Rivaroxaban

10 mg, 15 mg and 20 mg

Film-coated tablets

1.8.2 Safety Risk Management Plan

Active substance(s) (INN or common name):	Rivaroxaban
Pharmaco-therapeutic group (ATC Code):	Direct factor Xa inhibitors (B01AF01)
Name of Marketing Authorization Holder or Applicant:	Sandoz
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	[Nationally completed name] 10 mg, 15 mg and 20 mg Film-coated tablets
Version number	1.4
Data lock point for this RMP	01 Sep 2017
Date of final sign off	01 Sep 2017

List of abbreviations

ACS	Acute Coronary Syndrome
AE	Adverse Event
AF	Atrial Fibrillation
APCC	Activated Prothrombin Complex Concentrate
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	Area Under Curve
C_{max}	Maximum Serum Concentration
CYP3A4	Cytochrome P450 3A4
DCP	Decentralized Procedure
DVT	Deep Vein Thrombosis
EEA	European Economic Area
EU	European Union
HCP	Healthcare Professionals
HIV	Human Immunodeficiency Virus
INR	International Normalized Ratio
mg	Milligram
n	Number Of Patients
N/A	Not Applicable
PCC	Prothrombin Complex Concentrate
PCI	Percutaneous coronary intervention
PE	Pulmonary Embolism
P-gp	P-Glycoprotein
PhV	Pharmacovigilance
PIL	Package Information Leaflet
PK	Pharmacokinetic
QPPV	Qualified Person For Pharmacovigilance
RECORD	REgulation Of Coagulation In ORthopaedic Surgery To Prevent Deep Vein Thrombosis And Pulmonary Embolism
r-FVIIa	Recombinant Factor Viia
RMP	Risk Management Plan
RR	Relative Risk
SEE	Systemic Embolic Events
SmPC	Summary Of Product Characteristics
SPAF	Stroke Prevention In Patients With Non-Valvular Atrial Fibrillation
TEE	Transesophageal Echocardiogram
VKA	Vitamin K Antagonists
VTE	Venous thromboembolism
XAMOS	Xarelto In The Prophylaxis Of Post-Surgical Venous Thromboembolism After Elective Major Orthopaedic Surgery Of Hip Or Knee

1.1 Part VI.2 Elements for a Public Summary

1.1.1 Part VI.2.1 Overview of disease epidemiology

Stroke

Stroke (brain death due to lack of supply of blood) is the second leading cause of disability in Europe after heart disease and is the sixth leading cause worldwide. Women have a higher lifetime risk of stroke than men [Stroke, 2013]. Every year, 15 million people worldwide suffer a stroke. Nearly five million are left permanently disabled and six million die. Disability may include loss of vision and or speech, paralysis and confusion. Globally, stroke is the second leading cause of death above the age of 60 years, and the fifth leading cause of death in people aged 15 to 59 years old. Stroke is less common in people under 40 years. In young people the most common cause for stroke is high blood pressure [WHF, 2016]. Europe averages approximately 650,000 stroke deaths each year [ISC, 2016].

DVT (deep vein thrombosis):

DVT (blood clot, which occurs when blood thickens and clumps together in a vein deep in the body) is a common cause for death in bedridden or hospitalized patients, as well as generally healthy individuals. Approximately 1 person in 20 develops a DVT in the course of his or her lifetime. In elderly persons, the incidence is increased 4-fold. In hospitalized patients, the incidence is considerably higher and varies from 20-70%. Venous ulceration (wounds due to improper functioning of venous valves) and venous insufficiency of the lower leg, which are long-term complications of DVT, affect 0.5% of the entire population. DVT usually affects individuals older than 40 years. The male-to-female ratio is 1.2:1, indicating that males have a higher risk of DVT than females [Kaushal P, 2016]. The occurrence of DVT in Europe is estimated to be 684,000, and in United States it is estimated to be more than 376,000 per year [TA, 2016].

PE (pulmonary embolism):

PE is present in 60-80% of patients with DVT, even though more than half of these patients do not show any symptoms. PE is the third most common cause of death in hospitalized patients, with at least 650,000 cases occurring annually. Post-mortem studies have shown that approximately 60% of patients who have died in hospital had pulmonary embolism, with the diagnosis having been missed in up to 70% of the cases. Death rates from PE were 20-30% higher among men than among women. The incidence of pulmonary embolism appears to be significantly higher in blacks than in whites. Death rates from PE for blacks have been 50% higher than those for whites, and those for whites have been 50% higher than those for people of other races. PE is increasingly prevalent among elderly patients. PE may account for 15% of deaths during or after a surgical operation [Ouellette DR, 2016].

VTE (venous thrombo-embolism):

VTE is the formation of blood clots in the vein and is a leading cause of death and disability worldwide. Every year, there are approximately 10 million cases of VTE worldwide. In Europe, there are 544,000 VTE-related deaths every year. In the U.S. and Europe, VTE-related events kill more people than AIDS, breast cancer, prostate cancer and motor vehicle crashes combined. Up to 60% of VTE cases occur during or after hospitalization, making it a leading preventable cause of hospital death. It affects people of all ages, races and occurs in both men and women [WTD, 2016]. In North America and Europe, the annual incidence of VTE is estimated to be approximately 160 per 100,000 for DVT, 50 per 100,000 for fatal (deadly) PE and 20 per 100,000 for non-fatal PE [Bouee S, 2016].

Systemic Embolism [obstruction of arteries (blood vessel that supply blood to whole body) by a blood clot that travels through the bloodstream, lodging in a blood vessel and plugging the vessel.]

According to a study of pooled data of 37,973 individuals from 4 studies it was observed that 221 systemic embolic events (SEEs) occurred in 219 individuals during follow-up of 2.4 years. The occurrence of SEEs was lower than brain embolism and comprised 12% of clinically-recognized blood clot events. Anatomically, about 60% of SEEs involved the hip to toe region, whereas about 30% occurred in the gut and stomach blood vessels, and only 11% occurred in the shoulder to finger region. Several clinical characteristics were more prevalent in patients with SEEs compared to stroke including female gender and white race as well as a history of smoking, prior heart attack and previous SEEs. Others risk factors include increasing age and severe left ventricular (left part of heart) dysfunction [Chatterjee NA, 2015].

1.1.2 Part VI.2.2 Summary of treatment benefits

International phase III RECORD (REgulation of Coagulation in ORthopaedic surgery to prevent Deep vein thrombosis and pulmonary embolism) study, which consisted of four studies conducted in total of 12,729 patients across 617 centers in 41 countries, demonstrated superior efficacy of rivaroxaban for the prevention of total VTE compared with the European or American enoxaparin regimens.

XAMOS (XArelto in the prophylaxis of post-surgical venous thromboembolism after elective Major Orthopaedic Surgery of hip or knee), and ORTHO-TEP both real-world study conducted to assess the safety and effectiveness of oral rivaroxaban compared with any other VTE prevention medicines in everyday clinical practice in 17,701 and 5061 patients respectively after major orthopaedic surgery, involved in correction of deformities of skeletal system (bone framework in body), showed that the incidence of clotting events and associated symptoms were significantly low in the rivaroxaban group [Kwong L, 2015].
In Rocket AF study comparing rivaroxaban with warfarin in 14,264 patients with non-valvular AF (condition where the heart rhythm or beat disturbance is not due to significant disease of heart valves) who were at moderate-to-high risk for stroke, rivaroxaban was non inferior to warfarin in the prevention of subsequent stroke or systemic embolism [Patel MR, 2011].

Einstein DVT study in 3449 patients, showed that rivaroxaban alone is as effective as standard therapy, with similar safety, for the treatment of DVT and that when treatment is continued, rivaroxaban is very effective in preventing recurrences, as compared with placebo (inactive medicine) [Bauersachs R, 2010]. Results from the Einstein -extension study where rivaroxaban was compared with placebo in patients who completed their standard treatment course after VTE, suggest that rivaroxaban can be a valid alternative to warfarin for patients requiring long-term secondary prevention of VTE [Romualdi E, 2011].

1.1.3 Part VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of rivaroxaban in children aged 0 to 18 years have not been established. No data are available and there are no data in patients with severe hepatic impairment.

The efficacy of rivaroxaban has not been studied in clinical trials in patients undergoing hip fracture surgery.

Safety and efficacy of rivaroxaban have not been studied in patients with prosthetic heart valves.

The efficacy of rivaroxaban has not been established in hemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy.

1.1.4 Part VI.2.4 Summary of safety concerns

Table 5-1 Important identified risks

Risk	What is known	Preventability
Rapid loss of blood (Hemorrhage)	Like other similar medicines (antithrombotic agents (drugs used to prevent blood clot)), rivaroxaban may cause bleeding which may potentially be life threatening. Excessive bleeding may lead to a sudden drop in blood pressure (shock). In some cases the bleeding may not be obvious. Possible side effects include excessive bleeding, exceptional weakness, tiredness, paleness, dizziness, headache, unexplained swelling, breathlessness, chest pain or angina pectoris, which may be the signs of bleeding. Common side effects affecting 1 in 10 people include bleeding in the stomach or bowel, urogenital bleeding (including blood in the urine and heavy menstrual bleeding), nose bleed, bleeding in the gum, bleeding into the eye (including bleeding from the whites of the eyes), bleeding into tissue or a cavity of the body (hematoma, bruising), coughing up blood, bleeding from the skin or under the skin, bleeding following an operation, oozing of blood or fluid from surgical wound, reduction in red blood cells which can make the skin pale and cause weakness or breathlessness Uncommon side effects affecting 1 in 100 people include bleeding into the brain or inside the skull, bleeding into a joint causing pain and swelling. Rare side effects affecting 1 in 1000 people include bleeding into a muscle, collection of blood (hematoma) in the groin as a	Patient is advised not to take rivaroxaban if he/she is bleeding excessively and should use the drug with caution if suffering from a disease or condition in an organ of the body that increases the risk of serious bleeding (e.g., stomach ulcer, injury or bleeding in the brain, recent surgery of the brain or eyes); if he/she is taking medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), except when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open; if he/she has a liver disease which leads to an increased risk of bleeding; if he/she has severe kidney disease which affects the amount of medicine that works in the body; if he/she has very high blood pressure, not controlled by medical treatment; if he/she has a problem with the blood vessels in the back of the eyes (retinopathy); or a lung disease where bronchi are widened and filled with pus (bronchiectasis), or previous bleeding from the lung. In such conditions, the doctor should be informed so that he/she can decide, if the patient should be treated with this medicine and kept under closer observation. The doctor should be immediately consulted if the patient has taken too many

Risk	What is known	Preventability
	complication of the cardiac procedure where a catheter is inserted in your leg artery (pseudoaneurysm) Increased pressure within muscles of the legs or arms after a bleeding, which leads to pain, swelling, altered sensation, numbness or paralysis (compartment syndrome after a bleeding), kidney failure after a severe bleeding are side effects with unknown frequency.	rivaroxaban tablets as it increases the risk of bleeding. If the doctor thinks that the patient is at an increased risk of developing stomach or bowel ulcers, then the doctor might also use a preventative ulcer treatment. If the patient underwent an operation involving a catheter or injection into the spinal column (e.g. for epidural or spinal anesthesia or pain reduction): • it is very important to take rivaroxaban exactly at the times as told by the doctor • doctor should be informed immediately if patient experiences numbness or weakness of legs or problems associated with bowel or bladder after the end of anesthesia, because urgent care is necessary.

Table 5-2 Important potential risks

Risk	What is known
Injury to the embryo/fetus which may result in death, growth retardation, or abnormal development of a part due to the toxic effects of a substance that crosses the placental membrane. (Embryo-fetal toxicity)	Rivaroxaban should not be used during pregnancy as it increases the risk of bleeding and there is evidence that rivaroxaban passes through the placenta (an organ attached to the lining of the womb during pregnancy). Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Table 5-3 Missing information

Risk	What is known
Safety in patients undergoing major surgeries of musculoskeletal system (i.e. joints, bones and ligaments) other than emergency hip or knee replacement surgery	Rivaroxaban has not been studied in clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety.

Risk	What is known
(Safety in patients undergoing orthopedic surgery other than elective hip or knee replacement surgery)	
Safety in patients with severe kidney problems (creatinine clearance (test to measure the kidney function) < 30 mL/min) (Safety in patients with severe renal Impairment (creatinine clearance < 30 mL/min))	Special care should be taken if the patient has an increased risk of bleeding, such as severe kidney disease, where kidney function may affect the amount of medicine that works in the body. In patients with severe kidney problems (creatinine clearance < 30 mL/min) rivaroxaban blood levels may be significantly increased which may lead to an increased bleeding risk. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 mL/min. Use is not recommended in patients with creatinine clearance < 15 mL/min.
Remedial procoagulant therapy for excessive hemorrhage (Safety regarding use of clotting agents that reverses the process of anticoagulation (process that prevents blood clotting) to control bleeding caused by rivaroxaban)	Administration of specific procoagulant reversal agent (agents that reverses the process of anticoagulation) should be considered, (such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa) so as to control the bleeding caused by rivaroxaban. There is currently very limited clinical experience with the use of specific procoagulant reversal agents in individuals receiving rivaroxaban.
Safety in patients receiving treatment with drugs that cause inactivation of the enzyme via the formation of metabolic intermediates that bind irreversibly to the enzyme and then inactivate it (cytochrome CYP3A4 inhibitors) and drugs which blocks the important protein of the cell membrane that pumps many foreign substances out of cells (P-gp inhibitors) other that anti fungals (e.g. ketoconazole) and drugs for the treatment of HIV (e.g. ritonavir) (Safety in patients receiving systemic treatment with Cytochrome P450 3A4 (CYP3A4) and P-gp inhibitors other than azole-antimycotics (e.g. ketoconazole) and HIV protease inhibitors (e.g. ritonavir))	Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban concentrations in blood to a lesser extent. Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in rivaroxaban concentration in blood. Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase rivaroxaban concentration in blood.

Risk	What is known
Safety in pregnant or breast feeding women	Safety and efficacy of rivaroxaban have not been established in pregnant and breast feeding women. The patient is advised not to take rivaroxaban if she is pregnant or breast feeding. If there is a chance that the patient might become pregnant, a reliable contraceptive should be used while taking rivaroxaban.
Safety in patients with irregular and often very fast heart rate and a device implanted in the heart of a patient with damage to or a defect in one of the four heart valves (Safety in patients with AF secondary to significant valvular heart disease and a prosthetic heart valve)	Special care should be taken while using rivaroxaban if the patient has a prosthetic heart valve. Safety and efficacy of rivaroxaban have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that rivaroxaban 20 mg (15 mg in patients with moderate or severe renal impairment) provides adequate anticoagulation in this patient population.
Safety regarding long term therapy with rivaroxaban for treating blood clots in deep vein (DVT), blockage of a blood vessel in lungs by a clot that has traveled from elsewhere in the body through the bloodstream (PE), prevention of brain death from lack of blood supply to brain in patients with irregular abnormal heart beat (SPAF) and a disease affecting the blood flow in the coronary arteries resulting in inability of the heart to function properly (ACS) in real-life setting (Safety regarding long term therapy with rivaroxaban for treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), stroke prevention in patients with non-valvular atrial fibrillation (SPAF) and acute coronary syndrome (ACS) in real-life setting)	Therapy with rivaroxaban should be continued long term provided the benefit of prevention of stroke and systemic embolism is more than the risk of bleeding. The duration of therapy should be determined after careful assessment of the treatment benefit against the risk for bleeding. Short duration of therapy (at least 3 months) should be based on risk factors (e.g. recent surgery, trauma, and immobilization) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.
Safety in patients with severe liver dysfunction [Safety in patients with significant liver diseases (severe hepatic impairment/Child Pugh C)]	There are no data in patients with severe hepatic impairment. Thepatient is advised not to take rivaroxaban if he/she is suffering from a liver disease which leads to an increased risk of bleeding.

Risk	What is known
Safety in patients <18 years of age	Rivaroxaban is not recommended for people under 18 years of age. There is not enough information on its use in children and adolescents.

1.1.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing 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 minimization measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimization measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published in rivaroxaban's EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimization measures are for the following risk:

Table 5-8 Rapid loss of blood (Hemorrhage)

Risk minimization measure(s)

Summary description of main additional risk minimization measures:

Prescriber's guide and Patient Alert Card.

Objective and rationale: The additional risk minimization activities are meant to remind HCPs of the importance of recognizing the risk of hemorrhage and the need to instruct patients on correct usage of rivaroxaban, identification of signs and symptoms they need to look out for and what actions are needed to be taken.

Proposed action: Provision of Prescriber's guide to HCPs and Patient Alert Card to patients.

Prescriber guide

The Prescriber guide encourages the HCPs to use this tool in conjunction with the Summary of Product Characteristics during every rivaroxaban consultation in order to minimize the risk of hemorrhage. The prescriber guide includes advice on the following:

- Need to provide Patient Alert Card to patients
- Dosing Recommendations for different indications
- Method of use of rivaroxaban
- Populations potentially at higher risk of bleeding
- Contraindications of rivaroxaban
- Symptoms and management of overdose
- Need for Coagulation (blood clotting) Testing

Patient Alert Card

In order to minimize the risk for hemorrhage from use of rivaroxaban, a patient alert card has been developed. All HCPs who are most likely to prescribe rivaroxaban are provided with a Patient Alert

Risk minimization measure(s)

Card for distribution to patients receiving rivaroxaban. The patient alert card includes advice on the following:
• Request to keep the patient alert card during and after treatment
• Request to show the patient alert card to any treating doctor
• Information that rivaroxaban can increase the risk for hemorrhage:
  ○ Advice that rivaroxaban thins blood
  ○ Instruction to immediately seek for medical attention after detection of symptoms of bleeding
  ○ Request to inform the HCP about any other medicines patient is currently taking, took recently or intend to start taking, before starting rivaroxaban
  ○ Request to inform the HCP that patient is taking rivaroxaban before any surgery or invasive procedure
• Instruction about when to seek advice from HCP
• Signs or symptoms of bleeding
• Instruction on how to use rivaroxaban
• Box for adding additional information:
  ○ Patient details
  ○ Emergency contact details

1.1.6 Part VI.2.6 Planned post authorization development plan

None

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

N/A (first submission).