Part VI: Summary of the risk management plan

This is a summary of the risk management plan (RMP) for Rivaroxaban beta Filmtabletten. The RMP details important risks of Rivaroxaban beta, how these risks can be minimised, and how more information will be obtained about Rivaroxaban beta's risks and uncertainties (missing information).

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

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

I. The medicine and what it is used for

Rivaroxaban beta 2,5 mg Filmtabletten is authorised for the prevention of atherothrombotic events in adult patients either co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine and in combination with ASA for prevention of atherothrombotic events in patients with coronary artery disease (CAD)/ peripheral artery disease (PAD) (see SmPC for the full indication).

Rivaroxaban beta 10 mg Filmtabletten is authorised for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery as well as treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (see SmPC for the full indication).

Rivaroxaban beta 15 mg Filmtabletten and Rivaroxaban beta 20 mg Filmtabletten are authorised for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (see SmPC for the full indication).

Rivaroxaban beta contains rivaroxaban as the active substance and it is given by mouth.

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

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

II.A List of important risks and missing information

Important risks of Rivaroxaban beta 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 Rivaroxaban beta. 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	• Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic inhibitors of CYP3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Remedial pro-coagulant therapy for excessive haemorrhage • Pregnant or breast-feeding women • Patients with atrial fibrillation (AF) and a prosthetic heart valve • Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting • Patients with significant liver diseases (severe hepatic impairment/Child Pugh C) • Patients < 18 years • Patients with CAD/PAD and history of haemorrhagic or lacunar stroke, and patients with any stroke within a month

II.B Summary of important risks

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

Important identified risk: Bleeding (Haemorrhage)	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4,3, 4.4, 4.5 and 4.8* *PL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Contraindication in patients with lesion or condition, if considered to be a significant risk for major bleeding or concomitant treatment of any other coagulants is included in SmPC section 4.3 and PL section 2.* *Additional contraindication of concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack in SmPC section 4.3 for 2.5 mg.* *Recommendation that the use of rivaroxaban in combination with dual antiplatelet therapy in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events and that these patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment is included in SmPC section 4.4 for 2.5 mg.* *Recommendation for clinical surveillance in line with anticoagulation practice throughout the treatment period is included in SmPC section 4.4 only for 10 mg (VTE-P).* Other routine risk minimisation measures beyond the Product Information: *Prescription-only medicine* Additional risk minimisation measures: • *Educational material for prescribers (Prescriber guide)* • *Patient alert card*

Important potential risk: Potential defects in the unborn child (Embryo-fetal toxicity)

Important potential risk: Potential defects in the unborn child (Embryo-fetal toxicity)	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.3, 4.6 and 5.3* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Contraindication during pregnancy and breast-feeding is included in SmPC section 4.3 and PL section 2.* Other routine risk minimisation measures beyond the Product Information: *Prescription-only medicine* Additional risk minimisation measures: *None*

Missing information: Patients with severe kidney impairment (Patients with severe renal impairment (CrCl < 30 mL/min))	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2 and 4.4* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation to use rivaroxaban with caution in patients with renal impairment is included in SmPCs section 4.2 and 4.2* Other routine risk minimisation measures beyond the Product Information: *Prescription-only medicine* Additional risk minimisation measures: *None*

Missing information: Patients receiving concomitant systemic inhibitors of CYP3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir)	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.4 and 4.5* *PL section 2* Routine risk minimisation activities recommending

Missing information: Patients receiving concomitant systemic inhibitors of CYP3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir)	
	specific clinical measures to address the risk: *Recommendation to use rivaroxaban with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations is included in SmPCs section 4.4* Other routine risk minimisation measures beyond the Product Information: *Prescription-only medicine* Additional risk minimisation measures: *None*

Missing information: Use of drugs to promote clotting of the blood for excessive bleeding (Remedial pro-coagulant therapy for excessive haemorrhage)	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.9* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Guidance for management of bleeding is included in SmPC section 4.9.* Other routine risk minimisation measures beyond the Product Information: *Prescription-only medicine* Additional risk minimisation measures: *None*

Missing information: Pregnant or breast-feeding women	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.3, 4.6 and 5.3* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Contraindication during pregnancy and breast-feeding is included in SmPC section 4.3 and PL section 2.* Other routine risk minimisation measures beyond the

Missing information: Pregnant or breast-feeding women	
	Product Information: *Prescription-only medicine* Additional risk minimisation measures: *None*

Missing information: Patients with atrial fibrillation (AF) and a prosthetic heart valve	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 only for 15 mg/20 mg (VTE-T, SPAF)* *PL section 2 only for 15 mg/20 mg (VTE-T, SPAF)* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation not to treat patients with prosthetic valves is included in SmPC section 4.4.* Other routine risk minimisation measures beyond the Product Information: *Prescription-only medicine* Additional risk minimisation measures: *None*

Missing information: Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting	
Risk minimisation measures	Routine risk minimisation measures: *None* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Prescription-only medicine* Additional risk minimisation measures: *None*

Missing information: Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2, 4.3 and 5.2* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Contraindication in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C is included in SmPC sections 4.2 and 4.3 and PL section 2.* Other routine risk minimisation measures beyond the Product Information: *Prescription-only medicine* Additional risk minimisation measures: *None*

Missing information: Patients < 18 years	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2 and 5.2* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation not to use in children below 18 years of age is included in SmPC section 4.2 and PL section 2.* Other routine risk minimisation measures beyond the Product Information: *Prescription-only medicine* Additional risk minimisation measures: *None*

Missing information: Patients with CAD/PAD and history of haemorrhagic or lacunar stroke, and patients with any stroke within a month	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.3, 4.4 and 5.1* *PL section 2*

Missing information: Patients with CAD/PAD and history of haemorrhagic or lacunar stroke, and patients with any stroke within a month	
	Routine risk minimisation activities recommending specific clinical measures to address the risk: *Contraindication of concomitant treatment of CAD/PAD with ASA in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month is included in SmPC section and PL section 2 for 2.5 mg.* Other routine risk minimisation measures beyond the Product Information: *Prescription-only medicine* Additional risk minimisation measures: *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 Rivaroxaban beta Filmtabletten.

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

There are no studies required for Rivaroxaban beta Filmtabletten.