. This study is completed.

PASS: ETNA-VTE-Europe (DSE-EDO-05-14-EU)

Purpose of the study: 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. This study is completed.

PAM (DU176b-C-E314): Edoxaban in Atrial Fibrillation and High Creatinine Clearance

Purpose of the study: To compare the exposure (based on Cav, Cmin, and Anti-FXa) of an edoxaban 75-mg QD dose in patients with CrCL >100 mL/min to that of an edoxaban 60-mg QD dose seen in the same patients treated for 12 months. This study is completed.