VI.2 Elements for a Public Summary

VI.2.1 Overview of diseases epidemiology

The indications described in this Risk Management Plan (RMP) comprise the following approved indications:

- 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.
- Prevention of venous thromboembolic events (VTE) in adult patients undergoing elective hip or knee replacement knee replacement surgery.

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

The 2010 prevalence of total hip and total knee replacement in the total U.S. population was 0.83% and 1.52%, respectively. Prevalence was higher among women than among men and increased with age, reaching 5.26% for total hip replacement (THR) and 10.38% for total knee replacement (TKR) at eighty years. These estimates corresponded to 2.5 million individuals (1.4 million women and 1.1 million men) with THR and 4.7 million individuals (3.0 million women and 1.7 million men) with TKR in 2010.[1]

The rate of THR and THK has increased over the past ten years in many European countries, due in part to population ageing but also the growing use of these interventions to improve functioning among elderly people. In Denmark, the THR rate increased by 40% between 2000 and 2010, while the TKR rate more than tripled. Similarly, in Spain, the THR rate increased by 25% and the TKR replacement rate more than doubled during the past decade. The growth rate for both interventions was somewhat slower in France, but still THR rate increased by nearly 10% while TKR rate rose by 60% between 2000 and 2010.[2]

After surgery with preventative treatment, VTE develops in about 10 of 1000 people after total or partial knee replacement, and in about 5 of 1000 after total or partial hip replacement.[3] About 300,000–600,000 Americans develop VTE each year, with about 60,000–100,000 deaths attributable to PE.[4]

The prevalence of atrial fibrillation (AF) varies with age and sex. AF is present in 0.12%–0.16% of those younger than 49 years, in 3.7%–4.2% of those aged 60–70 years, and in 10%–17% of those aged 80 years or older. In addition, it occurs more frequently in males. AF is frequently associated with cardiac disease and comorbidities. The most common concomitant diseases are coronary artery disease, valvular heart disease, and cardiomyopathy. The most common comorbidities are hypertension, diabetes, heart failure, chronic obstructive pulmonary disease, renal failure, stroke, and cognitive disturbance. It is estimated that the number of patients with AF in 2030 in Europe will be 14–17 million and the number of new cases of AF per year at 120,000–215,000.[5]

Venous thrombosis, including deep vein thrombosis and pulmonary embolism, occurs at an annual incidence of about 1 per 1000 adults. Rates increase sharply after around age 45 years, and are slightly higher in men than women in older age. Major risk factors for thrombosis, other than age, include exogenous factors such as surgery, hospitalization, immobility, trauma, pregnancy and the puerperium and hormone use, and endogenous factors such as cancer, obesity, and inherited and acquired disorders of hypercoagulation. This review focuses on epidemiology of venous thrombosis and the general implications of this in patient management.[6]

Blood clots in the vessels supplying the heart muscle can cause unstable angina pectoris or a heart attack (myocardial infarction [MI]); both are types of acute coronary syndrome (ACS). Accumulated fatty deposits (plaques) in the walls of the arteries may rupture and lead to thrombosis (known as atherothrombosis), which can cause ACS. In the USA, 3.1% of adults aged over 20 years have a history of MI Mortality in the first year after MI in patients aged over 45 years is 19% in men and 26% in women.[7]

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2. OECD (2012), Hip and knee replacement, in Health at a Glance: Europe 2012, OECD Publishing.
3. Januel JM, Chen G, Ruffieux C, et al. Symptomatic in-hospital deep vein thrombosis and pulmonary embolism following hip and knee arthroplasty among patients receiving recommended prophylaxis: A systematic review. 2012. JAMA 307 (3): 294–303.
4. Beckman MG et al. Venous thromboembolism: a public health concern. Am J Prev Med. 2010 Apr;38(4 Suppl):S495-501.
5. Massimo Zoni-Berisso et al. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014; 6: 213–220.
6. Mary Cushman et al. Epidemiology and Risk Factors for Venous Thrombosis, Seminars in Hematology, Volume 44, Issue 2, April 2007, Pages 62-69.
7. Roger VL et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2012 update: a report from the American Heart Association. Circulation. 2012 Jan 3;125(1):e2-e220.

