SUMMARY OF THE RISK MANAGEMENT PLAN FOR Eliquis® (Apixaban)

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Disclaimer:

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 Eliquis® (Apixaban) 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 Eliquis® (Apixaban) in Switzerland is the "Arzneimittelinformation/Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Bristol-Myers Squibb SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of Eliquis® (Apixaban).

1 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for ELIQUIS (apixaban)

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

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

This summary of the RMP for ELIQUIS 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 ELIQUIS's RMP.

I. The medicine and what it is used for

ELIQUIS is authorised for the following indications (see SmPC for the full indication):

- Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery
- Prevention of stroke and systemic embolism (SE) 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 (New York Heart Association [NYHA] Class ≥ II and 3)
- Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults
- Treatment of VTE and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age

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

Further information about the evaluation of ELIQUIS's benefits can be found in ELIQUIS's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/eliquis

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

Important risks of ELIQUIS, together with measures to minimise such risks and the proposed studies for learning more about ELIQUIS'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/or caregivers 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 (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

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 ELIQUIS is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of ELIQUIS 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 ELIQUIS. 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 (eg, on the long-term use of the medicine).

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 risks

Bleeding	
Evidence for linking the risk to the medicine	The risk of bleeding associated with apixaban has been comprehensively evaluated in the nonclinical and clinical apixaban programmes. The most clinically significant treatment-related ARs associated with apixaban are bleeding ARs. The majority of bleeding-related events were non-serious and mild to moderate in severity. A bleeding event can be serious if it occurs in a critical anatomical site such as in the brain. Intracranial bleeding can be fatal. Low rates of intracranial bleeding and fatal bleeding were reported. The overall bleeding risk of apixaban was found to be similar to ASA and superior to warfarin in the non-valvular AF programme, similar to enoxaparin in the orthopaedic VTE prevention programme, and superior to enoxaparin/warfarin in VTE treatment patients.

Important identified risks

Bleeding	
Risk factors and risk groups	Concurrent use of other anticoagulants or antiplatelet therapies Patient characteristics: comorbid conditions (eg, 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 (eg, previous stroke, prior GI bleeding) Coadministration of strong inhibitors of both CYP3A4 and P-glycoprotein (P-gp) (eg, azole antifungals, protease inhibitors) may increase apixaban blood concentration and risk of bleeding. Therefore, coadministration of apixaban with strong inhibitors of both CYP3A4 and P-gp is not recommended. **Orthopaedic VTE Prevention indication** 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 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** Coadministration 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 coadministration of apixaban with strong inducers of both CYP3A4 and P-gp compared with using apixaban alone.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8, and 4.9 Additional risk minimisation measures: Patient Card

Important Potential Risks

Liver Injury	
Evidence for linking the risk to the medicine	Across the apixaban clinical program, there have been infrequent reports of liver-related AEs, SAEs, and laboratory abnormalities. In the VTE prevention orthopaedic population, the majority of events were post-operative transient elevations of ALT, AST, total bilirubin, and/or ALP that either resolved while study drug continued or during follow-up period. In the AF indication, the low frequency of LFT elevations and liver-related safety events is clinically important, and supports the favourable safety profile of apixaban for this indication. In VTE Treatment and Prevention of Recurrent VTE indication, most patients who experienced hepatic enzyme elevation were asymptomatic, however, some patients experienced symptoms depending on the severity of the condition.
Risk factors and risk groups	Prior hepatitis, cirrhosis, fatty liver, alcohol consumption, poor nutrition, co-existing chronic disease, co-administration of hepatically metabolized drugs

	(eg, statins), medication overdose, hypoperfusion, transfusion, halogen-anesthetics, analgesics, hepatotoxic antibiotics, autoimmune disease (autoimmune hepatitis), viruses (primarily HAV, HBV, HCV), hereditary conditions (eg, Wilson's disease)
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, 4.4, and 4.8 Additional risk minimisation measures: None
Potential risk of bleeding or thrombosis due to overdose or underdose	
Evidence for linking the risk to the medicine	Although post-marketing data has shown that medication errors occur infrequently, overdose as the most prevalent medication error has potentially serious consequences because of the increased risk of bleeding. The majority of events reported under the Medication errors HGLT for apixaban in pivotal studies were SAEs. The vast majority of cases reporting overdose, accidental overdose, intentional overdose or accidental exposure were asymptomatic. There was a single fatal outcome as a consequence of intentional suicidal overdose with phenazepam and alcohol.
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: SmPC Sections 4.2, and 4.9 Additional risk minimisation measures: None

Missing information

Use in patients with severe Renal Impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 5.2 SmPC provides the dosing recommendation for patients with severe renal impairment for each indication 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 ELIQUIS.

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

There are no studies required for apixaban.