EU Risk Management Plan for
Apixaban Accord 2.5 mg film-coated Tablets
Apixaban Accord 5 mg film-coated Tablets
(Apixaban)

RMP version to be assessed as part of this application:

RMP Version number	2.0
Data lock point for this RMP	31-Dec-2024
Date of final sign off	07-Mar-2025

Rationale for submitting an updated RMP: This RMP has been updated in-line with the updated SmPC and ELIQUIS (Apixaban) EPAR-RMP (Version 21.3, dated 27-May-2024) published on EMA website on 19-Aug-2024.

Summary of significant changes in this RMP:

Significant changes have been done in the following sections of this RMP: Part-I, Part-II, Part V, Part VI and Part VII (Annex 4, Annex 6, Annex 7 and Annex 8).

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP: Not applicable

Version	Procedure	Approval date
1.2	Centralised Procedure (EMEA/H/C/005358)	28-May-2020

QPPV Name : Arletta Werynska

QPPV Signature : 

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Part I: Products Overview

Table 1: Product Overview

Active substance (INN or common name)	Apixaban
Pharmacotherapeutic group(s)(ATC Code)	**Pharmacotherapeutic group:** Antithrombotic agents, direct factor Xa inhibitors **ATC code:** B01AF02
Marketing Authorisation Holder	Accord Healthcare S.L.U., Spain
Medicinal products to which this RMP refers	02
Invented names in the European Economic Area (EEA)	Apixaban Accord 2.5 mg film-coated tablets Apixaban Accord 5 mg film-coated tablets
Marketing authorisation procedure	Centralised Procedure (EMEA/H/C/005358)
Brief description of the product	*Chemical class:* Apixaban is a pyrazolopyridine derivative and it is a direct and highly selective active site inhibitor of factor Xa.
	Summary of mode of action: Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development. Preclinical studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that preserved haemostasis.

[redacted]

	Important information about its composition *Apixaban Accord 2.5 mg film coated Tablets:* Each film-coated tablet contains 2.5 mg apixaban. *Excipients with known effect:* Each 2.5 mg film-coated tablet contains 51.97 mg lactose. *Apixaban Accord 5 mg film coated Tablets:* Each film-coated tablet contains 5 mg apixaban. *Excipients with known effect:* Each 5 mg film-coated tablet contains 103.95 mg lactose.
Hyperlink to the Product Information	Module 1.3.1 for Product Information
Indications	***Current:*** *Apixaban Accord 2.5 mg film coated tablets are indicated for:* Adults 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 Accord 5 mg film coated tablets are indicated for:* Adults 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.
	Proposed: *Apixaban Accord 2.5 mg/ 5 mg film coated tablets* Paediatric population Treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age.
Dosage	***Current:*** *Posology:* *Apixaban Accord 2.5 mg film coated tablets:* *Prevention of VTE (VTEp): elective hip or knee replacement surgery in adults* The recommended dose of apixaban is 2.5 mg taken orally twice daily. The initial dose should be taken 12 to 24 hours after surgery. Physicians may consider the potential benefits of earlier anticoagulation for VTE prophylaxis as well as the risks of post-surgical bleeding in deciding on the time of administration within this time window. *In patients undergoing hip replacement surgery* The recommended duration of treatment is 32 to 38 days. *In patients undergoing knee replacement surgery* The recommended duration of treatment is 10 to 14 days.

[redacted]

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF)

The recommended dose of apixaban is 5 mg taken orally twice daily.

Dose reduction:

The recommended dose of apixaban is 2.5 mg taken orally twice daily in patients with NVAF and at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 micromole/L).

Therapy should be continued long-term.

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) in adults

The recommended dose of apixaban for the treatment of acute DVT and treatment of PE is 10 mg taken orally twice daily for the first 7 days followed by 5 mg taken orally twice daily. As per available medical guidelines, short duration of treatment (at least 3 months) should be based on transient risk factors (e.g., recent surgery, trauma, immobilisation).

