Part VI: Summary of the risk management plan

Summary of risk management plan for Arxebo 15 mg, 30 mg, 60 mg filmdragerade tabletter (Edoxaban)

This is a summary of the risk management plan (RMP) for Arxebo 15 mg, 30 mg, 60 mg filmdragerade tabletter [Arxebo]. The RMP details important risks of Arxebo, how these risks can be minimised, and how more information will be obtained about Arxebo's risks and uncertainties (missing information).

Arxebo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Arxebo should be used.

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

I. The medicine and what it is used for

Arxebo is authorised for:

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

It contains edoxaban as the active substance and it is given by oral route.

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

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

II.A List of important risks and missing information

Important risks of Arxebo 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 Arxebo. 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 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 clearance; NSAID = nonsteroidal anti-inflammatory drug; NVAF = nonvalvular atrial fibrillation; P-gp = P-glycoprotein.

II.B Summary of important risks

<table>
<tr><td colspan="2">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 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)</td></tr>
<tr><td>Risk minimisation measures</td><td><u>Routine risk minimisation measures:</u>

SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8, 4.9 and 5.1.

PL sections 2, 3 and 4.

Recommendation for the appropriate posology in patients with specific clinical factors is included in SmPC section 4.2 and 4.5.

Recommendation for renal function assessment by calculating the CrCl prior to initiation of treatment and when a change in renal function is suspected during treatment is included in SmPC section 4.2 and 4.4.

Recommendation for adequate clinical surveillance for identifying signs and symptoms of bleeding complications and anaemia and laboratory testing of haemoglobin/haematocrit is included in SmPC section 4.4 and 4.8.

Recommendation for discontinuation of edoxaban as soon as possible and preferably at least 24 hours before surgical or other procedures and guidance on re-initiation of treatment after the surgery/other intervention is included in SmPC section 4.4.

Recommendation for management of bleeding is included in SmPC section 4.9.

Subject to medical prescription

<u>Additional risk minimisation measures:</u>

Prescriber Guide

Patient Alert Card</td></tr>
<tr><td colspan="2">Missing Information: Lack of reversal agent</td></tr>
<tr><td>Risk minimisation measures</td><td><u>Routine risk minimisation measures:</u>

SmPC sections 4.4 and 4.9.</td></tr>
</table>

	Subject to medical prescription Additional risk minimisation measures: Prescriber Guide
Missing Information: Reproductive and development toxicity (Pregnancy and lactation)	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.6 and 5.3. PL section 2. Advice for using a reliable contraceptive while on treatment with edoxaban is included in PL section 2. Subject to medical prescription Additional risk minimisation measures: Prescriber Guide
Missing Information: Patients with hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4 and 5.2. PL section 2. Recommendation for liver function testing prior to initiating edoxaban is included in SmPC section 4.2 and 4.4. Subject to medical prescription Additional risk minimisation measures: Prescriber Guide
Missing Information: Patients with severe renal impairment (CrCL <30 mL/min) or end-stage renal disease (CrCL <15mL/min or on dialysis)	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 5.2. PL sections 2 and 3. Recommendation for renal function assessment by calculating the CrCl prior to initiation of treatment and when a change in renal function is suspected during treatment is included in SmPC section 4.2 and 4.4. Subject to medical prescription

	Additional risk minimisation measures: Prescriber Guide
Missing Information: Patients with mechanical heart valves	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4. PL section 2. Subject to medical prescription Additional risk minimisation measures: Prescriber Guide
Missing Information: Combination with dual antiplatelet therapy	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.5. PL section 2. Subject to medical prescription Additional risk minimisation measures: Prescriber Guide
Missing Information: Off-label use in Europe in populations or indications outside the approved indications per European SmPC	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.1, 4.2, 4.3 and 4.6. PL sections 1 and 2. Subject to medical prescription 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 Arxebo.

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

There are no studies required for Arxebo.