EU Risk Management Plan for Dabigatran etexilate Leon Farma 75, 110 and 150 mg hard capsules (dabigatran)

RMP version to be assessed as part of this application:

RMP Version number: 3.0
Data lock point for this RMP: 21-April-2024
Date of final sign off: 10-June-2024

Rationale for submitting an updated RMP: This RMP V 3.0 is updated to align to the reference product Pradaxa's RMP, published on the EMA's website on 14-February-2024

Summary of significant changes in this RMP:

- Part I: Product(s) Overview: change indication from 'birth' to 'the time the child is able to swallow soft food'

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

Version number: 2.0
Approved with procedure: EMEA/H/C/0005922
Date of approval: 19-February-2024

QPPV name:

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Reason:I Approve this Document

IVAN ARIAS

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Part I: Product(s) Overview

The reference product for Dabigatran etexilate 75, 110 and 150 mg hard capsules is Pradaxa® launched by Boehringer Ingelheim International GmbH.

Table Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Dabigatran etexilate (as mesylate)
Pharmacotherapeutic group(s) (ATC Code)	Antithrombotic agents, direct thrombin inhibitors (B01AE07)
Marketing Authorisation Holder(s)	Laboratorios León Farma
Medicinal products to which this RMP refers	Three (03)
Invented name(s) in the European Economic Area (EEA)	Dabigatran etexilate León Farma 75, 110 and 150 mg hard capsules
Marketing authorisation procedure	EMEA/H/C/005922/0000
Brief description of the product	Chemical class: Benzimidazoles
	Summary of mode of action: Dabigatran etexilate is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma. Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.
	Important information about its composition: Not applicable
Hyperlink to the Product Information	Please refer to module 1.3 of the dossier
Indication(s) in the EEA	Current: • Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (referred to as pVTEp for the purpose of this RMP) • 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 ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class≥II); diabetes mellitus; hypertension (referred to as SPAF for the purpose of this RMP)

	• Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (referred to as aVTEt/sVTEp for the purpose of this RMP) • Treatment of VTE and prevention of recurrent VTE in paediatric patients from the time the child is able to swallow soft food to less than 18 years of age (referred to as paediatric VTE for the purpose of this RMP)
	Proposed: Not applicable
Dosage in the EEA	Current: PVTEp: 220 mg once daily, 150 mg once daily, or 75 mg once daily SPAF: 150 mg b.i.d. or 110 mg b.i.d. aVTEt/sVTEp: 150 mg b.i.d. and 110 mg b.i.d. *Paediatric VTE* The recommended dose is based on the patient's age and weight (please refer to the SmPC for full posology)
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: 75, 110 and 150 mg hard capsules
	Proposed: Not applicable
Will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

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

Not applicable for generic applications.

Part II: Module SII – Non-clinical part of the Safety Specification

Not applicable for generic applications.

Part II: Module SIII – Clinical trial exposure

Not applicable for generic applications.

Part II: Module SIV – Populations not studied in clinical trials

Not applicable for generic applications.

Part II: Module SV – Post-Authorization Experience

Not applicable for initial applications.

Part II: Module SVI – Additional EU requirements for the Safety Specification

Not applicable for generic applications.

Part II: Module SVII – Identified and potential risks

Not applicable since the reference product has an RMP.

Part II: Module SVIII – Summary of the safety concerns

The safety concerns for Dabigatran etexilate 75, 110 and 150 mg hard capsules are based on the safety concerns of the reference product, Pradaxa® (RMP version 41.2, sign-off 14-July-2023).

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Haemorrhage
Important potential risks	• None
Missing information	• Patients aged 0 to 2 years who were born prematurely • Paediatric patients with renal dysfunction (eGFR<50ml/min)

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 the important identified risk 'Haemorrhage':

A questionnaire to collect standardized data to follow-up on serious haemorrhagic events is used for all spontaneous case reports where such a haemorrhagic event has been reported (Appendix 4-Bleeding event form). The questionnaire collects information on details of the reported bleeding event, such as the anatomic location, time of occurrence of the first signs or symptoms, outcome, medical history of bleeding events, alternative explanations, risk factors (e.g., liver diseases, injuries), renal impairment, treatment for bleeding, concomitant medication, action taken and reporter's causality.