The recommended dose of apixaban for the prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily. When prevention of recurrent DVT and PE is indicated, the 2.5 mg twice daily dose should be initiated following completion of 6 months of treatment with apixaban 5 mg twice daily or with another anticoagulant, as indicated in table below:

	Dosing schedule	Maximum daily dose
Treatment of DVT or PE	10 mg twice daily for the first 7 days	20 mg
	followed by 5 mg twice daily	10 mg

Prevention of recurrent DVT and/or PE following completion of 6 months of treatment for DVT or PE	2.5 mg twice daily	5 mg

The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding.

Apixaban Accord 5 mg film coated tablet:

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF)

The recommended dose of apixaban is 5 mg taken orally twice daily.

Dose reduction:

The recommended dose of apixaban is 2.5 mg taken orally twice daily in patients with NVAF and at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 micromole/L).

Therapy should be continued long-term.

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) in adults

The recommended dose of apixaban for the treatment of acute DVT and treatment of PE is 10 mg taken orally twice daily for the first 7 days followed by 5 mg taken orally twice daily. As per available medical guidelines, short duration of treatment (at least 3 months) should be based on transient risk factors (e.g., recent surgery, trauma, immobilisation).

The recommended dose of apixaban for the prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily. When

[redacted]

prevention of recurrent DVT and PE is indicated, the 2.5 mg twice daily dose should be initiated following completion of 6 months of treatment with apixaban 5 mg twice daily or with another anticoagulant, as indicated in table below:

	Dosing schedule	Maximum daily dose
Treatment of DVT or PE	10 mg twice daily for the first	20 mg
	followed by 5 mg twice daily	10 mg
Prevention of recurrent DVT and/or PE following completion of 6 months of treatment for DVT or PE	2.5 mg twice daily	5 mg

The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding.

Method of administration:

For Oral use.

Apixaban tablets should be swallowed with water, with or without food.

For patients who are unable to swallow whole tablets, Apixaban tablets tablets may be crushed and suspended in water, or 5% dextrose in water (D5W), or apple juice or mixed with apple puree and immediately administered orally. Alternatively, Apixaban tablets may be crushed and suspended in 60 mL of water or D5W and immediately delivered through a nasogastric tube. Crushed Apixaban tablets are stable in water, D5W, apple juice, and apple puree for up to 4 hours.

[redacted]

Proposed:

Apixaban Accord 2.5 mg/ 5 mg film coated tablets

Treatment of VTE and prevention of recurrent VTE in paediatric patients

Apixaban treatment for paediatric patients from 28 days to less than 18 years of age should be initiated following at least 5 days of initial parenteral anticoagulation therapy

Treatment with apixaban in paediatric patients is based on weight-tiered dosing.The recommended dose of apixaban in paediatric patients weighing ≥ 35 kg.

Dose recommendation for treatment of VTE and prevention of recurrent VTE in paediatric patients weighing ≥ 35 kg

	Days 1-7		Day 8 and beyond	
Body weight (kg)	Dosing schedule	Maximum daily dose	Dosing schedule	Maximum daily dose
≥ 35	10 mg twice daily	20 mg	5 mg twice daily	10 mg

For paediatric patients weighing < 35 kg, refer to the summary of product characteristics for other marketed apixaban Accord granules in capsules for opening and apixaban Accord coated granules in sachets.

Based on VTE treatment guidelines in the paediatric population, duration of overall therapy should be individualised after careful assessment of the treatment benefit and the risk for bleeding.

[redacted]

Pharmaceutical forms and strengths	**Current:** **Pharmaceutical forms:** Film-coated tablets **Strengths:** 2.5 mg and 5 mg
Is the product subject to additional monitoring in EU?	No

[redacted]

Part II: Safety specification

Module SI – Epidemiology of the indication(s) and target population(s)

Not applicable

Module SII – Non-clinical part of the safety specification

Not applicable

Module SIII – Clinical trial exposure

Not applicable

Module SIV – Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Not applicable

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Not applicable

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not applicable

Module SV – Post-authorisation experience

Not applicable

Module SVI – Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Not applicable

[redacted]

Module SVII - Identified and potential risks

The safety concern has been considered as per EPAR-RMP available for the medicinal product Eliquis (Apixaban), Version 21.3, dated 27-May-2024, published on EMA website on 19-Aug-2024. There is no change proposed by MAH in safety concerns mentioned in Module SVIII.

Hence, this section remains "Not applicable".

