13 Part VI: Summary of the risk management plan for Rivaroxaban, 2.5 mg, 10 mg, 15 mg and 20 mg, Film-coated tablets

This is a summary of the Risk management plan (RMP) for rivaroxaban, 2.5 mg, 10 mg, 15 mg and 20 mg, film-coated tablets. The RMP details important risks of rivaroxaban film-coated tablets, how these risks can be minimized, and how more information will be obtained about rivaroxaban film-coated tablets' risks and uncertainties (missing information).

Rivaroxaban film-coated tablets' summary of product characteristics (SmPCs) and its package leaflet (PLs) give essential information to healthcare professionals (HCPs) and patients on how rivaroxaban film-coated tablets' should be used.

Important new concerns or changes to the current ones will be included in updates of rivaroxaban film-coated tablets' RMP.

13.1 Part VI: I. The medicine and what it is used for

Rivaroxaban, film-coated tablets are authorized for:

2.5 mg

Rivaroxaban co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

Rivaroxaban co-administered with ASA, is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischemic events.

10 mg

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 adults.

15 mg and 20 mg

Adults

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack.

Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.

Pediatric population

15 mg

Treatment of 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.

20 mg

Treatment of 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.

It contains rivaroxaban as an active substance and is given orally as film-coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg).

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of rivaroxaban, film-coated tablets, together with measures to minimize such risks and the proposed studies for learning more about rivaroxaban, film-coated tablet's risks are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PLs and SmPCs addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized 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 minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of rivaroxaban, film-coated tablets, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report (PSUR), *(if applicable)* assessment 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 rivaroxaban, film-coated tablets is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI – II.A: List of important risks and missing information

Important risks of rivaroxaban, film-coated tablets are risks that need special risk management activities to further investigate or minimize 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 rivaroxaban, 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).

Table 13-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	Hemorrhage
Important potential risks	Embryo-fetal toxicity
Missing information	Safety in patients with severe renal impairment (creatinine clearance (CrCl) < 30 mL/min)
	Remedial procoagulant therapy for excessive hemorrhage
	Safety in patients receiving systemic treatment with Cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) inhibitors other than azole-antimycotics (e.g. ketoconazole) and Human immunodeficiency virus (HIV) protease inhibitors (e.g. ritonavir)
	Safety in pregnant or breast-feeding women
	Safety in patients with AF secondary to significant valvular heart disease and a prosthetic heart valve
	Safety regarding long term therapy with rivaroxaban for treatment of DVT, PE, stroke prevention in patients with non-valvular AF (SPAF) and ACS in real-life setting
	Safety in patients with significant liver diseases (severe hepatic impairment/Child Pugh C)

13.2.2 Part VI – II.B: Summary of important risks

The safety information in the proposed Product Information is aligned to the originator product.

Table 13-2 Important identified risk: Hemorrhage

Risk minimization measures	**Routine risk minimization measures:** SmPC sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2 and 5.3 PL sections 2, 3 where patients are advised to immediately visit a doctor in case of prolonged or excessive bleeding which may be bleeding in the stomach, urogenital bleeding, bleeding in nose, eye, gum, skin, in tissue or a cavity of the body, muscles, and in brain/skull or into joints causing pain and swelling and section 4. Legal status: Prescription only **Additional risk minimization measures:** Prescriber's guide and Patient alert card

Table 13-3 Important potential risk: Embryo-fetal toxicity

Risk minimization measures	**Routine risk minimization measures:** SmPC section 4.6 where patients are suggested not to use rivaroxaban in pregnancy due to transplacental passage of rivaroxaban resulting in embryo-fetal reproductive toxicity, and section 5.3 PL sections 2 where recommendations are given to patients to use a reliable contraceptive If there is a chance that they could become pregnant while taking rivaroxaban and consult their doctor immediately if they become pregnant while taking rivaroxaban Legal status: Prescription only **Additional risk minimization measures:** None

Table 13-4	Missing Information: Safety in patients with severe renal impairment (CrCl< 30 mL/min)
Risk minimization measures	**Routine risk minimization measures:** SmPC sections 4.2, 4.4 where recommendations are made not to use rivaroxaban in patients with renal impairment due to increased risk of bleeding, and section 5.2 PL sections 2, 3 where advice is given to patients to use rivaroxaban administered with care in case of severe kidney disease and dose should be decided after consulting with the doctor, and section 4 Legal status: Prescription only **Additional risk minimization measures:** None

Table 13-5	Missing Information: Remedial procoagulant therapy for excessive hemorrhage
Risk minimization measures	**Routine risk minimization measures:** SmPC section 4.9 where patients are recommended to delay or discontinue rivaroxaban if bleeding complications are observed Legal status: Prescription only **Additional risk minimization measures:** None

Table 13-6	Missing Information: Safety in patients receiving systemic treatment with CYP3A4 and P-gp inhibitors other than azole-antimycotics (e.g. ketoconazole) and HIV protease inhibitors (e.g. ritonavir)
Risk minimization measures	**Routine risk minimization measures:** SmPC section 4.5 where the patients are informed, erythromycin and renal impairment may lead to additive effect leading to increased rivaroxaban concentrations Legal status: Prescription only **Additional risk minimization measures:** None

Table 13-7	Missing Information: Safety in pregnant or breast-feeding women
Risk minimization measures	**Routine risk minimization measures:** SmPC section 4.6 where patients are suggested not to use rivaroxaban in pregnancy due to transplacental passage of rivaroxaban and increased risk of bleeding, and sections 4.3 and 5.3 PL section 2 where recommendations are given to patients not to take rivaroxaban during pregnancy and lactation and to use a reliable contraceptive If there is a chance that they could become pregnant while taking rivaroxaban and consult their doctor immediately if they become pregnant while taking rivaroxaban Legal status: Prescription only **Additional risk minimization measures:** None

Table 13-8	Missing Information: Safety in patients with AF secondary to significant valvular heart disease and a prosthetic heart valve
Risk minimization measures	**Routine risk minimization measures:** SmPC section 4.4 and PL section 2 where advise is given to take special care in patients with prosthetic heart valves undergoing rivaroxaban therapy Legal status: Prescription only **Additional risk minimization measures:** None

Table 13-9	Missing Information: Safety regarding long term therapy with rivaroxaban for treatment of DVT, PE, SPAF and ACS in real-life setting
Risk minimization measures	**Routine risk minimization measures:** SmPC sections 4.2, 4.4 where treatment continuation is recommended only if benefits outweigh the associated risks, and section 5.1 PL section 2 where close monitoring is recommended in patients with very high blood pressure, not controlled by medical treatment, medical conditions that determines unstable blood pressure and undergoing surgical procedure to remove the blood clots and section 3 Legal status: Prescription only **Additional risk minimization measures:** None

Table 13-10	Missing Information: Safety in patients with significant liver diseases (severe hepatic impairment/Child Pugh C)
Risk minimization measures	**Routine risk minimization measures:** SmPC sections 4.2, 4.3, 4.8 and 5.2 PL section 2 where it is advised not to initiate rivaroxaban in patients with liver disease associated with bleeding, and section 4Legal status: Prescription only **Additional risk minimization measures:** None

13.2.3 Part VI – II.C: Post-authorization development plan

13.2.3.1 II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of rivaroxaban, film-coated tablets.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no studies required for rivaroxaban, film-coated tablets.