Summary of the Risk Management Plan for Xarelto® / Xarelto® junior / Xarelto® vascular

Active substance: Rivaroxaban

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Based on the EU-RMP v.14.3 for Xarelto® (dated 24-AUG-2023)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Xarelto®, Xarelto® junior, and Xarelto® vascular is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Xarelto®, Xarelto® junior and Xarelto® vascular in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Bayer (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Xarelto®/ Xarelto® junior and Xarelto® vascular.

The Summary of Risk Management Plan for Xarelto®, Xarelto® junior, and Xarelto® vascular (rivaroxaban) v5.1 is based on the Summary of the Risk Management Plan for Xarelto® (rivaroxaban) of the EU-RMP v.14.3, dated 24-AUG-2023. Deviations in the risk minimisation measures applicable for Switzerland from the EU-RMP are possible.

In Switzerland, Xarelto® is the product name for 10/15/20mg rivaroxaban, Xarelto® junior is the product name for 1 mg/mL granules for oral suspension rivaroxaban and Xarelto® vascular corresponds to 2.5mg rivaroxaban. In the EU, only one product (Xarelto®) covering all rivaroxaban dosages exists.

Therefore, subsequently, only Xarelto® is mentioned and not Xarelto® vascular / Xarelto® junior and the specifications made do not reflect the Swiss specifications for Xarelto® vascular / Xarelto® junior but the European specifications for Xarelto® as described in the EU RMP v14.3.

Summary of risk management plan for Xarelto (rivaroxaban)

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

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

This summary of the EU RMP for Xarelto should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

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

1. The medicine and what it is used for

Xarelto is authorised 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 adults (See section 4.4 for haemodynamically unstable PE patients).
- 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.
- Xarelto co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events inadult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (see SmPC for the full indication).
- Xarelto, co-administered with acetylsalicylic acid (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 ischaemic events.
- Xarelto is indicated for the treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children, and adolescents aged less than 18 years after at least five days of initial parenteral anticoagulation treatment.

It contains rivaroxaban as the active substance, and it is given by oral administration.

Further information about the evaluation of Xarelto's benefits can be found in Xarelto's EPAR, including in its plain-language summary, available on the EMA website, once this document is approved.

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

Important risks of Xarelto, together with measures to minimise such risks and the proposed studies for learning more about Xarelto'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 Xarelto, 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*. Special activities or measures beyond, e.g. a PASS, can be taken and build additional pharmacovigilance activities.

If important information that may affect the safe use of Xarelto is not yet available, it is listed under 'missing information' below.

2.1 List of important risks and missing Information

Important risks of Xarelto 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 Xarelto. 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.

Table Part VI.1: Summary of safety concerns		
List of important risks and missing information		
Important identified risks	-	Haemorrhage
Important potential risks	-	Embryo-fetal toxicity
	-	Medication errors in relation to the reconstitution of the oral suspension and dosing with the pharmaceutical form 1 mg/mL granules for oral suspension
Missing information	-	Remedial pro-coagulant therapy for excessive haemorrhage
	-	Patients with atrial fibrillation (AF) and a prosthetic heart valve

2.2 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 inhibitionof factor Xa). Evidence was mainly taken from pivotal studies and PBRERs/PSURs.
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 (hypermenorrhoea).
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: 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[1]:** Educational material for prescribers Patient alert cards

[1]Additional risk minimisation measures as stated in the EU-RMP are not implemented in Switzerland. Instead, the following materials are applicable for Switzerland:
- Rivaroxaban Anwendungskarte
- Patientenausweis
- Patientenausweis für das Kind
- Anwendungsguide für Eltern

Additional pharmacovigilance activities	Xarelto Pediatric VTE PASS Drug Utilization Study An observational, longitudinal, multi-source drug utilization safety study to evaluate the drug use patterns and safety of rivaroxaban oral suspension in children under two years with venous thromboembolism (XAPAEDUS).

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 DVTwas 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 measures	**Routine risk minimisation measures:** SmPCs: 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

Important potential risk: Medication errors in relation to the reconstitution of the oral suspension and dosing with the pharmaceutical form 1 mg/mL granules for oral suspension	
Evidence for linking the risk to the medicine	For children too young or unable to swallow rivaroxaban tablets, the drug will be administered orally as a suspension. The drug-device combination product including the pharmaceutical form 1 mg/mL granules for oral suspension needs to be prepared by the child's caregiver using the drug-device combination kit. Errors in the preparation of the suspension, as well as its subsequent application, may result in over- or underdosing. Overdose 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 inhibitionof factor Xa). Evidence was mainly taken from pivotal studies, EU RMPs and PBRERs/PSURs. Underdose Lack of drug effect; recurrence of VTE
Risk factors and risk groups	Children diagnosed with VTE and too young or unable to swallow rivaroxaban tablets who are treated with the liquid formulation granules for oral suspension.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC (Xarelto 1 mg/mL granules for oral suspension) Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 6.5 (Nature and contents of container) Section 6.6 (Special precautions for disposal and other handling) Prescription-only medicine Limited pack sizes **Additional risk minimisation measures[2]:** Educational material for prescribers Patient alert cards Video

[2] Additional risk minimisation measures as stated in the EU-RMP are not implemented in Switzerland. Instead, the following materials are applicable for Switzerland:
- Rivaroxaban Anwendungskarte
- Patientenausweis für das Kind
- Anwendungsguide für Eltern

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:** SmPCs: Section 4.9 (Overdose) Prescription-only medicine Limited pack sizes Exclusion from clinical development program **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:** SmPCs: Section 4.4 (Special warnings and precaution for use) Prescription-only medicine Limited pack sizes **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	None

2.3 Post-authorisation development plan

2.3.1 Studies which are conditions of the marketing authorisation

None

2.3.2 Other studies in post-authorisation development plan

Children from birth to less than 2 years diagnosed with VTE and treated with rivaroxaban

Xarelto Pediatric VTE PASS Drug Utilization Study: An observational, longitudinal, multi-source drug utilization safety study to evaluate the drug use patterns and safety of rivaroxaban oral suspension in children under two years with venous thromboembolism (SN 22195)

Study Status	Summary of objectives	Safety concerns/efficacy issue addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Xarelto Pediatric VTE PASS Drug Utilization Study (SN 22195)	An observational, longitudinal, multi-source drug utilization safety study to evaluate the drug use patterns and safety of rivaroxaban oral suspension in children under two years with venous thromboembolism (XAPAEDUS)	**Important identified risk:** • Haemorrhage	Feasibility report	Submission Q1 2021 (completed)
			Protocol submission	Q1 2022 (completed)
			Start of data collection: 12 months from the PRAC endorsement of the study protocol[3] (10 NOV 2022)	Q4 2023
			Interim reports (study progress reports)[4]	Annually 1. Q4 2023 2. Q4 2024 3. Q4 2025 4. Q4 2026 5. Q4 2027
			End of data collection	Q2 2029 (estimated)
			Final report of study results (6 months after end of data collection)	Q4 2029 (estimated)

[3] The number of patients for the study population actually accrued in the data sources will be monitored over time to inform the decision as to when to launch the analyses with intention to finalise the study earlier than Q4 2029 depending on follow-up of the overall uptake of rivaroxaban oral suspension reported in annual progress reports.
[4] To monitor the uptake of rivaroxaban oral suspension and follow-up the number of patients for the study population.