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable

SVII.3.2. Presentation of the missing information

Not Applicable

Module SVIII - Summary of the safety concerns

Table 2: Summary of safety concerns

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

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for "Bleeding" and "Liver injury":

MAH has proposed specific adverse drug reaction follow-up forms for the safety concerns "Bleeding" and "Liver injury" which are appended in Annex 4 of this RMP.

Purpose: For collection and reporting of safety information with the use of Apixaban.

III.2 Additional pharmacovigilance activities

None proposed

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

[redacted]

Part IV: Plans for post-authorisation efficacy studies

Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1. Routine Risk Minimisation Measures

Table 3: Description of routine risk minimisation measures by safety concern

[redacted]

Safety concern	**Routine risk minimisation activities**
Important Identified Risks	
Bleeding	Routine risk communication: • SmPC Sections: 4.2, 4.3, 4.4, 4.5, 4.8, and 4.9 . • PIL Sections: 2, 3 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • The SmPC provides explicit description of measures to take to avoid haemorrhage and measures to be taken in the event of haemorrhagic complications. Other routine risk minimisation measures beyond the product information: • Legal status: Prescription only medicine
Important potential risks	
Liver injury	Routine risk communication: • SmPC Sections: 4.2, 4.3, 4.4 and 4.8. • PIL Section: 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the product information: • Legal status: Prescription only medicine

Safety concern	**Routine risk minimisation activities**
Potential risk of bleeding or thrombosis due to overdose or underdose	Routine risk communication: • SmPC Section: 4.2 and 4.9 • PIL Section: 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: • The SmPC provides the dosing recommendation for each indication along with the trade name, packaging, labeling, and distinguishing features (color and size) of the marketed tablet. • Spontaneous reports of medication errors will be closely monitored to clarify the factors involved in medication errors and will provide useful information on the context of medication errors. This will guide future risk mitigation actions. Other routine risk minimisation measures beyond the product information: • Legal status: Prescription only medicine
Missing information	

Safety concern	**Routine risk minimisation activities**
Use in patients with severe renal impairment	**Routine risk communication:** • SmPC Sections: 4.2, 4.4, and 5.2 • PIL Sections: 2 and 3 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> • The SmPC provides the dosing recommendation for patients with severe renal impairment for each indication. <u>Other routine risk minimisation measures beyond the product information:</u> • Legal status: Prescription only medicine

V.2. Additional Risk Minimisation Measures

In line with reference medicinal product, Additional Risk Minimisation Measures (aRMMs) have been proposed for following risks:

- Bleeding
- Potential risk of bleeding or thrombosis due to overdose or underdose

Proposed additional risk minimisation measures are listed below and are detailed summarised in Annex 6.

Prescriber Guide

Objectives:

To further raise awareness of healthcare professionals on important risks of bleeding, and medication errors during treatment with apixaban, and their appropriate management.

Rationale for the additional risk minimisation activity:

Opportunity to reinforce key messages to early recognition and appropriate management of important risks to maintain favourable benefit/risk of apixaban in market use.

Target audience and planned distribution path:

Prescriber. The MAH must agree to the content and format of the educational material, together with a communication plan, with the national competent authority in each member state prior to distribution of the educational pack in their territory.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine Pharmacovigilance activities will provide information on any changes in the occurrence, severity, and outcome of the important identified risk of bleeding as it related to the established safety profile.

Spontaneous reports of medication errors will be closely monitored to clarify the factors involved in medication errors and will provide useful information on the context of medication

[redacted]

errors. This will guide future risk mitigation action. The MAH has included a posology section in the prescriber guide for the NVAF, VTE treatment and VTE prevention indications in order to reduce the risk of potential medication error as an additional risk minimisation measure.

Patient Alert Card

Objectives:

To further raise awareness of patients and/or caregivers and healthcare professionals on the important identified risk bleeding during treatment with apixaban and its appropriate management.

Rationale for the additional risk minimisation activity:

Opportunity to reinforce key messages to early recognition and appropriate management of important identified risk of bleeding to maintain favourable benefit/risk of apixaban in market use.

Target audience and planned distribution path:

Patients and/or caregivers. The Patient Alert Card has been included inside the Apixaban Accord product pack together with the Package Leaflet, which is now the primary mode of distribution.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance activities will provide information on any changes in the occurrence, severity, and outcome of the important identified risk of bleeding as it relates to the established safety profile.

