14 December 2023
EMA/12212/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dabigatran Etexilate Leon Farma

International non-proprietary name: dabigatran etexilate

Procedure No. EMEA/H/C/005922/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
BCS	Biopharmaceutics Classification System
BDL	Below the limit of detection
CEP	Certificate of Suitability of the Ph. Eur.
CHMP	the Committee for Medicinal Products for Human Use
CoA	Certificate of Analysis
CPCA	Carcinogenic Potency Categorisation Approach
CQA	Critical Quality Attribute
CRS	Chemical reference substance
DL	Detection Limit
DSC	Differential Scanning Calorimetry
EC	European Commision
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EP	European Pharmacopoeia
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration
FID	Flame ionisation detection
FP	Finished product
FPM	Finished product manufacturer
FT-IR	Fourier transmission infra-red (spectroscopy)
HPLC	High performance liquid chromatography
IPC	In-process control test
GC	Gas chromatography
GC-MS	Gas chromatography mass spectrometry
ICH	International conference on harmonisation
IR	Infra-red
KF	Karl Fischer titration
LCMS	Liquid chromatography mass spectrometry
LoA	Letter of Access
LOD	Loss on Drying
LoD	Limit of Detection
LoQ	Limit of Quantitation
MAH	Marketing Authorisation Holder
MO	Major Objection
MS	Mass spectroscopy
NCO	Non-Clinical Overview
NfG	Note for guidance
NIR	Near infra-red
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
PEC	Predicted Environmental Concentration
PDA	Photo diode array
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PNEC	Predicted No-Effect Concentration
PVC	Polyvinyl chloride
PVdC	Polyvinylidene chloride
PXRD	Powder X-ray diffraction
QbD	Quality by Design
QL	Quantitation limit
QOS	Quality Overall Summary

QTPP	Quality target product profile
RH	Relative Humidity
RSD	Relative standard deviation
Rrt	Relative retention time
Rt	Retention time
SD	Standard deviation
SEM	Scanning electron microscopic
SmPC	Summary of Product Characteristics
SWP	Safety Working Party
TGA	Thermo-Gravimetric Analysis
TLC	Thin layer chromatography
UV	Ultra violet
XRD	X-Ray Diffraction

Not all abbreviations may be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Laboratorios Leon Farma S.A. submitted on 4 February 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Dabigatran Etexilate Leon Farma, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 April 2021.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Dabigatran etexilate Leon Farma 75 mg hard capsule

Primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

Treatment of VTE and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.

For age appropriate dose forms, see section 4.2.

Dabigatran etexilate Leon Farma 110 mg hard capsule

Primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total 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 ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.

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

Treatment of VTE and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.

For age appropriate dose forms, see section 4.2.

Dabigatran etexilate Leon Farma 150 mg hard capsule

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.

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

Treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.

For age appropriate dose forms, see section 4.2.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Pradaxa instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Pradaxa, 75 mg, 110 mg and 150 mg, hard capsules
- Marketing authorisation holder: Boehringer Ingelheim International GmbH
- Date of authorisation: 18-03-2008
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/08/442

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Pradaxa, 75 mg, 110 mg and 150 mg, hard capsules
- Marketing authorisation holder: Boehringer Ingelheim International GmbH
- Date of authorisation: 18-03-2008
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/08/442

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Pradaxa, 150 mg, hard capsules
- Marketing authorisation holder: Boehringer Ingelheim International GmbH
- Date of authorisation: 18-03-2008
- Marketing authorisation granted by:
  - Union
- Marketing authorisation numbers: EU/1/08/442/009-0013, EU/1/08/442/0016, EU/1/08/442/0019
- Bioavailability study number(s): protocol numbers 20-VIN-0032 [2020-DABI0291-PK-04] and 20-VIN-0033 [2020-DABI0291-PK-03]

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Simona Badoi

The application was received by the EMA on	4 February 2022
The procedure started on	24 February 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 May 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	25 May 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 June 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 December 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on	30 January 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	9 February 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on	15 February 2023
The CHMP agreed on a List of Outstanding Issues in writing to be sent to the applicant on	23 February 2023
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	24 April 2023

The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 May 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on	17 May 2023
The CHMP agreed on the 2nd List of Outstanding Issues in writing to be sent to the applicant on	25 May 2023
The applicant submitted the responses to the CHMP consolidated 2nd List of Outstanding Issues on	11 September 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP and PRAC members on	27 September 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP and PRAC members on	5 October 2023
The CHMP agreed on the 3rd List of outstanding issues in writing to be sent to the applicant on	12 October 2023
The applicant submitted the responses to the CHMP consolidated 3rd List of Outstanding Issues on	13 November 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the 3rd List of Outstanding Issues to all CHMP and PRAC members on	30 November 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the applicant's responses to the 3rd List of Outstanding Issues to all CHMP and PRAC members on	7 December 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Dabigatran Etexilate Leon Farma on	14 December 2023

2. Scientific discussion

2.1. Introduction

This is a generic application of a centrally authorised medicinal product according to Article 10(1) of Directive 2001/83/EC as amended. The reference product is reference product is Pradaxa 75 mg, 110 mg, 150 mg hard capsules, which contains the same active substances in the same strengths and was approved in the European Union on 18 March 2008 via the centralised procedure (EU/1/08/442).

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 active form 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.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 75 mg, 110 mg and 150 mg of dabigatran etexilate (as mesilate) as active substance.

Other ingredients are:

Capsule content: tartaric acid, hydroxy propyl cellulose, talc, and hypromellose.

Capsule shell: indigo carmine (E132), potassium chloride, carrageenan, titanium dioxide (E171), and hypromellose.

The product is available in aluminium-OPA/Alu/PVC blister as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of the active substance is ethyl-(2-(((4-(N-hexyloxy)carbonyl) carbamimidoyl) phenyl) amino)methyl)-1-methyl-N-(pyridine-2-yl)- 1H-benzo[d] imidazole-5-carboxamido) propanoate methane sulfonate or ethyl N-((2-(((4-((E)-amino(((hexyloxy)carbonyl) imino)methyl)phenyl)amino)methyl)-1-methyl-1-Hbenzimidazol-5-yl) carbonyl)-N-pyridin-2-yl-β-alaninate methane sulfonate corresponding to the molecular formula $C_{35}H_{45}N_7O_8S$. It has a relative molecular weight of 723.86 and the following structure:

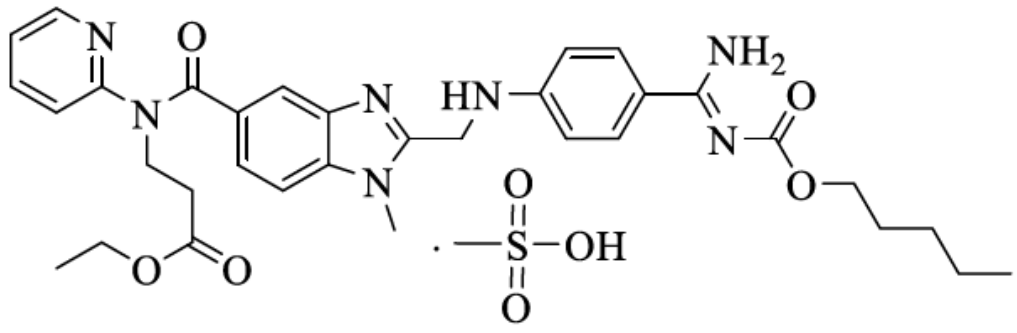

Figure 1: Active substance structure

The chemical structure of the active substance was elucidated by a combination of thermal analysis, UV study, FT-IR study, NMR Study [^{1}HNMR, ^{13}CNMR], mass spectra, X- ray powder diffraction, and elemental analysis. The solid state properties of the active substance were measured by IR, DSC and XDRD.

The active substance is a non-hygroscopic yellow-white to yellow powder freely soluble in methanol, soluble in ethanol and practically insoluble in ethyl acetate

The active substance has a non - chiral molecular structure.

The active substance exhibits polymorphism. The manufacturing process followed by the manufacturers consistently produce Form-I. Form-I is routinely tested at release and shown to be stable polymorphic form throughout the re-test period of the active substance.

Manufacture, characterisation and process controls

The active substance is manufactured by three manufacturing sites.

Detailed information on the manufacturing of the active substance by the three manufacturers has been provided in the respective restricted parts of the three ASMFs and it was considered satisfactory.

Two of the three ASMFs have been previously assessed and accepted in the context of MAA for other products in the EU. The CHMP considered the submitted information from all three ASMFs during the present application but details for these two ASMFs are not provided in this report. The synthetic processes are similar to that of the third manufacturer described below. The manufacturing process of the third manufacturer is described in 5 stages of branched synthesis, comprising 9 steps. There are four well defined starting materials with acceptable specifications and 4 isolated intermediates. During evaluation, there was a MO for one of the manufacturers in relation to the acceptability of one of the starting materials, the applicant justified the selection of this starting material and it was considered satisfactory.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. The impurities limits are according to ICH guidelines and are acceptable.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in clear polyethylene bag and tied with plastic strip which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification tested by the finished product manufacturer shown in Table 1 includes tests for description (visual), identification (IR, HPLC), water content (KF), loss on drying (Ph. Eur.), polymorphism (PXRD), methane sulfonic acid content (GC), sulphated ash (Ph. Eur.), related substances (HPLC), assay (HPLC), residual solvents (GC), particle size (laser)and mutagenic impurities (GC-MS), and nitrosamine impurities (LC-MS).

The active specification includes specific tests depending on the source of the active substance. The specification complies with the requirements in ICH Q3A, Q3C and ICH M7.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

Skip testing for an identified impurity has been proposed and accepted for AS sourced by one of the suppliers. The CHMP recommended to implement the skip testing for the other two active substance

suppliers post-approval after results for at least 6 consecutive pilot scale or 3 consecutive production scale batches will be available (REC).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data of 14 commercial scale of the active substance from all three suppliers were provided. The results are within the specifications and consistent from batch to batch. The quality of the AS is consistent among the three suppliers.

Stability

Stability data from 16 commercial scale batches of active substance from one of the suppliers, stored equivalent to the commercial packaging for up to 60 months under long term conditions (5±3 °C) and for up to 6 months under accelerated conditions (25±2 °C/60±5% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, identification, water content, related Substances, assay, X-ray diffraction, and N-nitroso dabigatran content. The analytical methods used were the same as for release and were stability indicating.

Based on the successful data of 6 months accelerated stability data for ongoing and 18 months long term (5 °C±3 °C) stability study data, the retest period of 24 months storage at 5-8°C has been assigned for active substance manufactured by this supplier.

Stability data from 6 commercial scale batches (3 process validation batches and 3 micronized batches) of active substance from second source, stored market simulated packaging to the commercial packaging for up to 48 months under long term conditions (25±2 °C/50±5% RH) and for up to 6 months under accelerated conditions (40±2 °C/75±5% RH) according to the ICH guidelines were provided.

The following parameters were tested: description, identification, water content, related substances, assay, polymorphism. The analytical methods used were the same as for release and were stability indicating.

The results of six months accelerated and 48 months long-term stability data show that there is no significant change in any of the parameters studied.

Based on the currently available 6 months accelerated and 48 months long-term stability data, the re-test is proposed 48 months as per the real time stability data for the active substance manufactured by this second supplier.