Other forms of routine pharmacovigilance activities:

Not applicable.

III.2 Additional pharmacovigilance activities

Not applicable.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Haemorrhage	Routine risk communication: *SmPC Section 4.8* *PL Section 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *SmPC* • *Section 4.2, where advice is given on estimating kidney function prior to treatment initiation and periodically as clinically indicated. This section also includes a description of patients at risk of haemorrhage* • *Section 4.3, where treatment is contraindicated in patient populations at risk* • *Section 4.4, where advice is given on patients at risk of haemorrhage. This section also provides information on the availability of the specific reversal agent Praxbind (idaruzicumab) for use when rapid reversal of anticoagulation is required* • *Section 4.5, which describes drug-drug interactions that might lead to an increased risk of haemorrhagic events* • *Section 4.9, where advice is given on management of overdose situations, including a reference to the specific reversal agent Praxbind (idaruzicumab)* *PL* • *Conditions and concomitant medications increasing the risk of bleeding are detailed in PL Sections 2 and 3* Other risk minimisation measures beyond the Product Information: *Praxbind (idarucizumab) has been approved in adult patients as a specific reversal agent for rapid reversal of the anticoagulation effect of dabigatran in case of emergency surgery or urgent procedures for situations of life threatening or uncontrolled bleeding. A paediatric investigation plan for idarucizumab has been completed. In paediatric patients for whom the specific reversal agent cannot be used, haemodialysis can remove dabigatran.*
Missing information	
Patients aged 0 to 2 years who were born prematurely	Routine risk communication: none Routine risk minimisation activities recommending specific clinical measures to address the risk: none Other risk minimisation measures beyond the Product Information: *None*
Paediatric patients with renal dysfunction (eGFR<50ml/min)	Routine risk communication: none Routine risk minimisation activities recommending specific clinical measures to address the risk: *SmPC Sections 4.2 and 4.4* *PL Section 2* Other risk minimisation measures beyond the Product Information: none

V.2. Additional Risk Minimisation Measures

Prescriber Guide for Health Care Professionals (HCPs) and Patient Alert Card for patients

Objectives:
A Prescriber Guide is available for each approved indication. In addition, a Patient Alert Card that is valid for all indications is included in every package of Dabigatran.

The Prescriber Guide and Patient Alert Card is aimed at increasing awareness about the potential risk of bleeding during treatment with Dabigatran and providing guidance on how to manage that risk.

Rationale for the additional risk minimisation activity:
The Dabigatran Prescriber Guide and Patient Alert Card are implemented to alert prescribers and patients, respectively, to the risk of haemorrhage when taking Dabigatran and to prevent the use of Dabigatran in patients with increased haemorrhage risks.

Target audience and planned distribution path:
The target audience for the Dabigatran Prescriber Guide are physicians who prescribe Dabigatran. These are cardiologists and general practitioners.

The details of the distribution plan will be agreed with each national competent authority prior to the launch of Dabigatran.

Target audience for Dabigatran Patient Alert Card are patients who receive Dabigatran prescriptions. Patients receive the Patient Alert Card at each prescription, since the Patient Alert Card is included in every Dabigatran package.

Plans to evaluate the effectiveness of the interventions and criteria for success:
Effectiveness will be measured by means of routine pharmacovigilance activities, including signal detection, follow-up requests, etc. Success of the measures will be achieved if a low number of adverse event reports is observed after the implementation of the additional risk minimisation measures.

V.3. Summary of Risk Minimisation Measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Haemorrhage	Routine risk minimisation measures: *SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8, and 4.9* *PL Sections 2, 3, and 4* Other risk minimisation measures: *Praxbind (idarucizumab) has been approved in adult patients as a specific reversal agent for rapid reversal of the anticoagulation effect of dabigatran in case of emergency surgery or urgent procedures for situations of life threatening or uncontrolled bleeding. For paediatric patients, haemodialysis can remove dabigatran.* Additional risk minimisation measures: *Prescriber guide and patient alert card*	Routine Pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Adverse event follow-up form for adverse reaction* Additional Pharmacovigilance activities: none

