SUMMARY OF RISK MANAGEMENT PLAN FOR AXABAN-DENK (APIXABAN)-VERSION 1.0

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

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

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

I. The medicine and what it is used for

Axaban-Denk is authorized for prevention of stroke and systemic embolism and for prevention and treatment of deep vein thrombosis and pulmonary embolism (see SmPC for the full indication). It contains apixaban as the active substance and it is taken by mouth.

II. Risks associated with the medicine and activities to minimize or further characterize the risks.

Important risks of Axaban-Denk, together with measures to minimize such risks and the proposed studies for learning more about Axaban-Denk’s risks, are outlined below.

Measures to minimize 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 authorized 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 minimizes its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Response (PSUR) assessment - so that immediate action can be taken as necessary.

These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Axaban-Denk are risks that need special risk management activities to further investigate or minimize 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 Axaban-Denk. 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).

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 non-clinical and clinical apixaban programmes. The most clinically significant treatment related adverse reactions associated with apixaban are bleeding adverse reactions. The majority of the 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 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 or superior to warfarin in the non-valvular AF programme, similar to enoxaparin in the orthopeadic Venous thromboembolic events prevention programme, and superior to enoxaparin/warfarin in the Venous thromboembolic Event treatment patients
Risk factors and risk groups	Concurrent use of other anticoagulants or antiplatelets therapies Patient characteristics: comorbid conditions (eg congenital or acquired bleeding disorders; active

	ulcerative gastrointestinal disease; history of haemorrhagic stroke; severe uncontrolled hypertension; and recent brain, spinal, or ophthalmological surgery). Past medical history (previous stroke, prior gastrointestinal bleeding) Co-administration of strong inhibitors of both CYP3A4 and P-gp) (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 Venous thromboembolic events 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 off 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 medical products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural puncture. Venous thromboembolic events Treatment indications 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 Deep Vein Thrombosis and Pulmonary Embolism. In a clinical study in atrial fibrillation patients, diminished efficacy and a higher risk of bleeding were observed with coadministration of both CYP3A4 and P-gp compared with using apixaban alone.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 “Posology and method of administration” • SmPC Section 4.3 “Contraindications”

	• SmPC Section 4.4 “Special warnings and precautions for use” • SmPC Section 4.5 “Interaction with other medicinal products and other forms of interaction” • SmPC Section 4.8 “Undesirable effects” • SmPC Section 4.9 “Overdose” Additional risk minimization measures: • Patient Alert 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 adverse events, serious adverse events and laboratory abnormalities. In the Venous thromboembolic events prevention orthopaedic population, the majority of the 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 in clinically important and supports the favourable safety profile of apixaban for this indication. In Venous thromboembolic events treatment and prevention of recurrent Venous thromboembolic events, most patients who experienced hepatic enzyme elevation were asymptomatic, however, some patients experienced symptoms depending on the severity of the condition.
Risk Factors	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-anaesthetics, analgesics, hepatotoxic antibiotics, autoimmune disease (autoimmune hepatitis), viruses (primarily HAV, HBV, HCV), hereditary conditions (eg Wilson’s disease)
Risk minimization measures	Routine risk minimisation measures: • SmPC Section 4.2 “Posology and method of administration”

	• SmPC Section 4.3 “Contraindications” • SmPC Section 4.4 “Special warnings and precautions for use” • SmPC Section 4.8 “Undesirable effects” 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 been shown that medication errors occur infrequently, overdose as the 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 was asymptomatic. There was a single fatal outcome as a consequence of intentional suicidal overdose with phenazepam and alcohol.
Risk Factors	Risk factors include complex/unclear patient information, packaging, and product label, and use of the product in emergency situations.
Risk minimization measures	Routine risk minimisation measures: • SmPC section 4.2 “Posology and method of administration” • SmPC section 4.9 “Overdose” Additional risk minimization measures: • Prescriber Guide

Missing information

Use in patients with severe Renal Impairment	
Risk minimization measures	Routine risk minimisation measures: • SmPC Section 4.2 “Posology and method of administration” • SmPC Section 4.4 “Special warnings and precautions for use” • SmPC Section 5.2 “Pharmacokinetic properties” • SmPC provides the dosing recommendations for patients with severe renal impairment for each indication.

	Additional risk minimization measures: • None

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization.

No studies are conditions of the marketing authorization or specific obligations of Axaban-Denk.

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

Not applicable.