Part VI: Summary of the Risk Management Plan

As the safety concerns and their management are identical for all products covered by this RMP, the information in Part VI is presented only once together for all products.

Summary of risk management plan for Edoxaban Zentiva/Edirnex (Edoxaban)
This is a summary of the risk management plan (RMP) for Edoxaban Zentiva/Edirnex. The RMP details important risks of Edoxaban Zentiva/Edirnex, how these risks can be minimised, and how more information will be obtained about Edoxaban Zentiva/Edirnex's risks and uncertainties (missing information).
Edoxaban Zentiva/Edirnex's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Edoxaban Zentiva/Edirnex should be used.

Important new concerns or changes to the current ones will be included in updates of Edoxaban Zentiva/Edirnex's RMP.

I. The medicine and what it is used for

Edoxaban Zentiva/Edirnex 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 edoxaban tosilate monohydrate as the active substance and it is given by oral administration.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

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

- 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 (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Edoxaban Zentiva/Edirnex, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

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

If important information that may affect the safe use of Edoxaban Zentiva/Edirnex is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of Edoxaban Zentiva/Edirnex are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Zentiva/Edirnex. 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 (e.g. on the long-term use of the medicine).

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 e.g. aspirin, NSAIDs - inappropriate administration of the 60-mg dose /inadvertent overdose by use of the 60-mg dose, e.g., 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

II.B Summary of important risks

Summary of important risk that have corresponding additional pharmacovigilance/risk minimisation activities are:

Important identified risk: Bleeding or Bleeding due to: - drug interaction in combination with other drugs known to increase the risk of bleeding e.g. aspirin, NSAIDs - inappropriate administration of the 60-mg dose /inadvertent overdose by use of the 60-mg dose, e.g., 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	<u>Routine risk minimisation measures:</u> SmPC Section 4.2 Posology and method of administration SmPC Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions for use

	SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction SmPC Section 4.6 Fertility, pregnancy and lactation SmPC Section 4.8 Undesirable effects SmPC Section 4.9 Overdose PL sections 2, 3 and 4 Prescription only medicine Additional risk minimisation measures: Prescriber Guide Patient Alert Card
Missing information (including reversability, pregnancy and lactation, hepatic impairment, renal impairment, mechanical heart valves, combination with antiplatelets and off-label use)	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.6 SmPC Section 4.9 SmPC Section 5.2 PL sections 2 and 4 Prescription only medicine Additional risk minimisation measures: Prescriber Guide

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Edoxaban Zentiva/Edirnex.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Edoxaban Zentiva/Edirnex.