Stability data from 6 commercial scale batches of active substance from the last source, stored market simulated packaging to the commercial packaging for up to 12 months under long term conditions (5 °C ± 3°C.) and for up to 6 months under accelerated conditions (25 °C±2 °C and 60%±5%) according to the ICH guidelines were provided.

The following parameters were tested: description, identification, loss of drying, assay, and related substances . The analytical methods used were the same as for release and were stability indicating.

No significant changes in any of the analytical parameters are observed in the batches within 6 months in accelerated conditions 25 °C ± 2 °C, 60%± 5% RH and 12 months in long-term conditions 5 °C ± 3 °C.

Stress degradation studies under pH and oxidative conditions, stress temperature conditions (80ºC during 24 hours), stress humidity conditions were carried out. Several degradation impurities appear in oxidative conditions, the results obtained showed that the product is not stable up to 80 °C, no significant variations in the impurity content are observed under . Therefore, the active substance is stable at humidity conditions studied.

Samples of one batch were exposed to light according to current ICH guidelines. It is considered that the exposure to light affects the active substance since significant variations in the content of impurities are observed. The obtained results show that the product is photosensitive. The packaging used assure that light do not affect product quality

Based on the currently stability data, the proposed re-test period of 12 months stored in a refrigerator 5 °C ± 3 °C is justified for the active substance manufactured by this last supplier.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The 75 mg capsule strength is presented as hard capsule size "2" (approximately 18 mm) with white, opaque cap and white, opaque body containing off white to yellowish pellets.

The 110 mg capsule strength is presented as hard capsule size "1" (approximately 19 mm) with light blue, opaque cap and light blue, opaque body containing off white to yellowish pellets.

The 150 mg capsule strength is presented as hard is a capsule size "0" (approximately 22 mm) with light blue, opaque cap and white, opaque body containing off white to yellowish pellets.

The goal of the pharmaceutical development is to develop the generic medicinal version which is comparable in in-vitro and in-vivo properties as the reference medicinal product (Pradaxa).

The physico-chemical characterisation of the reference medicinal product has been provided. The layers structure of reference medicinal product pellets was studied using Scanning Electron Microscopy (SEM), that reveals a tartaric acid core, a seal coating on tartaric acid and an active substance layer on the outside. Also, the comparison between reference medicinal product and the generic medicinal product impurity profiles has been provided.

A quality target product profile (QTPP) was defined based on the clinical and pharmacokinetic (PK) characteristics as well as the in vitro dissolution and physicochemical characteristics. The generic medicinal product was designed to achieve all of the attributes in the QTPP. The investigation during pharmaceutical development focused on those critical quality attributes (CQAs) that could be impacted by a realistic change to the finished product formulation or manufacturing process. Assay, content uniformity, dissolution and related substances were considered as CQAs of the finished product. No design space has been claimed.

Excipient-active substance compatibility studies were performed and assessed through HPLC analysis of binary mixtures of the active substance and excipients in the solid state. The excipients were chosen based on the reference medicinal product characterisation and on the compatibility of the excipients with the active substance and desired characteristics of the finished product. Selected ingredients and their functions in the formulation have been described. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The finished product is available as 75 mg, 110 mg and 150 mg strength

The formulation development was initiated with the experience of similar formulation design. The formulation optimisation trials were initiated with respect to 150 mg strength.

The active substance is a BCS class II compound, and it has shown pH dependent solubility across the physiological pH range.

Data were provided in order to demonstrate the discriminatory nature of the dissolution method. The method used was by increasing the quantity of binder and modifying the manufacturing process parameters indicating that the dissolution method is discriminative.

During evaluation three multicisplinary MOs in relation to the dissolution method were agreed by the CHMP. The responses from the applicant were considered satisfactory.

A second MO was raised by the CHMP requesting additional information regarding the bootstrap analysis used to calculate the f2 similarity factor. In response, the applicant provided additional information requested, which was considered satisfactory.

Moreover two manufacturers of the finished product were initially proposed. The dissolution comparison of batches across the pH range from the two finished product manufacturers was incomplete and some additional comparisons were requested as a MO. In addition it was requested to demonstrate similarity between the profiles of batches from these two different sites for each strength to show consistency between sites. The dissolution results from batches manufactured in the proposed site (at pH 1.2, 4.5 and 6.8) were provided, while the second site was removed as manufacturer of the finished product from the dossier; these responses were considered satisfactory.

A risk assessment of the overall finished product manufacturing process was performed to identify the high-risk steps that may affect the CQAs of the finished product. For each process step, a risk assessment was conducted to identify potentially high-risk process variables which could impact the identified finished product CQAs. These variables were then investigated in order to understand the manufacturing process better and to develop a control strategy to reduce the risk. The potential impact of the manufacturing process steps on the finished product CQA's and the justifications for the same were provided.

Based on the above, several manufacturing process development studies have been performed with satisfactory results

The primary packaging is OPA-Alu-PVC/Alu blister. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.

The manufacturing process consists in the manufacture of pellets of dabigatran by fluid bed technology. The process is considered to be a non-standard manufacturing process.

Holding time studies were carried out on two batches of following intermediates stored at 25±2 °C/60±5% RH. No significant changes were found for tested parameters. Hold time validation for the storage of intermediate product is a GMP matter. Information about holding time for bulk capsule has been presented. It is confirmed that the Note for Guidance on Start of shelf-life of the finished dosage form is applied, i.e., shelf-life starts upon combining the active substance with the other ingredients.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Critical steps and the respective in-process controls were presented. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form appearance (visual), identification (HPLC, UV), water content (KF), uniformity of dosage units by content uniformity (Ph. Eur.), assay (HPLC), dissolution test (Ph. Eur./HPLC), related substances (HPLC), residual solvents (GC), N-nitroso dabigatran impurity (LC-MS) and microbial limit (Ph. Eur.).

Impurities specification in finished product are based on the specifications set forth for

current guideline Note for Guidance on Impurities in New Drug Products (CPMP/ICH/2738/99).

Residual solvent in finished product are based on the specifications set in the current guideline, Guideline for residual solvents (EMA/CHMP/ICH/82260/2006 Corr).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

Initially, the provided risk assessment concerning the potential presence of nitrosamine impurities in the finished product was not considered acceptable and confirmatory testing of finished product was requested by the CHMP as MO. Then, an updated nitrosamines risk assessment was provided. N-nitroso dabigatran impurity was detected in a number of batches of the generic medicinal product and also in a number of batches of the reference medicinal product. The levels detected were above the limit derived from the acceptable intake of 18 ng/day adopted by CHMP. As well, the risk assessment was incomplete as formation of other nitrosamines in presence of nitrite from excipients and the secondary amines occur in the synthesis of the active substance and that might be present in the active substance as related substances/ impurities was not discussed. Furthermore, N-nitrosodabigatran impurity should have been included in release and shelf-life specification of finished product. Therefore, a MO was requested by the CHMP to resolve all these issues. The applicant resolved these issues in as satisfactory manner and , the possible presence of other nitrosamines from dabigatran's declared impurities that are secondary amines were evaluated following the new approaches for nitrosamine AI establishment – Carcinogenic Potency Categorisation Approach (CPCA). The finished product specification limit for N-nitroso dabigatran impurity was set based on the defined acceptable intake of 400 ng/day (limit based on CPCA). Results for N-nitroso dabigatran impurity from sample packed in Alu-Alu blister, stored at 25ºC/60%RH and 30ºC/75%RH tested at 18 months or at 9 months have been provided. All results are within specification.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 4 minimum commercial batch size and for 3 maximum commercial batch size per strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 18 months under long term conditions (25 ºC / 60% RH), for up 12 months under intermediate conditions (30 ºC/65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in Alu-Alu blister proposed for marketing.

Samples were tested for appearance, water content, assay, dissolution test, related substances and microbiological testing. The analytical procedures used are stability indicating.

The finished product keeps all their physical, pharmaceutical, and chemical characteristics within specifications: after 18 months of storage at 25 ºC/60% RH and after 12 months of storage at 30 ºC/65% RH even though the product does not comply after 6 months of storage at 40 ºC/75% RH (significant change in Assay and Related substances) in OPA-Alu-PVC/Alu blister.

In addition, 8 batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The photostability study carried out meets with the acceptance criteria. Therefore, it could be considered a photostable product in bulk and when packaged in blister packaging.

Bulk stability study was carried out on two batches for up 12 months under long term conditions (25 ºC / 60% RH).

Bulk stability study up to 6 months was provided for 4 batches of each 75 mg and 150 mg strength of the finished product packaged in a plastic bag of low-density polyethylene (LDPE) followed by black LDPE bag with a bag of desiccant and introduced these into HDPE containers. All tested parameters were compliant with the acceptance criteria set in the specification. No trends can be observed (no decreasing of assay and no increasing of impurities and water). Based on 6 months holding time results, which are within proposed release specifications it is considered acceptable to declare a holding time for 6 months when bulk finished product are stored below 25±2ºC/60±5%RH.

Based on available stability data, the proposed shelf-life of 18 months and storage conditions "do not store above 30 ºC" as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During evaluation 4 major objections were raised by the CHMP in relation to stating materials, dissolution results, dissolution test method and risk assessment of nitrosamines. The responses from the applicant to the MOs were considered satisfactory and all the issues were considered to be resolved, as explained above.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertain to implementation of the skip testing of a specified impurity for two of the active substance suppliers post-approval after results for at least 6 consecutive pilot scale or 3 consecutive production scale batches will be available. This point is put forward and agreed as recommendations for future quality development.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- To implement the skip testing for active substance supplier post-approval after results for at least 6 consecutive pilot scale or 3 consecutive production scale batches will be available.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

The applicant submitted a complete Environmental Risk Assessment (ERA) based on bibliographic data. As $PEC_{surfacewater}$ exceeded the limit established in the *Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2)*, a Phase II assessment was submitted. The applicant presented data from bibliographic literature related to physico-chemical properties of dabigatran Etexilate, as well as ecotoxicity studies on green algae, crustacea and fish. Based on the results of the studies, the ratio PEC/PNEC≤0,1, therefore the environmental risk of dabigatran etexilate can be considered insignificant.

2.3.3. Discussion on non-clinical aspects

The non-clinical overview submitted by the applicant is considered acceptable, based on the established pharmacological, pharmacokinetic and toxicological profile and the experience from therapeutic use of the active substance. The impurity profile is considered acceptable.

The safety of Titanium dioxide (E171) as excipient in Dabigatran etexilate Leon Farma hard capsules is considered to be acceptable, taking into consideration *the Commission Regulation (EU) 2022/63 of 14 January 2022 amending Annexes II and III to Regulation (EC) NO.1333/2008 of the European Parliament and of the Council as regards the food additive titanium dioxide (E171).*

According to Directive 2001/83/EC, applicants are required to submit an ERA also for applications under legal basis Article 10(1). For this reason, the applicant submitted a complete ERA based on bibliographic data. Initially, the sources of the data were not considered fully relevant due to the following: i) in the case of databases, the references to the original publication were not provided and therefore the quality of the studies could not be assessed; ii) data in FASS are provided by pharmaceutical companies, and therefore not considered sufficiently independent and credible iii) the scientific literature used was not largely described to support of statements included in Phase II ERA. Therefore, the applicant also submitted the consumption data of Dabigatran Etexilate Leon Farma in kg/year over time, for the last 7 years in concerned countries, in order to prove that the use of the product will not lead to an increase of the environmental exposure. Furthermore, an experimentally determined log K_{ow} has been provided, in accordance to *Q&A on the Guideline on Environmental Risk Assessment for Human Use (EMA/CHMP/SWP/44609/2010 Rev. 1).* Considering the data provided, it is agreed that the use of the product will not lead to an increase of the environmental exposure.