VI.2.2 Summary of treatment benefits

VI.2.2.1 Prevention of VTE in patients undergoing elective hip or knee replacement surgery

The four phase Ill RECORD studies compared rivaroxaban (10 mg once daily) with enoxaparin (the standard therapy at the time of the studies) in patients undergoing total hip or knee replacement. A pooled analysis of the four studies, including 12,729 patients, showed that rivaroxaban reduced the occurrence of VTE, compared with enoxaparin.

VI.2.2.2 Treatment of DVT and PE and prevention of recurrent DVT and PE

The phase Ill EINSTEIN-DVT and EINSTEIN-PE studies compared the use of rivaroxaban the reference product, (15 mg twice daily for 3 weeks followed by 20 mg once daily) with the use of standard therapy (enoxaparin in combination with vitamin K antagonists [VKA]) in 8281 patients with venous thromboembolism (VTE) over 3, 6 or 12 months. Rivaroxaban was at least as effective as enoxaparinNKA in treatment of VTE and preventing the recurrence of VTE.

In the phase Ill EINSTEIN Extension study, 1197 patients who had completed 6 - 12 months of treatment for VTE were administered rivaroxaban (20 mg once daily) or placebo for an additional 6 or 12 months; rivaroxaban reduced VTE recurrence compared with placebo.

VI.2.2.3 Prevention of stroke and embolism elsewhere in the body in patients with AF

The phase Ill ROCKET-AF study compared rivaroxaban (20 or 15 mg once daily) with standard therapy (warfarin) in 14,264 patients with non-valvular AF (treatment duration: up to 41 months). Rivaroxaban was at least as effective as warfarin at preventing stroke and embolism elsewhere in the body.

VI.2.2.4 Prevention of blood clots after ACS

The ATLAS ACS 2-TIMI 51 study compared rivaroxaban, the reference product, (2.5 or 5 mg twice daily) with placebo in 15,526 patients with a recent ACS (treatment duration: up to 31 months). All patients also received standard antiplatelet therapy (ASA alone or ASA plus Thienopyridine). Compared with placebo, rivaroxaban reduced the occurrence of cardiovascular-related deaths, stroke and MI.

VI.2.3 Unknowns relating to treatment benefits

The efficacy and safety in children aged 0 to 18 years have not been established.

The efficacy and safety in pregnant and breast feeding women have not been established.

The efficacy and safety have not been studied in patients with prosthetic heart valves.

The efficacy and safety have not been established in haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy.

There are no clinical data in patients with severe hepatic impairment and only limited clinical data in patients with severe renal impairment.

VI.2.4 Summary of safety concerns

Important identified risks and important identified interactions

Risk	What is known	Preventability
Bleeding (Haemorrhage)	Bleeding can occur at any site during therapy with rivaroxaban. An unexplained fall in haemoglobin (a protein in the red blood cells of all vertebrates) and/or haematocrit (volume percentage (%) of red blood cells in blood) or blood pressure should lead to a search for a bleeding site. In clinical studies, mucosal bleedings (bleeding from the nose, gums, gastrointestinal or genitourinary systems) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA (e.g. warfarin) treatment.	Rivaroxaban should be prescribed and used in accordance with the product information and the package leaflet. If you experience any bleeding event that does not stop by itself or if you experience signs of excessive bleeding (exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling) consult your doctor immediately. Your doctor may decide to keep you under closer observation or change your medicine. Patient alert cards may improve patient risk awareness.

Important potential risks and important potential interactions

Risk	What is known
Potential defects in the unborn child (embryo-fetal toxicity)	Animal studies have suggested that rivaroxaban can cross the placenta and cause birth defects in offspring. The drug was also found to increase the rate of miscarriage in animal studies. The use of rivaroxaban is contraindicated during pregnancy.

