Part VI: Summary of the risk management plan

Summary of risk management plan for Elmardya film-coated tablets (rivaroxaban)

This is a summary of the risk management plan (RMP) for Elmardya film-coated tablets. This RMP details important risks of Elmardya film-coated tablets, how these risks can be minimised, and how more information will be obtained about Elmardya film-coated tablets risks and uncertainties (missing information).

Elmardya film-coated tablets summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Elmardya film-coated tablets should be used.

I. The medicine and what it is used for

Elmardya 2.5mg film-coated tablets is indicated for

co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine

- prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

co-administered with acetylsalicylic acid (ASA)

- prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

Elmardya 10mg film-coated tablets is indicated for

- prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adult

Elmardya 15mg, 20mg film-coated tablets is indiacated for

Adults

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

Paediatric population

- Elmardya 15mg film-coated tablets
  Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30 kg to 50 kg after at least 5 days of initial parenteral anticoagulation treatment.
- Elmardya 20mg film-coated tablets
  Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing more than 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

Elmardya 15mg+20mg film-coated tablets is indicated for

- treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

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

Important risks of Elmardya film-coated tablets, together with measures to minimise such risks and the proposed studies for learning more about Elmardya tablets risks, are outlined below.

Measures to minimise the risks for Elmardya film-coated tablets include:

- 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 Elmardya, 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 necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Elmardya film-coated tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Elmardya film-coated tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Elmardya film-coated tablets. 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	• Haemorrhage
Important potential risks	• Embryo-fetal toxicity
Missing information	• Remedial pro-coagulant therapy for excessive haemorrhage • Patients with atrial fibrillation (AF) and a prosthetic heart valve

II.B Summary of important risks

The safety information in the proposed product information is aligned to the reference medicinal product.

Important identified risk: haemorrhage	
Evidence for linking the risk to the medicine	The increased risk for bleeding under treatment with an anticoagulant compound is contributable to its pharmacodynamic property in preventing blood from clotting (pharmacological mode of action is dose dependent inhibition of factor Xa). Evidence was mainly taken from pivotal studies, EU RMPs and PBRERs/PSURs of the innovator product.
Risk factors and risk groups	Patients with certain pre-existing conditions (e.g. active cancer, previous stroke, bronchiectasis, history of bleeding, anaemia, uncontrolled hypertension, renal impairment, known GI ulcerations), those receiving concurrent antithrombotics, or the elderly, may be at higher risk of bleeding. Post-operative patients are generally at high risk of bleeding, especially during treatment with anticoagulants. Pre-menopausal women may be at risk for menorrhagia.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC: Section 4.3 (Contraindications) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) Prescription-only medicine Limited pack sizes **Additional risk minimisation measures:** Educational material for prescribers Patient alert cards
Additional pharmacovigilance activities	None

Important potential risk: embryo-fetal toxicity	
Evidence for linking the risk to the medicine	Pregnant women were excluded from clinical trials and rivaroxaban is contraindicated in pregnancy according to the SmPC, due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta. Therefore, the overall experience is limited.
Risk factors and risk groups	The majority of patients receiving rivaroxaban are elderly patients. Only in patients with ACS, and those undergoing treatment for VTE, there may be a higher possibility of women with child-bearing potential receiving rivaroxaban. A large population-based study concluded that a history of DVT is an independent risk factor for spontaneous preterm delivery. This study compared all pregnancies of patients with and without a history of DVT: there were 212,086 deliveries, of which 122 (0.06%) occurred in patients with a history of DVT. No significant differences were noted between the groups regarding perinatal outcomes such as low Apgar scores, congenital malformations or perinatal mortality. Ben-Joseph et al. determined that patients with a history of DVT were more likely to have caesarean deliveries (OR, 2.6; 95% CI, 1.8–3.8; $p < 0.001$) than non-DVT patients, and DVT was an independent risk factor for preterm birth (OR, 1.8; 95% CI, 1.1–2.9; $p = 0.033$). In a study of 395 patients with a history of VTE and 313 control women stillbirth was slightly more frequent in patients (4.3%) than in controls (3.2%); the difference was not statistically significant. Miscarriage was equally frequent between groups. A population-based study in the USA showed that pregnant women with AF (n = 157) were more likely to have babies that needed to be admitted to the neonatal intensive care unit (NICU) than pregnant women without AF (n = 264 573) (NICU admissions: 10.8% vs 5.1%; $p = 0.003$).
Risk minimisation	**Routine risk minimisation measures:** SmPC:

Important potential risk: embryo-fetal toxicity	
measures	Section 4.3 (Contraindications) Section 4.6 (Fertility, pregnancy and breast-feeding) Section 5.3 (Preclinical safety data) Prescription-only medicine Limited pack sizes **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	None

Missing information: Remedial pro-coagulant therapy for excessive haemorrhage	
Evidence for linking the risk to the medicine	Clinical life scenarios, requests
Risk factors and risk groups	Health care professionals, patients
Risk minimisation measures	**Routine risk minimisation measures:** SmPC: Section 4.9 (Overdose) Prescription-only medicine Limited pack sizes **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	None

Missing information: Patients with atrial fibrillation (AF) and a prosthetic heart valve	
Evidence for linking the risk to the medicine	Patients with prosthetic heart valves not studied
Risk factors and risk groups	Respective patients
Risk minimisation measures	**Routine risk minimisation measures:** SmPC: Section 4.4 (Special warnings and precaution for use) Prescription-only medicine Limited pack sizes **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	None

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 Elmardya film-coated tablets.

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

There are no studies required for Elmardya film-coated tablets.