Missing information		
Patients aged 0 to 2 years who were born prematurely	Routine risk minimisation measures: none Additional risk minimisation measures: none	Routine Pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional Pharmacovigilance activities: *None*
Paediatric patients with renal dysfunction (eGFR<50ml/min)	Routine risk minimisation measures: *SmPC sections 4.2 and 4.4* *PL section 2* Additional risk minimisation measures: none	Routine Pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional Pharmacovigilance activities: none

Part VI: Summary of the risk management plan

Summary of risk management plan for Dabigatran etexilate Leon Farma 75, 110 and 150 mg hard capsules (dabigatran)

This is a summary of the risk management plan (RMP) for Dabigatran etexilate Leon Farma 75, 110 and 150 mg hard capsules. The RMP details important risks of Dabigatran etexilate Leon Farma 75, 110 and 150 mg hard capsules, how these risks can be minimised and how more information will be obtained about Dabigatran etexilate Leon Farma 75, 110 and 150 mg hard capsules risks and uncertainties (missing information).

Dabigatran etexilate Leon Farma 75, 110 and 150 mg hard capsule's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Dabigatran etexilate Leon Farma 75, 110 and 150 mg hard capsules should be used.

Important new concerns or changes to the current ones will be included in updates of Dabigatran etexilate Leon Farma 75, 110 and 150 mg hard capsule's RMP.

I. The medicine and what it is used for

Dabigatran etexilate Leon Farma 75, 110 and 150 mg hard capsules is authorized in adults for (see SmPC for the full indications):

- Prevent the formation of blood clots in the veins after knee or hip replacement surgery
- Prevent blood clots in the brain (stroke) and other blood vessels in the body if you have a form of irregular heart rhythm called nonvalvular atrial fibrillation and at least one additional risk factor
- Trear blood clots in the veins of your legs and lungs and to prevent blood clots from re-occurring in the vein of your legs and lungs

Dabigatran etexilate Leon Farma 75, 110 and 150 mg hard capsules is authorized in children to (see SmPC for the full indication):

- Treat blood clots and prevent blood clots from reoccurring

It contains dabigatran etexilate as the active substance and it is given via the oral route.

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

Important risks of Dabigatran etexilate Leon Farma 75, 110 and 150 mg hard capsules, 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 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 Dabigatran etexilate Leon Farma 75, 110 and 150 mg hard capsules, 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*.

II.A List of important risks and missing information

Important risks of Dabigatran etexilate Leon Farma 75, 110 and 150 mg hard capsules 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 Dabigatran etexilate Leon Farma 75, 110 and 150 mg hard capsules. 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	• Haemorrhage
Important potential risks	• None
Missing information	• Patients aged 0 to 2 years who were born prematurely • Paediatric patients with renal dysfunction (eGFR<50ml/min)

II.B Summary of important risks

Important identified risks: Haemorrhage	
Risk minimisation measures	Routine risk minimisation measures: *SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8 and 4.9* *PL Sections 2, 3 and 4* Other risk minimisation measures: *Praxbind (idarucizumab) has been approved in adult patients as a specific reversal agent for rapid reversal of the anticoagulation effect of dabigatran in case of emergency surgery or urgent procedures for*

	situations of life threatening or uncontrolled bleeding. For paediatric patients, haemodialysis can remove dabigatran. Additional risk minimisation measures: *Prescriber guide and patient alert card*
Missing information: Patients aged 0 to 2 years who were born prematurely	
Risk minimisation measures	Risk minimisation measures: *None*
Missing information: Paediatric patients with renal dysfunction (eGFR<50ml/min)	
Risk minimisation measures	Routine risk minimisation measures: *SmPC Sections 4.2 and 4.4* *PL Section 2*

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 Dabigatran etexilate Leon Farma 75, 110 and 150 mg hard capsules.

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

There are no studies required for Dabigatran etexilate Leon Farma 75, 110 and 150 mg hard capsules.

Part VII: Annexes

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Annex 1 – EudraVigilance Interface

Not applicable.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable.

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 - Specific adverse drug reaction follow-up forms

Questionnaire: Bleeding event form

1. What was the gastrointestinal location of the reported bleeding?

☐Gastrointestinal haemorrhage
☐ Hematemesis: red blood or coffee grounds material
☐ Melena: black, tarry, foul-smelling stool
☐ Haematochezia: bright red or maroon blood from the rectum
☐ Occult GI bleeding: blood in the stool in the absence of overt bleeding

2. What was the location of the reported bleeding?

☐ Intracranial haemorrhage
☐ Skin bleeding
☐ Blood in urine
☐ Genital haemorrhage
☐ Wound haemorrhage /procedural site haemorrhage
☐ Other site (specify)
☐ No location identified

3. When did the first signs or symptoms of the reported bleeding event occur?

☐ Prior to start of treatment with Dabigatran, please specify: ___days/___weeks

☐ After start of treatment with Dabigatran, please specify:

___days/___weeks

☐ Not known

4. Does the patient have any episodes of bleeding in the medical history?

☐ Yes ☐ No ☐ Not known

If "Yes" please specify: _____

5. Was there an alternative explanation, other than Dabigatran, for the bleeding event?

☐ Yes ☐ No ☐ Not known

If "Yes" please specify: _____

6. Did the patient suffer from liver diseases that might have influenced the bleeding event?

□ Yes □No □Not known

If "Yes" please specify: _____

7. Did the patient suffer from an injury (e.g. fall, trauma, accident) that might have influenced the bleeding event?

□ Yes □No □ Not known

If "Yes" please specify: _____

8. Did the patient suffer from renal impairment prior to or at the event onset of the bleeding event?

□ Yes, please specify: □No □Not known

- □ Renal function decreased prior to start with Dabigatran
- □ Renal function decreased prior to bleeding event

9. Parameter

Please provide date, value and unit for:

- Creatinine
- CrCl
- GFR

10. Which treatment for the bleeding event was initiated?

□ No treatment was initiated
□ Surgical procedure, please specify: _____
□ Blood transfusion: _____Units
□ Other drugs, please specify: _____
□ Not known

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable.

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

Physician educational material:

- The Summary of Product Characteristics
- Guide for healthcare professionals (prescriber guide)

The **Prescriber Guide** should contain the following key safety messages:

- Details of populations potentially at higher risk of bleeding
- Information on medicinal products that are contraindicated or which should be used with caution due to an increased risk of bleeding and/or increased dabigatran exposure
- Contraindication for patients with prosthetic heart valves requiring anticoagulant treatment
- Recommendation for kidney function measurement
- Recommendations for dose reduction in at risk populations
- Management of overdose situations

- The use of coagulation tests and their interpretation
- That all 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 about all medicines the patient is currently taking
  - The need to inform Health Care Professionals that they are taking Dabigatran etexilate if they need to have any surgery or invasive procedure.
  - An instruction how to take Dabigatran etexilate

The patient information pack:

- Patient information leaflet
- Patient alert card

The **Patient Alert Card** should contain the following key safety messages:

- Signs or symptoms of bleeding and when to seek attention from a healthcare provider
- Importance of treatment compliance
- Necessity to carry the patient alert card with them at all times
- The need to inform Health Care Professionals about all medicines they are currently taking
- The need to inform Health Care Professionals that they are taking Dabigatran if they need to have any surgery or invasive procedure

Annex 7 - Other supporting data (including referenced material)

Not applicable

Annex 8 – Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
1.0	Approval date: not approved Procedure: EMEA/H/C/005922/0000	First submission.
2.0	Approval date: 19-February-2024 Procedure: EMEA/H/C/005922/0000	Updated according to EMA's assessment for the centrally authorised product. Summary of significant changes in this RMP: • Part I: number of medicinal products has been changed from 3 to 1 • Change in the safety concerns included in the RMP: the following two risks are added as missing information following the reference product's RMP: – Patients aged 0 to 2 years who were born prematurely – Paediatric patients with renal dysfunction (eGFR<50ml/min)
3.0	Approval date: pending Procedure: EMEA/H/C/005922/0000	This RMP V 3.0 is updated to align to the reference product Pradaxa's RMP, published on the EMA's website on 14-February-2024. Summary of significant changes in this RMP: – Part I: Product(s) Overview: change indication from 'birth' to 'the time the child is able to swallow soft food'