[redacted]

V.3 Summary of risk minimisation measures

Table 4: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Bleeding	Routine risk minimisation measures: • SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8, and 4.9 • PIL section: 2, 3 and 4 • The SmPC provides explicit description of measures to take to avoid haemorrhage and measures to be taken in the event of haemorrhagic complications. • Legal status: Prescription only medicine Additional risk minimisation measures: • Prescribers Guide • Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Bleeding questionnaire Additional pharmacovigilance activity: • None
Important Potential Risks		

Liver injury	Routine risk minimisation measures: • SmPC Sections 4.2, 4.3, 4.4 and 4.8 • PIL section: 4 • Legal status: Prescription only medicine Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Questionnaire for spontaneous reports of liver events Additional pharmacovigilance activity: • None
Potential risk of bleeding or thrombosis due to overdose or underdose	Routine risk minimisation measures: • SmPC Section 4.2 and 4.9 • PIL section: 3 • The SmPC provides the dosing recommendation for each indication along with the trade name, packaging, labeling, and distinguishing features (color and size) of the marketed tablet. • Spontaneous reports of medication errors will be closely monitored to clarify the factors involved in medication errors and will provide useful information on the context of medication errors. This will guide future risk mitigation actions.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activity: • None

	• Legal status: Prescription only medicine Additional risk minimisation measures: • Prescriber Guide	
Missing information		
Use in patients with severe renal impairment	Routine risk minimisation measures: • SmPC Sections 4.2, 4.4, 5.2 • PIL section: 2 and 3 • The SmPC provides the dosing recommendation for patients with severe renal impairment for each indication • Legal status: Prescription only medicine Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activity: • None

Part VI: Summary of the risk management plan

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

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

Apixaban Accord 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 Apixaban Accord 2.5 mg/ 5 mg film-coated Tablets should be used.

This summary of the RMP for Apixaban Accord 2.5 mg/ 5 mg film-coated Tablets 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 Apixaban Accord 2.5 mg/ 5 mg film-coated Tablets' RMP.

I. The medicine and what it is used for

Apixaban Accord *2.5 mg film coated tablets are indicated for:*

Adults

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

Paediatric population

[redacted]

Treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age.

Apixaban Accord *5 mg film coated tablets are indicated for*:

Adults

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

Paediatric population

Treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age.

They contains apixaban as the active substance and they are given by oral route.

Further information about the evaluation of Apixaban 2.5 mg/ 5 mg film-coated Tablet's benefits can be found in Apixaban Accord 2.5 mg/ 5 mg film-coated Tablet'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/apixaban-accord

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

Apixaban Accord 2.5 mg/ 5 mg film-coated Tablets together with measures to minimise such risks and the proposed studies for learning more about Apixaban Accord 2.5 mg/ 5 mg film-coated Tablets' risks, are outlined below.

[redacted]

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 patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Apixaban Accord 2.5 mg/ 5 mg film-coated Tablets, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use Apixaban Accord 2.5 mg/ 5 mg film-coated Tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks Apixaban Accord 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. 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 Accord 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).

Important identified risks	• Bleeding
Important potential risks	• Liver injury

[redacted]

	• 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**	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections: 4.2, 4.3, 4.4, 4.5, 4.8 and 4.9 • PL section: 2, 3 and 4 • The SmPC provides explicit description of measures to take to avoid haemorrhage and measures to be taken in the event of haemorrhagic complications. • Legal status: Prescription only medicine Additional risk minimisation measures: • Prescribers Guide • Patient Alert Card
Important potential risks: Potential risk of bleeding or thrombosis due to overdose or underdose	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2 and 4.9 • PIL section: 3 • The SmPC provides the dosing recommendation for each indication along with the trade name, packaging, labeling, and distinguishing features (color and size) of the marketed tablet.

[redacted]

	• Spontaneous reports of medication errors will be closely monitored to clarify the factors involved in medication errors and will provide useful information on the context of medication errors. This will guide future risk mitigation actions • Legal status: Prescription only medicine Additional risk minimisation measures: • A Prescriber Guide

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 Apixaban Accord 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 Accord 2.5 mg/ 5 mg film-coated Tablets as post-authorisation development plan.

Annex 4 – Specific adverse drug reaction follow-up forms

MAH has proposed Specific adverse drug reaction follow-up forms for following risks concerning use of Apixaban

- Bleeding
- Liver injury/ Drug-induced liver injury (DILI)

Adverse Event Report Questionnaire – Bleeding Management

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM

Patient Demographic:
Patient's date of birth (DD/MMM/YYYY) or age:_____ Gender ☐ Male
Ethnicity:_____ ☐ Female
Patient's Weight:_____
Patient's Baseline serum creatinine (prior to bleed):_____
Country Report Origin:_____

Age Group: _____

(Age group definition: Neonate =0.002 years-0.077 years, Infant= 0.078 years-1.999 years, child= 2 years-11.999 year, Adolescent=12 years-17.999 years, Adult=18 years-64.999 years and Elderly=65 years-199 years)

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

	Suspect Product#1	**Suspect Product#2**	**Suspect Product#3**
Product Name	Apixaban Accord		
Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD/MMM/YYYY)			
Stop date (DD/MMM/YYYY)			
Lot/Batch Number (s)			
Expiration date (s)			

Adverse Event (AE) description: Please provide list diagnosis vs symptoms/sign if diagnosis is available.

	Bleeding
Site of Bleeding	
Date of onset (DD/MMM/YYYY)	
Hemodynamically unstable and required treatment for hypotension (Y/N)	
Outcome (Resolved completely/Resolved with sequelae/Did not resolve/Death/Unknown)	
Date of resolution (DD/MMM/YYYY)	

☐ Check if Apixaban was discontinued (even temporarily) as result of this bleeding event.

☐ Check if no other actions other than Apixaban discontinuation were used to stop bleeding.

Please check all of the following that were used to potentially reverse the patient's bleeding and provide any other details regarding the administration of any of these agents below:

☐ Whole blood of Packed Red blood ☐ Cells (PRBC)

[redacted]

☐ Fresh frozen plasma (FPP)
☐ Platelets
☐ Factor VIIa
☐ DDAVP (desmopressin)
☐ Prothrombin Complex concentrate (PCC) provide details such as type e.g. three factor, Four-factor or activated PCC (aPCC)
☐ Protamine
☐ Vitamin K
☐ Trasylol (aprotinin)
☐ Tranexamic acid
☐ Activated charcoal
☐ Surgery/other procedure (e.g. endoscopy)
☐ Cautery
☐ Hemodialysis
☐ Manual Compression
☐ Other, Specify_____

Additional information (e.g. how much was given, how often, type of procedure, effectiveness etc.)

_____

_____

_____

Please list signs and symptoms in chronological order:

_____

_____

_____

Diagnostic tests (use additional pages if needed): please indicate test unit where applicable.

Test name	Pre-Treatment Value	AE onset Value	AE resolution value	Normal low	Normal High
Anti-Factor Xa assay					
PT and INR					
PTT					
Thrombin Time					
Fibrin splits products (FSPs)					
Hemoglobin					
Hematocrit					
Platelets					
D-dimers					

Did the adverse event(s) abate after suspect product(s) was stopped or dose reduced (if applicable)?

[redacted]

☐ Yes ☐ No

Did the adverse event(s) re-appear after re-introduction of the suspect product(s) (if applicable)? ☐ Yes ☐ No

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

_____

Concomitant Medication (use additional pages if needed):

Did the patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown

Was the patient receiving any other medication, concomitantly with Apixaban Accord that may have contributed to this bleeding event (check all that apply and provide details in the table):

☐ Other anti-thrombotics
☐ Fibrinolytics
☐ Aspirin or other salicylates
☐ Non-steroidal and anti-inflammatory drugs
☐ Other antileptics drugs
☐ Azole-antimycotics (ketoconazole, voriconazole etc)
☐ HIV protease inhibitor

Please list ALL other medications and doses the patient was taking at the time of prior to (48 hours) the event below:

Medication Name	Daily dose and regimen	Route of administration	Indication	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)

Please provide any other patient details about the bleeding event and any attempts made to stop/control the bleeding:

Other Etiological Factors: ☐ Yes (Please complete below) ☐ None ☐ Unknown

☐ Relevant medical and/or drug history (please specify), including start date or duration:

_____

_____

_____

Please check any of the following risk factors or conditions that may have contributed to the bleeding event:

☐ Previous history of bleeding at this site
☐ Coagulopathy
☐ Heart failure
☐ Family history of bleeding
☐ Diabetes
☐ Trauma
☐ Other vascular pathology
☐ Prior stroke
☐ Renal Impairment
☐ Overdose
☐ Other, Please specify:___

[redacted]

☐ Liver Impairment ☐ Hypertension

Additional Questions:

_____

Health practitioner Name (Print)

_____

Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:

Description of event: *[narrative]*

[redacted]

Adverse Event Report Questionnaire – Liver injury/ Drug-induced liver injury (DILI)

INFORMATION PREVIOUSLY PROVIDED DOES NOT NEED TO BE REPEATED ON THIS FORM

Patient Demographic:

Patient's date of birth (DD/MMM/YYYY) or age:_____ Gender ☐ Male

Ethnicity_____ ☐ Female

Suspect Products: Please provide suspect product(s) information [those product(s) that are suspected to be associated with one or more adverse events]:

	Suspect Product#1	Suspect Product#2	Suspect Product#3
Product Name			
Daily dose and regimen			
Route of administration			
Indication			
Start date or treatment duration (DD/MMM/YYYY)			
Stop date (DD/MMM/YYYY)			
Lot/Batch Number (s)			
Expiration date (s)			

Adverse Event (AE) description: Please provide details of hepatic event and if patient experienced any additional events in the table below.

	Adverse Event #1	Adverse Event #2	Adverse Event #3	Adverse Event #4
Add diagnosis here				
Start Date (DD/MMM/YYYY)				
Stop Date (DD/MMM/YYYY)				
Time lag if AE occurred after cessation of treatment with the suspect(s):				
Required Hospitalisation (yes/no)				
Cause of Death (Y/N)				
Treatment of Adverse Event				
Outcome (recovery and sequelae, if any)				

[redacted]

Does the patient have any of the following signs and symptoms related to the hepatic event (If Yes, provide dates):

1. Fever?	☐ Yes	☐ No
2. Nausea?	☐ Yes	☐ No
3. Vomiting?	☐ Yes	☐ No
4. Abdominal pain?	☐ Yes	☐ No
5. Abdominal tenderness?	☐ Yes	☐ No
6. Joint pain/arthralgia?	☐ Yes	☐ No
7. Joint swelling?	☐ Yes	☐ No
8. Rash?	☐ Yes	☐ No
9. Urticaria?	☐ Yes	☐ No
10. Mucosal inflammation or ulceration?	☐ Yes	☐ No
11. Asterixis?	☐ Yes	☐ No
12. Confusion/disorientation?	☐ Yes	☐ No
13. Coma?	☐ Yes	☐ No
14. Jaundice?	☐ Yes	☐ No
15. Ascites?	☐ Yes	☐ No
16. Peripheral Oedema?	☐ Yes	☐ No
17. Palmar erythema?	☐ Yes	☐ No
18. Fatigue?	☐ Yes	☐ No
19. Lymphadenopathy?	☐ Yes	☐ No
20. Dark Urine?	☐ Yes	☐ No
21. Other liver related signs or symptoms?	☐ Yes	☐ No
If Yes, Please specify:		

Diagnostic tests (use additional page if needed):

1. **Please provide results of imaging studies performed for the Adverse Event:**

Test Name	Pre-treatment (Baseline with date)	At the time of AE (with date)
Magnetic resonance imaging (MRI)/ Magnetic Resonance Cholangiopancreatography (MRCP)		
Abdominal Ultrasound		
Computerised tomography (CT) scan		
ERCP (Endoscopic retrograde Cholangiopancreatography)		

[redacted]

Liver biopsy		
Any other imaging/diagnostic studies (Please specify)		

2. **Laboratory Tests (Provide test unit, if applicable)**

Lab specimen collection date for the following lab tests:			____/____/____ (dd/mm/yyyy)		
Test Name	**Pre-treatment value (Baseline)**	**AE Onset Value**	**AE resolution value**	**Normal low**	**Normal High**
Aspartate aminotransferase (AST)					
Alanine aminotransferase (ALT)					
Alkaline phosphatase (Alk-P)					
Liver-specific alkaline phosphatase					
Bone-specific alkaline phosphatase					
Albumin					
Prothrombin Time (PT)					
Serum bilirubin (Total/direct/indirect)					
PT-INR					
Haptoglobin					
Creatine Kinase					
Aldolase					
Gamma glutamyl transferase					
Bicarbonate					
Haemoglobin					
Haematocrit					
Platelets					
Leukocytes (WBC)					
Erythrocyte count (RBC)					

[redacted]

Eosinophils					
Neutrophils					
Lymphocytes					
Monocytes					
Basophils					
Histopathology					
Other (Please specify)					

3. **Immune-histochemistry/serology tests:**

Lab specimen collection date:		____/____/____(dd/mm/yyyy)		
Test	**Result**	**Unit**	**No Unit**	**Not done**
☐ Urine ethyglucuronide				
☐ Serum phosphatidylethanol				
☐ Urine toxicology				
☐ Antinuclear antibodies				
☐ Anti-smooth muscle antibody (or anti-actin)				
☐ Hepatitis B virus surface antigen				
☐ Hepatitis B virus core antibody				
☐ Hepatitis B virus DNA				
☐ Hepatitis B virus surface antibody				
☐ Hepatitis A virus antibody IgM				
☐ Hepatitis A virus antibody				
☐ Hepatitis E virus IgG antibody				
☐ Hepatitis E virus IgM antibody				
☐ Hepatitis E virus IgA antibody				
☐ Hepatitis E virus RNA				
☐ Hepatitis C virus antibody				
☐ Hepatitis C virus RNA				
☐ Other (please specify)				

Concomitant Medications (Use additional pages if needed):

Did the patient take any concomitant medication? ☐ Yes (please complete below) ☐ No ☐ Unknown

Please mark with and "x" all that apply, and specify medication details below:

☐ NSAIDs ☐ Amiodarone ☐ Birth control pills ☐ Chlorpromazine ☐ Antibiotics ☐ Statins

☐ Halothane ☐ Herbal supplements ☐ Chemotherapy ☐ Anti-retroviral therapy ☐ Anti-TB drugs

[redacted]

☐ Biologics ☐ Acetaminophen (paracetamol) ☐ Dietary or nutritional supplements ☐ Other, specify:

If any of the above is checked, please provide details below:

Medication Name	Daily dose regimen	Route of administration	Indication	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY) or ongoing

Has any of the following occurred within one week before the hepatic event?

☐ Has the subject taken acetaminophen (paracetamol)? If Yes, provide details.

_____

☐ Did the subject engage in vigorous physical exercise? If yes, provide details.

_____

☐ Did the subject eat wild mushrooms? If Yes, provide details.

_____

Did the adverse event(s) abate after suspect product(s) was stopped or dose reduced (if applicable)?

☐ Yes ☐ No

Did the adverse event(s) re-appear after re-introduction of the suspect product(s) (if applicable)? ☐ Yes ☐ No

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

_____

Medical history:

Does the subject have a history of any of the conditions below? a. If Yes, please give start date (dd/mm/yyyy)	If Yes in column (a): Is the condition/event still ongoing? If No, please give end date (dd/mm/yyyy)
Hepato-biliary disease/Gallbladder disease (please specify; Examples: gallbladder stones, cholecystitis, bile duct stones): ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Ischemic hepatitis (e.g: hypotension or congestive heart failure (CHF)): ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Viral hepatitis A, B, C, D or E (please specify type): ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Hyperlipidemia ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Bleeding disorders	☐ Yes ☐ No, ended: __/__/__

[redacted]