Missing information

Risk	What is known
Patients undergoing major orthopaedic surgery other than elective hip or knee replacement surgery	Clinical trials of rivaroxaban did not include patients undergoing hip fracture surgery. Therefore the use of rivaroxaban is not recommended.
Patients with severe renal impairment (creatinine clearance less than 30 mL/min)	Patients with severe renal impairment may be at risk of both haemorrhage and thrombosis. Limited data suggest that levels of rivaroxaban in the bloodstream are increased in patients with severe

Risk	What is known
	renal impairment. Therefore, rivaroxaban is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance less than 15 mL/min.
Concomitantly use with systemic inhibitors of CYP3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir)	The use of rivaroxaban with strong inhibitors of CYP3A4 and P- gp (such as ketoconazole [for fungal infections] or ritonavir [for HIV treatment]) results in increased levels of rivaroxaban in the bloodstream and is therefore not recommended.
Remedial procoagulant therapy for excessive haemorrhage	The use of drugs to promote clotting of the blood (procoagulants) may be required in the event of excessive bleeding. However, there is limited information on the use of procoagulants in patients receiving rivaroxaban.
Pregnant or breast feeding women	Due to lack of human data, rivaroxaban should not be used during pregnancy and should not be used during breast-feeding.
Patients with atrial fibrillation (AF) and a prosthetic heart valve	Safety and efficacy of rivaroxaban have not been studied in patients with prosthetic heart valves. Therefore, treatment with rivaroxaban is not recommended for these patients.
Long-term therapy for treatment of DVT, PE, SPAF and ACS in real-life setting	Clinical trial data are available in these patient groups, but the long-term use of rivaroxaban in a 'real-life' setting needs to be studied to quantify the risk of bleeding and unexpected adverse events, particularly in patients who have comorbidities or who are taking other medications.
Patients with significant liver disease (severe hepatic impairmen/Child Pugh C)	The risks of rivaroxaban use in patients with severe liver impairment are unknown, as these patients were excluded from clinical trials. Therefore, the use of rivaroxaban is contraindicated in these patients.
Patients < 18 years	No data are available regarding the safety and efficacy of rivaroxaban in paediatric group. Therefore, it is not recommended for use in patients below 18 years of age.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for this medicine may be found in the official portals of the national authorities.
This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material are included in Annex II of the product information which may be found in the official portals of the national authorities; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Safety concern (important identified risk)	**Haemorrhage**
Risk minimisation measure(s) key points	➢ Patient alert cards are introduced to reinforce patient counselling about key safety reminders during treatment with rivaroxaban, and as a consequence to redude the risk of bleeding. Patient alert cards must contain the following information: • Signs or symptoms of bleeding and when to seek attention from a health care provider. • Importance of treatment compliance • The need for intake of the 15 mg and 20 mg tablets with food • Necessity to carry the Patient Alert Card that is included in each pack, with them at all times • The need to inform Health Care Professionals that they are taking Rivaroxaban if they need to have any surgery or invasive procedure. A patient alert card will be part of the package insert and by this be included in every package of rivaroxaban. (see Part VII Annex 11) ➢ A prescriber guide for each indication will be prepared prior to launch of the medicinal product. The prescriber guide should contain the following key safety messages: • Details of populations potentially at higher risk of bleeding • Recommendations for dose reduction in at risk populations • Guidance regarding switching from or to rivaroxaban treatment ➢ The need for intake of the 15 mg and 20 mg tablets with food

Safety concern (important identified risk)	Haemorrhage
	➢ Management of overdose situations ➢ The use of coagulation tests and their interpretation ➢ That all patients should be provided with a Patient alert card and be counselled about: • Signs or symptoms of bleeding and when to seek attention from a health careprovider. • Importance of treatment compliance • The need for intake of the 15 mg and 20 mg tablets with food • Necessity to carry the Patient alert card with them at all times • The need to inform Health Care Professionals that they are taking rivaroxaban if they need to have any surgery or invasive procedure.
Objective and rational	These measures were implemented to alert patients to the risk of haemorrhage when taking rivaroxaban and to prevent the use of rivaroxaban in patients with increased haemorrhage risks.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable.