PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Apixaban 2.5 mg/ 5 mg film-coated Tablets (Apixaban)

This is a summary of the risk management plan (RMP) for apixaban 2.5 mg/5 mg film-coated Tablets. The RMP details important risks of apixaban, how these risks can be minimised, and how more information will be obtained about of apixaban's risks and uncertainties (missing information).

Apixaban 2.5 mg/5 mg film-coated Tablets' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how it should be used.

Important new concerns or changes to the current ones will be included in updates of apixaban 2.5 mg/5 mg film-coated Tablets' RMP.

I. The medicine and what it is used for

Apixaban 2.5 mg film coated tablet is authorised for:

Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or 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 ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Apixaban 5 mg film coated tablet is authorised for:

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 ischaemic attack (TIA); age≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

It contains apixaban as the active substance and it is given by oral route.

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

Important risks of apixaban 2.5 mg/5 mg film-coated tablets, together with measures to minimise such 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 public (e.g. with or without prescription) can help to minimises its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment (if applicable) and signal management activity, 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 apixaban is not yet available, it is listed under 'missing information' below.

In the case of apixaban, these routine measures are supplemented with additional risk minimisation measures, mentioned under relevant risks below.

II.A List of important risks and missing information

Important risks of apixaban 2.5 mg/5 mg film-coated tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken by patients. 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 apixaban 2.5 mg/5 mg 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/use in special patient populations etc.);

Table 5 Part VI: Summary of safety concerns

List of important risks and missing information	
Important identified risks	Bleeding
Important potential risks	Liver Injury Potential risk of bleeding or thrombosis due to overdose or underdose
Missing information	Use in patients with severe renal impairment

II.B Summary of important risks

Important Identified Risk: Bleeding	
Evidence for linking the risk to the medicine	The safety concerns available in the RMP for the reference medicinal product have been adopted by the MAH (the RMP summary for the reference product Eliquis published on the EMA website (Eliquis: EPAR -Risk-management-plan-summary dated 15-Nov-2019).
Risk factors and risk groups	Concurrent use of other anticoagulants or antiplatelet therapies Patient characteristics: comorbid conditions (e.g., congenital or acquired bleeding disorders; active ulcerative gastrointestinal disease; bacterial endocarditis; thrombocytopenia; platelet disorders; history of haemorrhagic stroke; severe uncontrolled hypertension; and recent brain, spinal, or ophthalmological surgery). Past medical history (e.g., previous stroke, prior GI bleeding) Co-administration of strong inhibitors of both CYP3A4 and P-glycoprotein (P-gp) (e.g., azole antifungals, protease inhibitors) may increase apixaban blood concentration and risk of bleeding. Therefore, co-administration of apixaban with strong inhibitors of both CYP3A4 and P-gp is not recommended. <u>Orthopaedic VTE Prevention indication</u> Patient characteristics: age > 75 years old. When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic

Important Identified Risk: Bleeding	
	complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. VTE Treatment indication Co-administration of strong inducers of both CYP3A4 and P-gp may lead to a reduction in apixaban exposure and is not recommended for the treatment of DVT and PE. In a clinical study in atrial fibrillation patients, diminished efficacy and a higher risk of bleeding were observed with co-administration of apixaban with strong inducers of both CYP3A4 and P-gp compared with using apixaban alone.
Risk minimisation measures	Routine risk minimisation measures: Sections 4.2, 4.3, 4.4, 4.5, 4.8, 4.9, 5.1 and 5.3 of Apixaban SmPC have information on this safety concern. Section 2, 3 and 4 of Apixaban Package leaflet has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: Prescriber Guide and Patient Alert Card

Important Potential Risk: Liver Injury	
Evidence for linking the risk to the medicine	The safety concerns available in the RMP for the reference medicinal product have been adopted by the MAH (the RMP summary for the reference product Eliquis published on the EMA website (Eliquis: EPAR -Risk-management-plan-summary dated 15-Nov-2019).
Risk factors and risk groups	Prior hepatitis, cirrhosis, fatty liver, alcohol consumption, poor nutrition, co-existing chronic disease, co-administration of hepatically metabolized drugs (e.g., statins), medication overdose, hypoperfusion, transfusion, halogen-anaesthetics, analgesics, hepatotoxic antibiotics, autoimmune disease (autoimmune hepatitis), viruses (primarily HAV, HBV, HCV), hereditary conditions (e.g., Wilson's disease).

Important Potential Risk: Liver Injury	
Risk minimisation measures	Routine risk minimisation measures: Sections 4.2, 4.3, 4.4, 4.5, 4.8, and 5.2 of Apixaban SmPC have information on this safety concern. Section 2 and 4 of Apixaban Package leaflet has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.

Important Potential Risk: Potential risk of bleeding or thrombosis due to overdose or underdose	
Evidence for linking the risk to the medicine	The safety concerns available in the RMP for the reference medicinal product have been adopted by the MAH (the RMP summary for the reference product Eliquis published on the EMA website (Eliquis: EPAR -Risk-management-plan-summary dated 15-Nov-2019).
Risk factors and risk groups	Risk factors include complex/unclear patient information, packaging, and product label, and use of the product in emergency situations.
Risk minimisation measures	Routine risk minimisation measures: Sections 4.2, 4.3, 4.4, 4.5, 4.8, 4.9, 5.1 and 5.3 of Apixaban SmPC have information on this safety concern. Section 2, 3 and 4 of Apixaban Package leaflet has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: Prescriber Guide

Missing information: Use in patients with severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures: Sections 4.2, 4.4, 4.8, 4.9, 5.1. and 5.2 of Apixaban SmPC have information on this safety concern.

Missing information: Use in patients with severe renal impairment	
	Section 2 and 3 Apixaban Package leaflet has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: Not applicable as there are no additional risk minimisation measures for this safety concern.

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 authorization or specific obligation of apixaban 2.5 mg/5 mg film-coated tablets.

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

There are no studies required for apixaban 2.5 mg/5 mg film-coated tablets as post-authorisation development plan.