2.3.4. Conclusion on the non-clinical aspects

The non-clinical information provided in this application is considered acceptable by CHMP to support the use of Dabigatran Etexilate Leon Farma in the applied indications.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for hard capsules containing dabigatran etexilate. To support the marketing authorisation application the applicant conducted two bioequivalence study with cross-over design under fasting conditions.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

GCP aspect

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The bioequivalence studies have been conducted with the highest strength i.e. dabigatran etexilate 150mg.

The applicant requested a biowaver for the dabigatran etexilate 75mg and 110mg strengths, based on the fulfilment of the criteria outlined in *Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1 – January. 2010)*. Dabigatran 75mg and 110mg meet the conditions for waiver of the bioequivalence studies conducted with Dabigatran 150 mg hard capsules, as follows:

a) Dabigatran etexilate 75 mg, 110 mg and 150 mg hard capsules are manufactured by the same manufacturing process;

b) The qualitative composition of the different strengths (75 mg, 110 mg and 150 mg) is the same;

c) The composition of Dabigatran etexilate 75 mg, 110 mg and 150 mg hard capsules is quantitatively proportional;

d) A comparative dissolution study was performed with the aim to assess if the in vitro behaviour of the three strengths 75 mg, 110 mg and 150 mg of dabigatran etexilate manufactured by Liconsa are comparable without any significative difference in order to demonstrate biowaiver for the 75 mg and 110 strengths. The results showed that the three strengths have a similar behaviour in the tested conditions and no significant differences exist.

e) All strengths exhibit linear and dose-proportional pharmacokinetics following single and multiple doses.

In vitro dissolution tests in support of biowaver of strengths

Dabigatran etexilate may be considered a low solubility compound with limited absorption. Its aqueous solubility is strongly pH dependent, with higher solubility in acidic media and lower/poor solubility in neutral and basic milieu.

In order to support the requested biowaiver, the similarity of the dissolution profiles between the 150 mg strength for which bioequivalence has been demonstrated and the additional strengths 75 mg and 110 mg has to be demonstrated. For this reason, the applicant conducted comparative dissolution studies.

The results of the bioequivalence studies conducted with Dabigatran Etexilate 150 mg Hard Capsule of Chemo India Formulation can be extrapolated to the other strengths 75 mg and 110 mg, according to conditions in the BE Guideline.

Tabular overview of clinical studies

To support the application, the applicant has submitted two bioequivalence studies.

Study 2020-DABI0291-PK-04 (protocol number 20-VIN-0032)	An Open Label, Balanced, Randomized, Single-Dose, Two-Treatment, Two-Sequence, Four-Period, Full Replicate crossover Oral Bioequivalence Study of Dabigatran etexilate 150 mg Hard Capsule of Laboratorios Liconsa S.A., Spain and PRADAXA (Dabigatran etexilate 150 mg hard capsules) 150 mg Hard Capsule of Boehringer Ingelheim International GmbH, Binger Str. 173 D-55216 Ingelheim am Rhein, Germany in Healthy, Adult, Human Subjects Under Fasting Conditions.
Study 2020-DABI0291-PK-03 (protocol number 20-VIN-0033)	An Open Label, Balanced, Randomized, Single-Dose, Two-Treatment, Two-Sequence, Four-Period, Full Replicate crossover Bioequivalence Study of Dabigatran etexilate 150 mg Hard Capsule of Laboratorios Liconsa S.A., Spain and PRADAXA (Dabigatran etexilate 150 mg hard capsules) 150 mg Hard Capsule of Boehringer Ingelheim International GmbH, Binger Str. 173 D-55216 Ingelheim am Rhein, Germany with multiple day Pre-treatment with a Proton Pump Inhibitor in Healthy, Adult, Human Subjects Under Fasting Conditions.

The applicant has submitted two bioequivalence studies since according to the Dabigatran etexilate hard capsules 75 mg, 110 mg and 150 mg product-specific bioequivalence guidance (EMA/CHMP/805498/2016), in addition to a fasting single-dose cross-over bioequivalence study, a study under conditions of multiple day pre-treatment with proton pump inhibitor (PPI), such as pantoprazole (40 mg b.i.d. for 4 days), should be conducted. This is due to the fact that the solubility of dabigatran etexilate is pH dependent and PPIs may affect the bioavailability of dabigatran differently depending on the formulation.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study 2020-DABI0291-PK-04 (20-VIN-0032): An Open Label, Balanced, Randomized, Single-Dose, Two-Treatment, Two-Sequence, Four-Period, Full Replicate crossover Oral Bioequivalence Study of Dabigatran etexilate 150 mg Hard Capsule of Laboratorios Liconsa S.A., Spain and PRADAXA (Dabigatran etexilate 150 mg hard capsules) 150 mg Hard Capsule of Boehringer Ingelheim International GmbH, Binger Str. 173 D-55216 Ingelheim am Rhein, Germany in Healthy, Adult, Human Subjects Under Fasting Conditions.

Methods

- **Study design**

This study was an open label, balanced, randomized, single-dose, two-treatment, two-sequence, four-period, fully replicate cross-over bioequivalence study in healthy, adult, human subjects under fasting conditions with a washout period of at least 10 days between each consecutive dosing periods of each group.

The final report is dated 11 August 2021.

Starting and end date of the study:

Clinical phase: 15 March 2021 to 27 May 2021

Bioanalytical phase: 11 May 2021 to 19 June 2021;

The clinical study details were as follows:

Group	Clinical phase	Admission	Dosing	Discharge	Completion date
Group 01: (subject no. 01 to 05, A06, 07 to 46, A47, 48 + 01 extra subject)	Period 01	15 Mar 2021	17 Mar 2021	19 Mar 2021	19 Mar 2021
	Period 02	30 Mar 2021	01 Apr 2021	03 Apr 2021	03 Apr 2021
	Period 03	09 Apr 2021	11 Apr 2021	13 Apr 2021	13 Apr 2021
	Period 04	23 Apr 2021	25 Apr 2021	27 Apr 2021	27 Apr 2021
Group 02: (subject no. 49 to 116 + 02 extra subjects)	Period 01	03 Apr 2021	05 Apr 2021	07 Apr 2021	07 Apr 2021
	Period 02	13 Apr 2021	15 Apr 2021	17 Apr 2021	17 Apr 2021
	Period 03	27 Apr 2021	29 Apr 2021	01 May 2021	01 May 2021
	Period 04	07 May 2021	09 May 2021	11 May 2021	11 May 2021
Group 03: (subject no. 117 to 137, A138, 139, 140 + 01 extra subject)	Period 01*	22 and 23 Apr 2021	25 Apr 2021	27 Apr 2021	27 Apr 2021
	Period 02	03 May 2021	05 May 2021	07 May 2021	07 May 2021
	Period 03	13 May 2021	15 May 2021	17 May 2021	17 May 2021
	Period 04	23 May 2021	25 May 2021	27 May 2021	27 May 2021

The study treatment allocation was as follows:

	Period 1	Period 2	Period 3	Period 4
Sequence 1 (n=70)	Test (T)	Reference (R)	Test (T)	Reference (R)
Sequence 2 (n=70)	Reference (R)	Test (T)	Reference (R)	Test (T)

Each subject number was assigned to one of the two sequences (TRTR or RTRT) by the randomisation schedule.

The subject numbers that were assigned the sequence TRTR was administered Test product in period-I, Reference product in period-II, Test product in period-III and Reference product in period-IV.

The subject numbers that were assigned the sequence RTRT was administered Reference product in period-I, Test product in period-II, Reference product in period-III and Test product in period-IV.

Drug administration

After an overnight fast for at least 10.00 hours, the investigational product, one capsule of the test formulation or reference formulation, allocated as per the randomisation schedule, was administered orally at scheduled dosing time to each subject and the subjects were instructed to swallow it with about 240 mL of water at ambient temperature in sitting position. They were instructed not to chew or open the capsule but to consume as a whole. Compliance for dosing was assessed by a thorough check of the oral cavity after dosing.

Standardise meal has been served at about 4.00, 8.00, 12.00, 24.00, 28.00, 32.00 and 36.00 hours after dosing in each period. During housing, all meal plans were identical for each period.

Water was restricted from one hour before dosing until four hours post-dose in each period (except for approximately 240 mL of water given for dosing and 240 mL of water given at two hours post-dose).

25 blood samples were collected during each period. The Pre-dose (0.00 hour) blood sample of 2.7 mL was collected within one hour prior to Dabigatran dosing. Post-dose blood samples of 2.7 mL each was drawn at 0.33, 0.67, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00- and 48.00-hours following dabigatran administration in each study period. Plasma samples have been collected over 48 hours. Frequent sampling has been planned and performed around the expected t_{max} (around 2.0 hours after oral administration). Taking into account the mean terminal half-life of 11 hours in healthy elderly subjects, the washout period of at least 10 days between each consecutive dosing periods of each group is considered sufficiently long to avoid the carry-over effect.

- **Test and reference products**

Dabigatran etexilate hard capsules 150mg manufactured by Chemo India Formulations Pvt. Ltd. (2batch No. EB19028B; exp. date June 2021) has been compared to Pradaxa Dabigatran etexilate 150mg hard capsules manufactured by Boehringer Ingelheim International GmbH (Batch No: 806218A, exp. date July 2021).

Certificates of analysis of the test and the reference product have been provided and the difference in content of active substance between reference and test product is less than 5.0%.

- **Population(s) studied**

140 healthy, adult male and female subjects (Asian race, mean age 33.15 ± 6.14 years, range [19 – 44 years], mean height 162.27 ± 8.34 cm, range [142.0 – 179.50 cm], mean weight 63.25 ± 8.99 kg [50.10 – 86.00 kg], mean BMI 24.07 ± 3.24 kg/m2, range [18.85 – 29.56 kg/m2]) were enrolled in the study. Only non-smokers have been enrolled in the study.

Due to the COVID-19 pandemic, the study was conducted in three groups, as follows:

In group 01: 48 [18 (Female) and 30 (Male)] + 01 extra male subject (Ex-01) healthy, adult, human male and female subjects were enrolled.

In group 02: 68 [17 (Female) and 51 (Male)] + 02 extra male subjects (Ex-02 and Ex-03) healthy, adult, human male and female subjects were enrolled.

In group 03: 24 [06 (Female) and 18 (Male)] + 01 extra male subject (Ex-04) healthy, adult, human male and female subjects were enrolled.

From 140 subjects included, 140 subjects have been dosed in Period I, 135 subjects in Period II, 128 subjects in Period III and 114 subjects in Period IV. 135 subjects completed the study, i.e. 47 subjects in Group I, 66 subjects in Group II and 22 subjects in Group III.

The demographic characteristics of the 135 subjects who completed the study are mean age 32.81 ± 6.53 years, range [19 – 44 years], mean height 160.06 ± 8.72 cm, range [142.0 – 177.00 cm], mean weight 62.65 ± 9.31 kg [51.00 – 84.00 kg], mean BMI 24.48 ± 3.22 kg/m2, range [19.00 – 29.51 kg/m2].

The study population was chosen according to the *Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01 – January 2010)*.

In accordance with the protocol, five subjects have been excluded from the Pharmacokinetic and Statistical analyses, i.e. Subject No. 130 who did not complete any period of study, Subject No. 10 who competed only one period with test product and Subjects No. 52, 76 and A138 who completed only one period with reference product. Thus, pharmacokinetic analyses were performed over plasma concentration data of 135 subjects who completed all the period or at least two periods (with one test and one reference treatment) of the study as per approved protocol.

117 subjects completed all the periods or both reference periods and have been included in the analysis of reference scaled average bioequivalence, according to the approved protocol.

- **Analytical methods**

Validation of the analytical method

A validation of the analytical technique was provided and can be summarised as follows:

The analytical method used was LCESI-MS/MS (Liquid Chromatography-Electro Spray Ionization-Mass Spectrometry/Mass Spectrometry), with human plasma as biological matrix. Samples were extracted using Solid Phase Extraction Method and injected by using LCESI-MS/MS. Dabigatran-D4 HCl was used as internal standard for the detection of dabigatran.

The method was validated for system suitability, linearity of response, sensitivity, selectivity, lower limit of quantification, calibration range, within-run and between run precision and accuracy, short term stability in biological matrix at room temperature or at sample processing temperature (bench top stability), autosampler storage stability, long-term stability of the stock solutions and working solutions, long-term stability in biological matrix, post-operative stability, freeze and thaw stability, dilution integrity, recovery, matrix effect, effect of concomitant medication, reinjection reproducibility, haemolysis effect and lipemic effect.

The pre-study validation of the analytical methods is satisfactory and demonstrated adequate precision and accuracy (both intra- and inter-run) within the calibration range, and showed adequate selectivity, sensitivity, no matrix effect and no-carry-over effect.

The bioanalytical method is acceptable and has been validated according to the *Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09)*.

A statement on GLP compliance was provided, and the handling of samples was adequate.

Within-study validation

Blood samples have been collected into sodium citrate tubes and centrifuged for 10 minutes at 4°C to separate plasma. The samples were stored 95 days from the first day of sample collection to the last day of sample analysis, at -15ºC between collection and shipment at the bioanalytical centre and afterwards at -78±8ºC until they have been analysed. This is considered acceptable since the long-term stability data of dabigatran in human plasma covers 495 days at -20±5°C and -78±8°C. The bioanalysis has been carried out between 13 May 2021 and 19 June 2021.

The plasma samples of subjects have been analysed using Dabigatran-D4 HCl as internal standard for the detection of dabigatran.

Quantitation was determined by peak area ratio method. Calibration curves were obtained using a linear equation with $1/x^2$ as weighting factor for peak area ratio (analyte/internal standards) versus the nominal concentration of the calibration standards. Study sample concentrations were obtained by interpolation from the run defined calibration curve. Calibration range used during the study was 1.000 ng/mL to 300.00 ng/mL.

Eight non-zero calibration standards and six levels of QC samples were used. The calibration standards were 1.000 ng/mL (STD8), 2.000 ng/mL (STD7), 6.000 ng/mL (STD6), 15.000 ng/mL (STD5), 30.000 ng/mL (STD4), 60.000 ng/mL (STD3), 150.000 ng/mL (SRD2) and 300.000 ng/mL (STD1). The QC concentrations were 1.000 ng/mL (LLOQ QC), 3.000 ng/mL (LQC), ng/mL, 20.000 ng/mL (MQC2), 125.000 ng/mL (MQC1), 250.000 ng/mL (HQC), 1200.000 ng/mL (DQC) for study sample analysis.

The method was linear over the declared range with regression (r^2) value higher than 0.98. Back-calculated calibration standard concentrations met the criteria of the Guideline on Bioanalytical Method Validation.

The results of intra- and inter-day accuracy and precision were acceptable demonstrating the reliability of the assay.

Selectivity of the bioanalytical method was evaluated using six (6) independent sources of sodium citrate human plasma, one (1) lot of lipemic and one (1) lot of hemolyzed human plasma having the same anticoagulant and one (1) lot containing Na Heparin as anticoagulant. The selectivity test met the acceptance criteria.

Selectivity was also demonstrated with respect to various potentially interfering drugs including paracetamol, cetirizine, domperidone, ranitidine, diclofenac, ibuprofen, nicotine, caffeine, cefixime, dycyclonine, amoxicillin, clavulanate and pheniramine.

Back calculated concentrations for calibration standard curves met the requirements of the Guideline on Bioanalytical Method Validation.

Matrix factors and IS-normalized matrix factors at low and high QC levels were reported for 10 different sources of human sodium citrate plasma including 2 lipemic and 2 hemolyzed plasma. The mean IS-normalized matrix factors were 1.037 (4.90%CV) and 1.118 (1.39%CV) at low and high level, respectively. The precision for IS normalized matrix factor at LQC and HQC was found ≤ 15% in line with requirement of the Guideline on the Bioanalytical Method Validation.

The LLOQ of the bioanalytical method 1.000 ng/mL was below 1/20 of the C_{max} (arithmetic means for Dabigatran: test 155.265 ± 72.8629 ng/mL, reference 155.797 ± 67.8145 ng/mL) and was adequate to detect any relevant carry-over effect between the treatment periods.

Dilution integrity was evaluated by preparing quality control samples having concentration 1200.000 ng/mL. A sample was diluted to 1/10 of the original concentration and analyzed against calibration curve. The accuracy of the dilution integrity samples of Dabigatran at 1/10 dilutions was -2.99%, which is within the acceptance criteria of ± 15% of nominal concentration. Precision of the quality control samples of Dabigatran at 1/10 dilutions was 1.55%, which is within the acceptance criteria of ≤ 15%.

Reasons for reanalysis of dabigatran samples (N=161; 1.26 %) were provided and considered acceptable.

The ISR was performed in a total of 690 samples, which is in accordance with section 6 "Incurred Samples reanalysis" of the *Guideline on bioanalytical method validation* that require at least 638 samples out of 12769 samples (10% of the samples should be reanalysed in case the number of samples is less than 1000 samples and 5% of the number of samples exceeding 1000 samples). For the samples reanalysed, the ISR was acceptable as 99.57% of the samples (687 samples) reanalysed were within the acceptance range (± 20%).

Chromatograms of calibration standards, QCs, and subject samples from at least 20% of the subject samples are included in the submission, in accordance with the *Guideline on bioanalytical method validation*.

The analytical method is considered valid for the estimation of Dabigatran in human plasma within a range of 1.000 ng/mL to 300.000 ng/mL.

Taking into account the following:

- As it is known that back-conversion of unstable glucuronide metabolites may affect the accuracy and precision of the analyte in the study samples, the stability of pharmacologically active dabigatran acylglucuronides was reviewed and based on the overall retrospective review of study data the possible back conversion during the analytical method was ruled out;
- The developed analytical method is selective and able to detect the analyte from the metabolite, chromatogram of the dabigatran and dabigatran acylglucuronides were provided indicating that the retention time for of the dabigatran acylglucuronides is well separated than the retention time of dabigatran;
- The dabigatran acylglucuronides are stable under the same storage conditions of study samples,
- Successful results of ISR samples that have been analyzed during the study period, with more than 90% of the reanalysed samples fulfilling the acceptance criteria of ISR analysis confirming the reliability of the reported sample analyte concentrations;
- In addition, based on literature review the obtained concentration data for study were matching with the literature data in terms of C_{max} data;
- For the current application, the analytical method was considered adequate for the quantification of dabigatran in human plasma and validated according to the ICH M10 Guideline on Bioanalytical method validation and study sample analysis.

the Applicant's arguments regarding the quantitation in plasma only of free dabigatran and not of total dabigatran also are acceptable.

- **Pharmacokinetic variables**

Non-compartmental model of Phoenix WinNonlin Enterprise Version 8.2 was used for computation of the following pharmacokinetic variables: C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $t_{1/2}$, T_{lag}, K_{el} and $AUC\_{\%Extrap\_obs}$.

The primary pharmacokinetic parameters are: C_{max} and AUC_{0-t}. Secondary parameters are $AUC_{0-\infty}$, T_{max}, $t_{1/2}$, T_{lag}, K_{el} and $AUC\_{\%Extrap\_obs}$.

Pharmacokinetic parameters have been calculated from individual plasma concentrations of 135 subjects who completed at least two periods (with one test and one reference treatment or both reference treatment periods) of the study as per approved protocol. In accordance with the protocol, five subjects have been excluded from the Pharmacokinetic and Statistical analyses.

117 subjects completed all the periods or both reference periods and have been included in the analysis of reference scaled average bioequivalence, according to the approved protocol.

The pharmacokinetic parameters are adequate for a bioequivalence trial with an immediate-release formulation.

- **Statistical methods**

The statistical analysis of the ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were planned to be performed for Dabigatran using SAS package.

The ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were analysed by analysis of variance (ANOVA) using PROC GLM in SAS Software Version 9.4.

The sequence, treatment, period and subject (sequence) effects were set as fixed effects. The sequence effect was tested using the subject (sequence) effect as the error term.

Main effects of period and formulation have been tested at 5% level of significance. Sequence effect was tested at 10% level of significance.

Each analysis of variance included calculation of least-square means, the difference between the adjusted formulation means and the standard error associated with the difference.

As the subjects were enrolled and dosed divided in three groups 1-2-weeks apart, the Applicant performed the statistical analysis with the ANOVA model including also the factors groups. The model included the fixed effects of Sequence, Treatment, group, group*sequence, period (group), subject within sequence*group as a fixed effect. However, the Group*Formulation interaction was not included in the model.

If p-value of group effect found significant at 5% ($p<0.05$) level of significance, then the same model was used to calculate 90% confidence interval. If p-value of group found non-significant at 5% ($p>0.05$) level of significance, then group term was dropped from the model and further 90% confidence interval was calculated using separate standard ANOVA model.

Ratio of Geometric least square means for Dabigatran of test and reference formulations has been computed and reported for Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

Ratio (%) of Test and Reference formulations for each individual subject has been provided for untransformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$for Dabigatran.

Criteria for conclusion of bioequivalence

Standard bioequivalence criteria have been proposed for the primary pharmacokinetic endpoint AUC_{0-t}, i.e. the 90% confidence intervals for geometric least square mean ratios of ln-transformed AUC_{0-t} of dabigatran should fall within 80.00-125%, which is adequate.

According to the *Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1*, widening of the bioequivalence criteria has been proposed for C_{max} as the intra-subject variability of the Reference product for C_{max} was found to be greater than 30%, i.e., 40.56%; the 90%CI could be widened to 74.33-134.55%.

The current guidance also allows to widen the bioequivalence criteria for the C_{max} if the intra-subject variability of the reference product is over 30% based on the replicate design. This has been shown for both studies.

However, no outlier test has been conducted in order to discard the influence of outliers in the observed intra-subject variability of C_{max}. This is considered acceptable, as the bioequivalence has been concluded based on the average bioequivalence analysis in the end.

