Part VI: Summary of the risk management plan

Summary of risk management plan for edoxaban by Krka (edoxaban)

This is a summary of the risk management plan (RMP) for edoxaban by Krka. The RMP details important risks of edoxaban by Krka, how these risks can be minimised, and how more information will be obtained about edoxaban by Krka's risks and uncertainties (missing information).
Edoxaban by Krka's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how edoxaban by Krka should be used.
Important new concerns or changes to the current ones will be included in updates of edoxaban by Krka's RMP.

I. The medicine and what it is used for

Edoxaban by Krka is authorised for prevention of stroke and systemic embolism in adult patients and for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE in adults (see SmPC for the full indication). It contains edoxaban as the active substance and it is given orally.

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

Important risks of edoxaban by Krka, together with measures to minimise such risks and the proposed studies for learning more about edoxaban by Krka'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 by Krka, 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 by Krka is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of edoxaban by Krka 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 by Krka. 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 risk of bleeding eg. Aspirin, NSAIDs - Inappropriate administration of 60 mg dose/inadvertent overdose by use of 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

CrCL = creatinine clearace; NSAID = nonsteroidal anti-inflammatory drug; NVAF = nonvalvular atrial fibrillation; P-gp = P-gycoprotein; 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 risk of bleeding eg. Aspirin, NSAIDs** - **Inappropriate administration of 60 mg dose/inadvertent overdose by use of 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	Routine risk minimisation measures SmPC section 4.3, 4.4, 4.5, 4.6, 4.8 and 4.9. PL section 2, 3 and 4 Additional risk minimisation measures Educational material: - Prescriber guide - Patient alert card

Hepatic dysfunction	
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.2, 4.3, 4.4 and 4.8 PL section 2 and 4 Additional risk minimisation measures None

Trend towards decreasing efficacy in NVAF subjects with high CrCL	
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.2 and 4.4 PL section 2 Additional risk minimisation measures None

Lack of reversal agent	
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4 Additional risk minimisation measures Educational material: - Prescriber guide

Reproductive and development toxicity (Pregnancy and lactation)	
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.3, 4.6 and 5.3 PL section 2 Additional risk minimisation measures Educational material: - Prescriber guide

Patients with hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.2, 4.3, 4.4 and 4.8 PL section 2 and 4 Additional risk minimisation measures Educational material: - Prescriber guide

Patients with severe renal impairment (CrCL < 30 mL/min) or end-stage renal disease (CrCL < 15 mL/min or on dialysis)	
Risk minimisation measures	Routine risk minimisation measures SmPC section: 4.2 and 4.4 PL section: 2 Additional risk minimisation measures Educational material: - Prescriber guide

Patients with mechanical heart valves	
Risk minimisation measures	Routine risk minimisation measures SmPC section: 4.4 PL section: 2 Additional risk minimisation measures Educational material: - Prescriber guide

Combination with dual antiplatelet therapy	
Risk minimisation measures	Routine risk minimisation measures SmPC section: 4.5 Additional risk minimisation measures Educational material: - Prescriber guide

Off-label use in Europe in populations or indications outside the approved indications per European SmPC	
Risk minimisation measures	Routine risk minimisation measures SmPC section: 4.1 PL section: 1 Additional risk minimisation measures Educational material: - Prescriber guide

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

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 by Krka.

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

There are no studies required for edoxaban by Krka.