☐ Yes, started: ____/____/_____ ☐ No	
Haemochromatosis ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Non-alcoholic fatty liver disease (NAFLD) ☐ Yes, started: ____/____/_____☐ No	☐ Yes ☐ No, ended: __/__/__
Non-alcoholic steatohepatitis (NASH) ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Alcohol related liver disease? Examples: alcohol related cirrhosis, alcohol related hepatitis, steatosis ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Drug-induced liver injury (DILI): ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Cardiovascular disease (please specify) ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Neoplasm (please specify): ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Autoimmune disease/Immune compromised status, including Autoimmune hepatitis? (please specify): ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Jaundice or hyperbilirubinaemia? ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
HIV infection? ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Tuberculosis? ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Right heart failure? ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Seizures? ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Systemic infection or sepsis? ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Herpes infection? ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Recent drop in blood pressure or shock? ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Hepatic metastasis? ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__
Diabetes/Uncontrolled diabetes mellitus? ☐ Yes, started: ____/____/_____ ☐ No	☐ Yes ☐ No, ended: __/__/__ If ongoing, does the subject require: ☐ Insulin? ☐ Other oral or parental agents? ☐ Dietary therapy alone?
Inflammatory bowel disease (Crohn's disease or ulcerative colitis)? ☐ Yes, started: _____/____/_____ ☐ No	
Obesity? ☐ Yes, started: ____/____/_____ ☐ No	
Recent vaccination (please specify):	
Recent travel to areas at risk for hepatitis (A, B, C, D and E)? (Examples include Hepatitis A-Mediterranean or South America; Hepatitis B-South East Asia; Hepatitis E-India, Mexico)	☐ Yes _____ _____

[redacted]

If yes: Please specify area(s):	
Exposure to an environmental or industrial toxin or a chemical agent? If Yes; Check **ALL** that apply: a) Exposure Date b) Industrial solvent c) Insecticide d) Aflatoxin e) Other	☐ Yes ___/___/____(dd/mm/yy) ☐ ☐ ☐ ☐ ☐ specify_____
Has the subject gained or lost more than 5lbs (2 kg) in weight? If Yes, please provide date of assessment and Amount of weight gained or lost in lbs or kg.	☐ Yes
Has the subject received parenteral nutrition? If Yes, provide details	
Has the subject had significant weight loss? If Yes, provide details	
Has the subject had a blood transfusion?	☐ Yes
Has the subject obtained a tattoo(s), acupuncture, or piercing?	☐ Yes
Has the subject been exposed to anyone with jaundice or hepatitis? If Yes, check ALL that apply with dates, a) Hepatitis A b) Hepatitis B c) Hepatitis C d) Hepatitis E e) Jaundice	☐ Yes ☐ ☐ ☐ ☐ ☐
Family history (please specify): a. Do any of the subject's first-degree relatives have alpha-1 antitrypsin deficiency? b. Do any of the subject's first-degree relatives have autoimmune disease? c. Do any of the subject's first-degree have hereditary haemochromatosis?	 ☐ ☐ ☐
Recreational drug/alcohol/tobacco abuse (please specify amount/day, years of intake):	
Others (please specify):	

Additional Questions:

_____
Health practitioner Name (Print)

_____
Health Practitioner Name (Signature)

Additional information regarding this Adverse Event Report:
Description of event: *[narrative]*

[redacted]

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

The Marketing Authorisation Holder shall ensure that in each Member State where Apixban Accord is marketed, all physicians who are expected to prescribe apixaban are provided with the following educational material:

• The Summary of Product Characteristics

• Prescriber Guide

• Patient Alert Cards

All patients and/or caregivers of paediatric patients who receive Apixaban Accord shall be provided with a Patient Alert Card (provided within each medicine pack).

Key Elements of the Prescriber Guide

• Details of populations potentially at higher risk of bleeding

• Recommended dosages and guidance on the posology for different indications

• Recommendations for dose adjustment in at risk populations, including renal or hepatic impairment patients

• Guidance regarding switching from or to Apixaban treatment

• Guidance regarding surgery or invasive procedure, and temporary discontinuation

• Management of overdose situations and haemorrhage

• The use of coagulation tests and their interpretation

• That all patients and/or caregivers of paediatric 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 care provider.
- Importance of treatment compliance
- Necessity to carry the Patient alert card with them at all times
- The need to inform Health Care Professionals that they are taking Apixaban if they need to have any surgery or invasive procedure.

Key Elements of the Patient Alert Card

• Signs or symptoms of bleeding and when to seek attention from a health care provider.

• Importance of treatment compliance

• Necessity to carry the Patient alert card with them at all times

• The need to inform Health Care Professionals that they are taking apixaban if they need to have any surgery or invasive procedure.

[redacted]