Results

Table 1. Pharmacokinetic parameters for Dabigatran (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD (CV%)	Arithmetic mean	SD (CV%)
$AUC_{(0-t)}$ (hr*ng/mL)	1352.217	628.4798 (46.48%)	1358.970	599.5639 (44.12%)
$AUC_{(0-\infty)}$ (hr*ng/mL)	1384.396	638.8946 (46.15%)	1391.765	611.3814 (43.93%)
C_{max} (ng/mL)	155.265	72.8629 (46.93%)	155.797	67.8145 (43.53%)
T_{max}* (hr)	2.250, 1.00 – 5.00		2.250, 1.00 – 4.50	
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (*median, range)			

Table 2. Statistical analysis for Dabigatran (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	97.34%	91.09%-104.02%	37.33%
C_{max}	97.05%	90.37%-104.22%	40.56%
* estimated from the Residual Mean Squares			

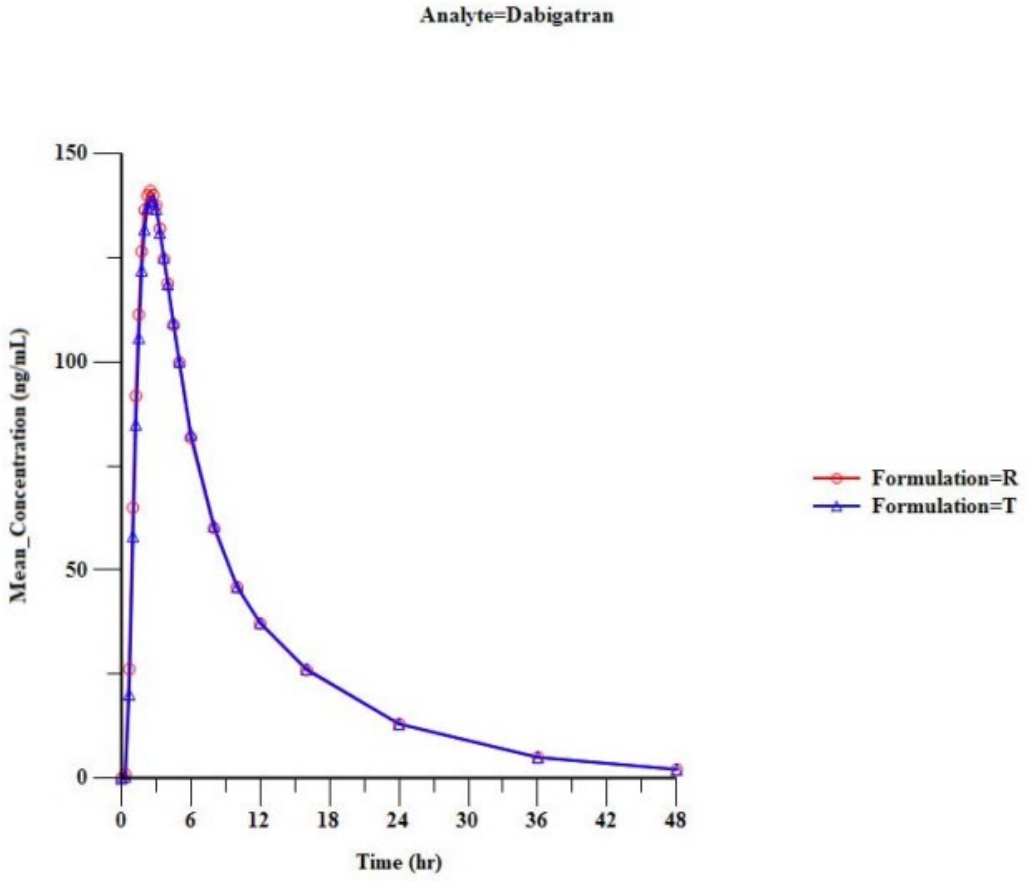

Figure 2. Linear plot of mean concentration vs time – dabigatran (reference and test formulations

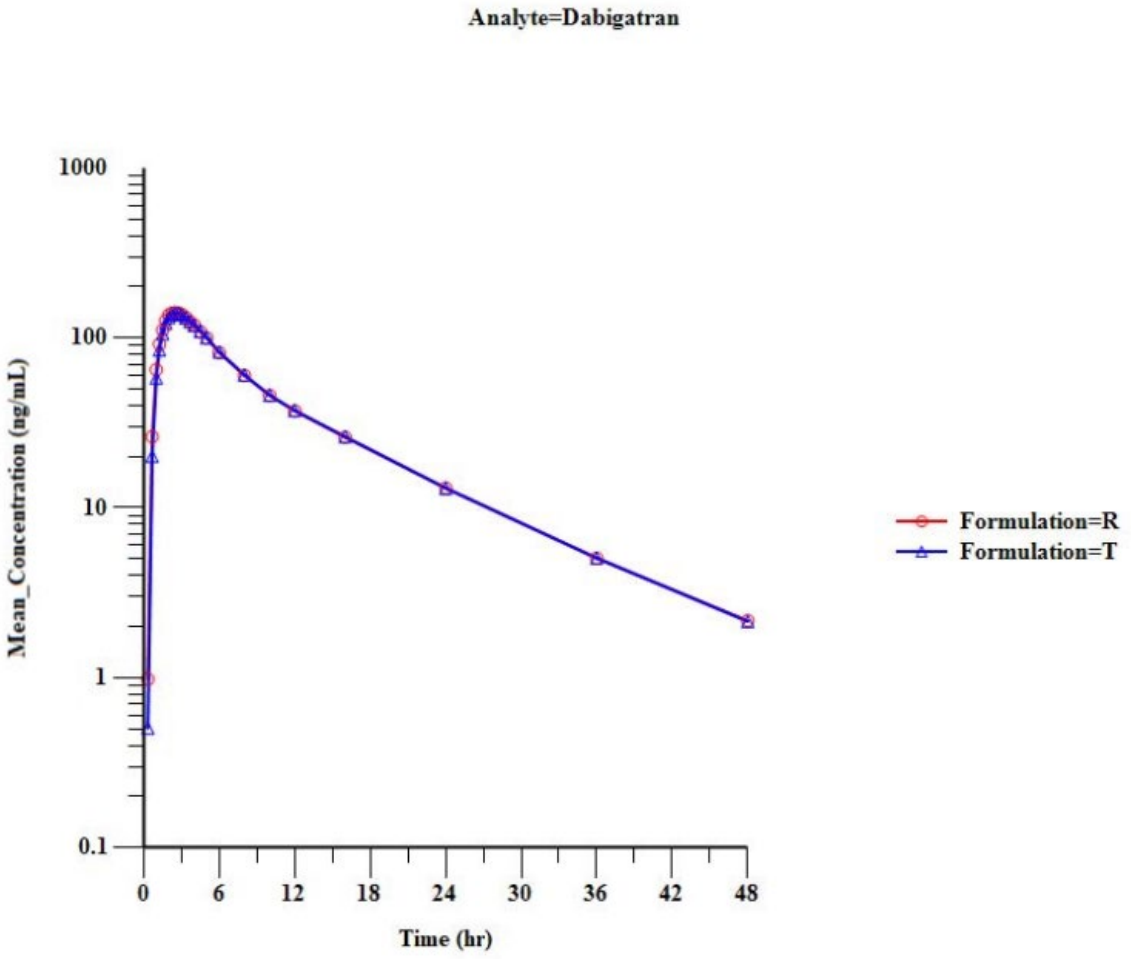

Figure 3. Semi-logarithmic plot mean concentration vs time – dabigatran (reference and test formulations

The pharmacokinetic parameter data including the confidence intervals and point estimates presented by the Applicant are in line with the acceptance criteria of the *Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1 – revised 2010)*.

For dabigatran (i.e., free dabigatran), individual linear and log-linear plots, as well as linear and semi-logarithmic plots mean concentration versus time were provided by the applicant.

The protocol defines the ANOVA model dependence on the p-value of the group effect.

The statistical model applied for the assessment of group effect included fixed effects of Sequence, formulation, group, group*sequence, period (group) and subject within sequence*group. If p-value of group effect was found significant at 5% ($p<0.05$) level of significance then the same model was used to calculate 90% confidence interval.

If p-value of group was found non-significant at 5% ($p>0.05$) level of significance then group term was dropped from the model and further 90% confidence interval was calculated using separate standard ANOVA model.

However, the Group*Formulation interaction was not included in the model. An exploratory analysis to assess if the group-by formulation is significant was conducted by the Applicant. For study 2020-DABI0291-PK-04 (code: 21-VIN-0032), the observed p-values for this Group*Formulation interaction effect were found to be not statistically significant for C_{max}, AUC_{0-t} and 0.4146 for $AUC_{0-\infty}$. The analyses have been conducted on the subjects included in the pharmacokinetic analyses (who completed all the periods or at least one test period and one reference period), i.e., 135 subjects.

As the Group*Formulation interaction was not found statistically significant, the groups' data can be combined.

No statistically significant effect was found for LnC_{max} for the group effect therefore, group term was dropped from the model and further 90% confidence interval was calculated using separate model with the group effect excluded from the model.

Therefore, the results presented are based on the average bioequivalence analysis including 135 subjects in the final statistical analysis who completed at least two periods of the study with at least one test and one reference product or all the periods with the standard bioequivalence criteria proposed for the primary pharmacokinetic endpoints C_{max} and AUC_{0-t}, i.e. the 90% confidence intervals for geometric least square mean ratios of ln-transformed C_{max} and AUC_{0-t} of dabigatran should fall within 80.00-125%.

The 90% confidence intervals for the ln-transformed values for C_{max} and AUC_{0-t} were within the 80.00 – 125% limit and are considered acceptable.

C_{max} was not observed in any subject at the first sample time point and pre-dose concentration has not been detected in any subject. The extrapolated AUC was not higher than 20%, except for one subject, i.e., Subject 61 after Dabigatran Test administration in period 2. Thus, the blood sampling schedule up to 48 h was defined adequately.

The Applicant did not found any statistically significant formulation, period or period(group) effect.

A statistically significant sequence effect for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ has been reported, which can indicate carry over effects. However, this can be disregarded considering that there are no pre-dose concentrations (>5% of C_{max}), it is a single dose study, conducted in healthy volunteers, the drug is not an endogenous substance and the study satisfies all the scientific and statistical criteria (e.g. protocol, validation, concentration data, statistical analysis, confidence interval).

For ln-transformed primary pharmacokinetic C_{max} parameter, group effect was not statistically significant. However, for ln-transformed AUC_{0-t} (primary pharmacokinetic parameter) and $AUC_{0-\infty}$, a statistically significant group effect was found.

- **Safety data**

A total of twenty-four (24) adverse events occurred in twenty-two (22) subjects during the study conduct and one serious adverse event which required subjects' hospitalization. From the twenty-four adverse events reported, twelve (12) were possible related to the study drug (i.e., vomiting, high WBC count) and one probably related (urticaria). Fourteen (14) (10.22%) adverse events have been reported in subjects dosed with Test product, from which nine (09) were judged as related and five (05) as not related, whereas eleven (11) (7.97%) adverse events have been reported in subjects dosed with Reference product, from which four (04) were judged as related and seven (07) as not related. All related adverse events reported in subjects dosed with Test product were mild, except urticarial, which was moderate. All related adverse events in subjects dosed with Reference product were mild, except one (asthenia) which was moderate. The number of related adverse events to the study drugs was slightly higher in subjects dosed with Test product as compared to subjects dosed with Reference product.

No severe adverse events have been reported during the study conduct.

A serious non-related adverse event of COVID-19 pneumonitis has been reported.

All adverse events and serious adverse event were resolved, except for post study adverse event of one subject who was lost to follow up.

Administrations of test and reference products to healthy subjects were safe and well tolerated.

Study 2020-DABI0291-PK-03 (20-VIN-0033): An Open Label, Balanced, Randomized, Single-Dose, Two-Treatment, Two-Sequence, Four-Period, Full Replicate crossover Bioequivalence Study of Dabigatran etexilate 150 mg Hard Capsule of Laboratorios Liconsa S.A., Spain and PRADAXA (Dabigatran etexilate 150 mg hard capsules) 150 mg Hard Capsule of Boehringer Ingelheim International GmbH, Binger Str. 173 D-55216 Ingelheim am Rhein, Germany with multiple day Pre-treatment with a Proton Pump Inhibitor in Healthy, Adult, Human Subjects Under Fasting Conditions.

Methods

- **Study design**

This was an open label, balanced, randomised, single-dose, two-treatment, two-sequence, four-period, fully replicate crossover relative bioavailability study with multiple day Pre-treatment with a proton pump inhibitor in healthy, adult, human subjects under fasting condition.

The final report is dated: 15 April 2021

Starting and end date of the study:

Clinical phase: 20 July 2020 to 06 October 2020

Bioanalytical phase: 01 October 2020 to 06 November 2020

The clinical study details were as follows:

Group	Clinical phase	Admission	Date of Concomitant medication dosing Day - 4 Morning and Evening	Date of Concomitant medication dosing Day - 3 Morning and Evening	Date of Concomitant medication dosing Day - 2 Morning and Evening	Date of Concomitant medication dosing Day - 1 Morning and Evening	Dosing of IP and concomitant Medication (Morning)	Discharge date	Completion date
Group 01: (subject no. 01 to 48 + 02 extra subjects) (Subject no. 01 to 18) - Female subjects and (Subject nos. 19 to 48)- Male subjects ex-01: Female subject and ex-02 : Male subject	Period 01	20 Jul 2020	21 Jul 2020	22 Jul 2020	23 Jul 2020	24 Jul 2020	25 Jul 2020	27 Jul 2020	27 Jul 2020
	Period 02	16 Aug 2020	17 Aug 2020	18 Aug 2020	19 Aug 2020	20 Aug 2020	21 Aug 2020	23 Aug 2020	23 Aug 2020
	Period 03	03 Sep 2020	04 Sep 2020	05 Sep 2020	06 Sep 2020	07 Sep 2020	08 Sep 2020	10 Sep 2020	10 Sep 2020
	Period 04	22 Sep 2020	23 Sep 2020	24 Sep 2020	25 Sep 2020	26 Sep 2020	27 Sep 2020	29 Sep 2020	29 Sep 2020
Group 02: (subject no. 49 to 96 + 02 extra subjects) (Subject no. 49 to 66) - Female subjects and (Subject no. 67 to 96)- Male subjects ex-03: Female subject and ex-04 Male subject	Period 01	04 Aug 2020	05 Aug 2020	06 Aug 2020	07 Aug 2020	08 Aug 2020	09 Aug 2020	11 Aug 2020	11 Aug 2020
	Period 02	27 Aug 2020	28 Aug 2020	29 Aug 2020	30 Aug 2020	31 Aug 2020	01 Sep 2020	03 Sep 2020	03 Sep 2020
	Period 03	15 Sep 2020	16 Sep 2020	17 Sep 2020	18 Sep 2020	19 Sep 2020	20 Sep 2020	22 Sep 2020	22 Sep 2020
	Period 04	29 Sep 2020	30 Sep 2020	01 Oct 2020	02 Oct 2020	03 Oct 2020	04 Oct 2020	06 Oct 2020	06 Oct 2020

Details of administration of concomitant medication, i.e. Pantozol (Pantoprazole) 40 mg tablet

Day	Details of administration
Day -4	Pantozol® (Pantoprazole) 40 mg tablets twice daily (Morning and Evening)
Day -3	Pantozol® (Pantoprazole) 40 mg tablets twice daily (Morning and Evening)
Day -2	Pantozol® (Pantoprazole) 40 mg tablets twice daily (Morning and Evening)
Day -1	Pantozol® (Pantoprazole) 40 mg tablets twice daily (Morning and Evening)
Day 0	Pantozol® (Pantoprazole) 40 mg tablets once (Morning dose to be administered along with administration of Investigational product)

The study treatment allocation was as follows:

	Period 1	Period 2	Period 3	Period 4
Sequence 1 (n=48)	Test (T)	Reference (R)	Test (T)	Reference (R)
Sequence 2 (n=48)	Reference (R)	Test (T)	Reference (R)	Test (T)

Each subject number was assigned to one of the two sequences (TRTR or RTRT) by the randomisation schedule.

For subject that were assigned the sequence TRTR, it was administered Test product in period-I, Reference product in period-II, Test product in period-III and Reference product in period-IV.

For subject that were assigned the sequence RTRT, it was administered Reference product in period-I, Test product in period-II, Reference product in period-III and Test product in period-IV.

Drug administration

After an overnight fast for at least 10.00 hours, the investigational product, one capsule of the test or reference formulation, allocated as per the randomized schedule, was administered orally at scheduled dosing time to each subject and the subjects were instructed to swallow it with about 240 mL of water at ambient temperature in sitting position. They were instructed not to chew or open the capsule but to consume as a whole.

Pantozol (Pantoprazole) 40 mg tablet was administered orally to each subject. The subjects were instructed to swallow it with approximately 240 of water at ambient temperature in sitting position. They were instructed not to chew or crush the tablet but to consume as a whole.

Pantozol (Pantoprazole 40 mg tablet) was administered twice daily five days starting four (4) days before the administration of the Test and Reference products. Evening dose of Pantozol (Pantoprazole) 40 mg tablet was administered 12 hours after the morning dose.

Compliance for dosing was assessed by a thorough check of the oral cavity after dosing of each study drug.

The washout period between each consecutive dosing periods of each group is considered sufficiently long to avoid the carry-over effect.Standardized meals have been served at about 4.00, 8.00, 12.00, 24.00 and 28.00, 32.00 and 36.00 hours after dosing in each period. During housing, all meal plans were identical for each period.

Morning dose of Pantozol (pantoprazole) 40 mg tablet was administered 30 minutes before schedule time of standard breakfast, except day of investigational product dosing, and evening dose of Pantozol (Pantoprazole) 40 mg tablet was administered 30 min before the schedule time of dinner.

Water was restricted from one hour before dosing until one-hour post-dose of concomitant medication from day -04 to day -01 in each period, except for approximately 240 mL of water given for dosing.

Water was restricted from one hour before dosing until four hours post-dose of investigational product (Dabigatran) in each period (except for approximately 240 mL of water given for dosing and 240 mL of water given at two hours post-dose).

25 blood samples were collected during each period. The Pre-dose (0.00 hour) blood sample of 2.7 mL was collected within one hour prior to Dabigatran dosing. Post-dose blood samples of 2.7 mL each was drawn at 0.33, 0.67, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00- and 48.00-hours following Dabigatran administration in each study period. Plasma samples have been collected over 48 hours. Frequent sampling has been planned and performed around the expected t_{max} (around 2.0 hours after oral administration).

- **Test and reference products**

Dabigatran etexilate hard capsules 150mg manufactured by Chemo India Formulations Pvt. Ltd. (2batch No. EB19028B; exp. date June 2021) has been compared to Pradaxa Dabigatran etexilate 150mg hard capsules manufactured by Boehringer Ingelheim International GmbH (Batch No: 806218A, exp. date July 2021).

Certificates of analysis of the test and the reference product have been provided and the difference in content of active substance between reference and test product is less than 5.0%.

- **Population(s) studied**

96 healthy, adult male and female subjects (Asian race, mean age 33.52 ± 6.43 years, range [20 – 44 years], mean height 161.46 ± 8.34 cm, range [139.0 – 176.50 cm], mean weight 62.99 ± 7.78 kg [50.50 – 82.20 kg], mean BMI 24.24 ± 3.05 kg/m2, range [18.88 – 29.69 kg/m2]) were enrolled in the study. Only non-smokers have been enrolled in the study.

Due to the COVID-19 pandemic, the study was conducted in two groups, as follows.

From 96 subjects included, 96 have been dosed in Period I, 87 in Period II, 84 in Period III and 82 in Period IV.

In accordance with the protocol, three subjects have been excluded from the Pharmacokinetic and Statistical analyses, i.e. subject No. 91 who did not completed any period of study, subject No. 22 who completed only one period with reference product and subject No. 56 who completed only one period with Test product. Thus, 93 subjects who completed all the periods or at least one test period and one reference period have been included in the analysis of average bioequivalence.

83 subjects, who completed at least two periods of the study with both reference formulation periods, have been included in the analysis of the reference scaled average bioequivalence.

- **Analytical methods**

Bioanalytical part of the study took place at Veeda Clinical Research Pvt. Ltd., Shivalik Plaza-A, Near I.I.M., Ambawadi, Ahmedabad -380 051, Gujarat, India, from 01 October 2020 and 06 November 2020.

The same analytical method was developed for determination of dabigatran in human plasma as for the BE study 20-VIN-0032 [2020-DABI0291-PK-04].

Validation of the analytical method

A validation of the analytical technique was provided. The method validation of determination of Dabigatran in human plasma was carried out as per Method Validation Protocol No. BRD-MVP-803-01, the same used for the method validation for study 2020-DABI0291-PK-04 [20-VIN-0032]. It can be summarised as follows:

The analytical method used was LCESI-MS/MS (Liquid Chromatography-Electro Spray Ionization-Mass Spectrometry/Mass Spectrometry), with human plasma as biological matrix. Samples were extracted using Solid Phase Extraction Method and injected by using LCESI-MS/MS. Dabigatran-D4 HCl was used as internal standard for the detection of dabigatran.

To use metabolite data instead of prodrug is in line with the current product-specific recommendations (EMA/CHMP/805498/2016).

The method was validated for system suitability, linearity of response, sensitivity, selectivity, lower limit of quantification, calibration range, within-run and between run precision and accuracy, short term stability in biological matrix at room temperature or at sample processing temperature (bench top stability), autosampler storage stability, long-term stability of the stock solutions and working solutions, long-term stability in biological matrix, post-operative stability, freeze and thaw stability, dilution integrity, recovery, matrix effect, effect of concomitant medication, reinjection reproducibility, haemolysis effect and lipemic effect.

The pre-study validation of the analytical methods is satisfactory and demonstrated adequate precision and accuracy (both intra- and inter-run) within the calibration range, and showed adequate selectivity, sensitivity, no matrix effect and no-carry-over effect.

The bioanalytical method is acceptable and has been validated according to the *Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09)*.

Statement on GLP compliance was provided, and the handling of samples was adequate.

Within-study validation

Blood samples have been collected into sodium citrate tubes and centrifuged at 4000 rpm for 10 minutes at 4°C to separate plasma. The samples have been stored 105 days from the first day of sample collection to the last day of sample analysis, at -15ºC between collection and shipment at the bioanalytical centre and afterwards at -78±8ºC until they have been analysed. This is considered acceptable since the long-term stability data of dabigatran in human plasma covers 495 days at -20±5°C and -78±8°C. The bioanalysis has been carried out between 01 October 2020 and 06 November 2020.

The plasma samples of subjects have been analysed using Dabigatran D4 HCl as internal standard for the detection of dabigatran.

Quantitation was determined by peak area ratio method. Calibration curves were obtained using a linear equation with 1/x2 as weighting factor for peak area ratio (analyte/internal standards) versus the nominal concentration of the calibration standards. Study sample concentrations were obtained by interpolation from the run defined calibration curve. Calibration range used during the study was 1.000 ng/mL to 300.00 ng/mL.

Eight non-zero calibration standards and six levels of QC samples were used. The calibration standards were 1.000 ng/mL (STD8), 2.000 ng/mL (STD7), 6.000 ng/mL (STD6), 15.000 ng/mL (STD5), 30.000 ng/mL (STD4), 60.000 ng/mL (STD3), 150.000 ng/mL (SRD2) and 300.000 ng/mL (STD1). The QC concentrations were 1.000 ng/mL (LLOQ QC), 3.000 ng/mL (LQC), ng/mL, 20.000 ng/mL (MQC2), 125.000 ng/mL (MQC1), 250.000 ng/mL (HQC), 1200.000 ng/mL (DQC) for study sample analysis.

The method was linear over the declared range with regression (r2) value higher than 0.98. Back-calculated calibration standard concentrations met the criteria of the Guideline on Bioanalytical Method Validation.

The results of intra- and inter-day accuracy and precision were acceptable demonstrating the reliability of the assay.

Selectivity of the bioanalytical method was evaluated using six (6) independent sources of sodium citrate human plasma, one (1) lot of lipemic and one (1) lot of hemolyzed human plasma having the same anticoagulant containing Na Heparin as anticoagulant. The selectivity test met the acceptance criteria.

Selectivity was also demonstrated with respect to various potentially interfering drugs including paracetamol, cetirizine, domperidone, ranitidine, diclofenac, ibuprofen, nicotine and caffeine.

Back calculated concentrations for calibration standard curves met the requirements of the Guideline on Bioanalytical Method Validation.

Matrix factors and IS-normalized matrix factors at low and high QC levels were reported for 10 different sources of human sodium citrate plasma including 2 lipemic and 2 hemolyzed plasma. The mean IS-normalized matrix factors were 1.037 (4.90%CV) and 1.118 (1.39%CV) at low and high level, respectively. The precision for IS normalized matrix factor at LQC and HQC was found ≤ 15% in line with requirement of the Guideline on the Bioanalytical Method Validation.

The LLOQ of the bioanalytical method 1.000 ng/mL was below 1/20 of the C_{max} (arithmetic means for Dabigatran: test 94.339 ± 51.0301 ng/mL, reference 101.532 ± 48.5946 ng/mL) and was adequate to detect any relevant carry-over effect between the treatment periods.

Dilution integrity was evaluated by preparing quality control samples having concentration 1200.000 ng/mL. A sample was diluted to 1/10 of the original concentration and analyzed against calibration curve. The accuracy of the dilution integrity samples of Dabigatran at 1/10 dilutions was -2.99%, which is within the acceptance criteria of ± 15% of nominal concentration. Precision of the quality control samples of Dabigatran at 1/10 dilutions was 1.55%, which is within the acceptance criteria of ≤ 15%.

Reasons for reanalysis of dabigatran samples (N=11; 0.13 %) were provided and considered acceptable.

Incurred sample reanalysis was evaluated to demonstrate that the results obtained from study sample analysis had been reproducible. The number of ISR samples and method of their selection were acceptable.

The ISR was performed in a total of 484 samples, which is in accordance with section 6 "Incurred Samples reanalysis" of the Guideline on bioanalytical method validation i.e. 10% of the samples should be reanalysed in case the number of samples is less than 1000 samples and 5% of the number of samples exceeding 1000 samples. For the samples reanalysed, the ISR was acceptable as 99.59% of the samples (482 samples) reanalysed were within the acceptance range (± 20%).

Chromatograms of calibration standards, QCs, and subject samples from at least 20% of the subject samples are included in the submission, in accordance with the *Guideline on bioanalytical method validation*.

The analytical method is considered valid for the estimation of Dabigatran in human plasma within a range of 1.000 ng/mL to 300.000 ng/mL.

Taking into account the following:

- As it is known that back-conversion of unstable glucuronide metabolites may affect the accuracy and precision of the analyte in the study samples, the stability of pharmacologically active dabigatran acylglucuronides was reviewed and based on the overall retrospective review of study data the possible back conversion during the analytical method was ruled out;
- The developed analytical method is selective and able to detect the analyte from the

metabolite, chromatogram of the dabigatran and dabigatran acylglucuronides were provided indicating that the retention time for of the dabigatran acylglucuronides is well separated than the retention time of dabigatran;

- The dabigatran acylglucuronides are stable under the same storage conditions of study samples,
- Successful results of ISR samples that have been analyzed during the study period, with more than 90% of the reanalysed samples fulfilling the acceptance criteria of ISR analysis confirming the reliability of the reported sample analyte concentrations;
- In addition, based on literature review the obtained concentration data for study were matching with the literature data in terms of C_{max} data;
- For the current application, the analytical method was considered adequate for the quantification of dabigatran in human plasma and validated according to the ICH M10 Guideline on Bioanalytical method validation and study sample analysis.

the Applicant's arguments regarding the quantitation in plasma only of free dabigatran and not of total dabigatran also are acceptable.

- **Pharmacokinetic variables**

Non-compartmental model of Phoenix WinNonlin Enterprise Version 8.0 was used for computation of the following pharmacokinetic variables: C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $t_{1/2}$, T_{lag}, K_{el} and $AUC_{\_\%Extrap\_obs}$.

The primary pharmacokinetic parameters are: C_{max} and AUC_{0-t}. Secondary parameters are $AUC_{0-\infty}$, T_{max}, $t_{1/2}$, T_{lag}, K_{el} and $AUC_{\_\%Extrap\_obs}$.

Pharmacokinetic parameters have been calculated from individual plasma concentrations of 93 subjects who completed at least two periods (with one test and one reference treatment or all treatment periods) of the study as per approved protocol. In accordance with the protocol, 3 subjects have been excluded from the Pharmacokinetic and Statistical analyses.

86 subjects completed all the periods or both reference periods and have been included in the analysis of reference scaled average bioequivalence, according to the approved protocol.

The pharmacokinetic parameters are adequate for a bioequivalence trial with an immediate-release formulation.

- **Statistical methods**

The statistical analysis of the ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were planned to be performed for Dabigatran using SAS package.

The ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were analysed by analysis of variance (ANOVA) using PROC GLM in SAS Software Version 9.4.

As the subjects were enrolled and dosed divided in two groups 1-2-weeks apart, the Applicant performed the statistical analysis with the ANOVA model including also the factors groups. The model included the fixed effects of Sequence, Treatment, group, group*sequence, period (group), subject within sequence*group as a fixed effect. However, the Group*Formulation interaction was not included in the model. Thus, the applicant provided an exploratory analysis to assess if the group-by formulation is significant was conducted by the Applicant. For study 2020-DABI0291-PK-03 (code: 21-VIN-0033), the observed p-values for this Group*Formulation interaction effect were found to be not statistically significant for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The analyses have been conducted on the subjects

included in the pharmacokinetic analyses (who completed all the periods, one test period and one reference period), i.e., 91 subjects.

As the Group*Formulation interaction was not found statistically significant, the groups' data can be combined.

Each analysis of variance included calculation of least-square means, the difference between the adjusted formulation means and the standard error associated with the difference.

Ratio of Geometric least square means for Dabigatran of test and reference formulations has been computed and reported for Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

Ratio (%) of Test and Reference formulations for each individual subject has been provided for untransformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Dabigatran.

Criteria for conclusion of bioequivalence

Standard bioequivalence criteria have been proposed for the primary pharmacokinetic endpoints C_{max} and AUC_{0-t}, i.e., the 90% confidence intervals for geometric least square mean ratios of ln-transformed C_{max} and AUC_{0-t} of dabigatran fall within 80.00-125%, which is adequate.

Considering the intra-subject co-efficient of variation for the reference formulation the bioequivalence criteria for C_{max} could have been widened to 69.84% - 143.19%.

The current guidance allows to widen the bioequivalence criteria for the C_{max} if the intra-subject variability of the reference product is over 30% based on the replicate design. This has been shown for both studies.

However, no outlier test has been conducted in order to discard the influence of outliers in the observed intra-subject variability of C_{max}. This is considered acceptable, as the bioequivalence has been concluded based on the average bioequivalence analysis in the end.

Results

Table 3. Pharmacokinetic parameters for Dabigatran (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD (CV%)	Arithmetic mean	SD (CV%)
$AUC_{(0-t)}$ (hr*ng/mL)	852.136	441.1915 (51.77%)	928.598	427.4526 (46.03%)
$AUC_{(0-\infty)}$ (hr*ng/mL)	877.517	446.4361 (50.87%)	955.986	434.7251 (45.47%)
C_{max} (ng/mL)	94.339	51.0301 (54.09%)	101.532	48.5946 (47.86%)
T_{max}* (hr)	2.250 (1.25-4.50)		2.250, (1.25-5.00)	
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (*median, range)			

Table 4. Statistical analysis for Dabigatran (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	87.19%	80.14%-94.86%	44.96%
C_{max}	88.08%	80.23%-96.71%	54.95%
* estimated from the Residual Mean Squares			

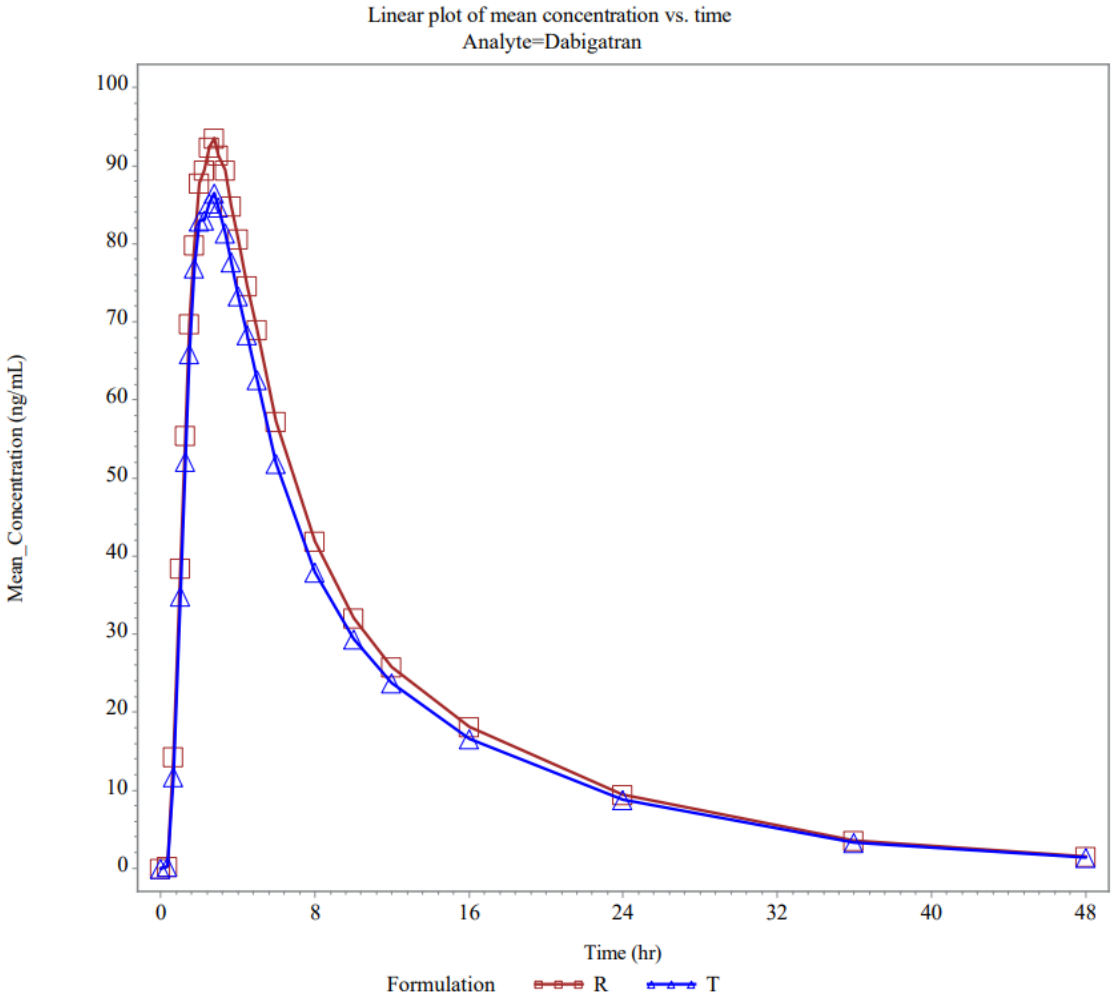

Figure 4. Linear plot of mean concentration vs time – dabigatran (reference and test formulations)

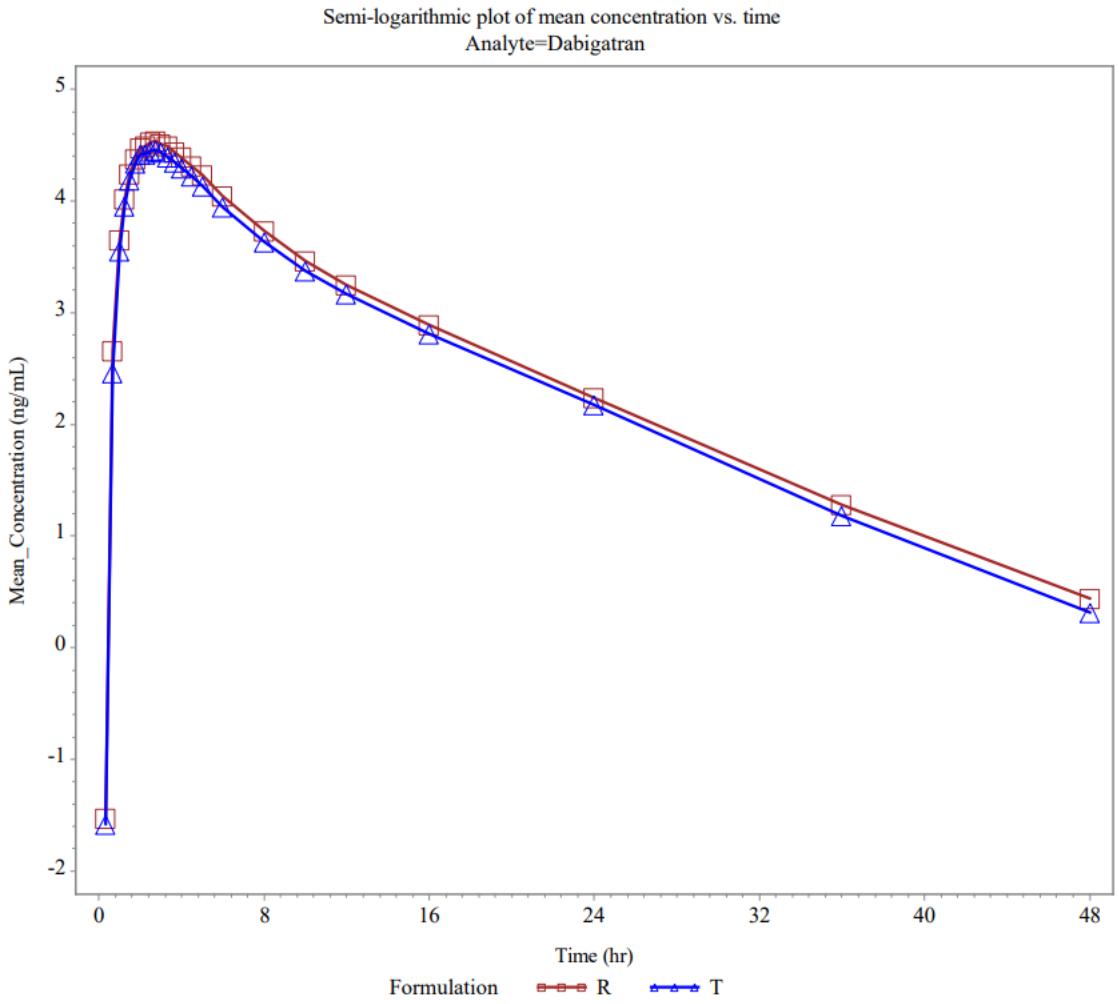

Figure 5. Semi-logarithmic plot mean concentration vs time – dabigatran (reference and test formulations

The pharmacokinetic parameter data including the confidence intervals and point estimates presented by the Applicant are in line with the acceptance criteria of the *Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1 – revised 2010).*

For dabigatran (i.e. free dabigatran), individual linear and log-linear plots, as well as linear and semi-logarithmic plots mean concentration versus time were provided by the applicant.

C_{max} was not observed in any subject at the first sample time point and pre-dose concentration has not been detected in any subject. The extrapolated AUC was not higher than 20%, except for one subject, i.e. Subject 27 after Dabigatran Reference administration in period 3 and Subject 5 after Dabigatran Test administration in period 3. Thus, the blood sampling schedule up to 48 h was defined adequately.

The study has been conducted in two groups and the statistical model included the assessment of the group effect, using the fixed effects of Sequence, Treatment, Period, group, group*sequence, period (group), subject sequence*group and Subject (Sequence). The Sequence effect has been tested using the Subject (Sequence) effect as the error term and the group effect has been tested using the subject (sequence*group) effect as the error term. The p-value of group effect was found non-significant at 5% ($p>0.05$) level of significance for all the PK parameters tested LnC_{max}, $LnAUC_{0-t}$ and $LnAUC_{0-inf}$. The group term was dropped from the model and further 90% confidence interval was calculated using separate model with the group effect excluded from the model.

Therefore, the results presented are based on the average bioequivalence analysis including 91 subjects in the final statistical analysis who completed at least two periods of the study with at least one test and one reference product or all the periods with the standard bioequivalence criteria proposed for the primary pharmacokinetic endpoints C_{max} and AUC_{0-t}, i.e. the 90% confidence intervals for geometric least square mean ratios of ln-transformed C_{max} and AUC_{0-t} of dabigatran should fall within 80.00-125%.

According to the protocol 20-VIN-0033, the Applicant presented the results for the relevant analysis based on the ANOVA model with the group effect included in the model, in line with the protocol, that also demonstrated the bioequivalence. For all PK parameters, C_{max}, AUC_{0-t} and AUC_{0-inf}, the 90% CI were contained in the standard bioequivalence range 80-125%. Significant p value was observed for Period (Group) and Formulation.

The group by treatment interaction has been also reported using the ANOVA model with the group effect included based on all 344 observations including also those subjects (2 subjects) that only have data for the reference.

It was noted that in the analysis of the group effect the number of observations is 344 for C_{max}, AUC_t and AUC_{inf}. In the analysis of the intra-subject CV (what is named incorrectly as reference scaled average bioequivalence) the number of observations is 166 for C_{max}, AUC_t and AUC_{inf} in a first analysis (which is the number of observations for the reference), 154 in a second one (which is the number of observations for the test), and 320 in a third one (which is the sum of both, but the total number of observations previously was 344). The Applicant clarified that only the analysis for evaluation of intra-subject CV of reference formulation was required, according to the "*Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1)*" and the protocol.

It was also noted that the 90% CI reported for $LnAUC_{0-t}$ and Ln AUC_{0-inf} in the analysis for the so-called reference scaled average bioequivalence fails to show bioequivalence being 78.23 – 93.18% and 78.92 – 93.22% respectively. However, this analysis cannot be used for the demonstration of the bioequivalence therefore is not considered relevant.

In the analysis of conventional bioequivalence, the number of observations is 172 in a first analysis (which are the observations for the reference), 168 in a second one (which are the observations for the test) and 340 in a third one for the sum of both, but the total number of observations should be 344.

A statistically significant effect for formulation effect for ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$was found by the Applicant, but it can be argued that this can be ignored as the decision of equivalence is based on the Schuirmann test and the 90% confidence interval is within the equivalence boundaries.

- **Safety data**

Safety parameters have been assessed in all subjects who were dosed in the study with either test or reference product.

A total of thirty-three (33) adverse events have been reported by twenty-four (24) subjects (24/96; 25.00%) during the BE study.

Eleven (11) (11/33 – 33.33%) adverse events were reported by ten subjects (10/93, 10.75%) after administration of test product (T). Twelve (12) (12/33 – 36.36%) adverse events were reported by twelve (12) subjects (12/95, 12.63%) after administration of reference product (R). Ten (10) (10/33 – 30.30%) adverse events were reported by nine subjects (09/96, 9.38 %) after administration of Concomitant Medication.

Out of 33 adverse events, twenty four (24/33- 72.73%) adverse events were possible in nature, out of twenty four adverse events, fifteen (15/33- 45.45%) adverse events were possibly related to investigational product and nine (09/33- 27.27%) adverse events were possibly related to concomitant medication, five (05/33- 15.15%) adverse events were not related to investigational product, one (01/33- 3.03%) adverse event was Probable/likely related to investigational product, three (03/33-

9.09%) adverse events were unlikely in nature, out of three adverse events, two (02/33-6.06 %) adverse events were unlikely to investigational product and one (01/33-3.03%) adverse event was unlikely to concomitant medication.

Out of thirty-three adverse events, fifteen (15/33 – 45.45%) adverse events were mild in nature and eighteen (18/33 – 54.55%) adverse event was moderate in nature.

All adverse events were resolved. No serious adverse events (SAE) and no deaths were reported for any of the subjects enrolled in this study. The adverse advents have been adequately analysed including incidence by treatment, relation with investigational medicinal product, intensity and time of onset and resolution.

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.3. Discussion on clinical aspects

To support the application, the company has submitted two bioequivalence studies (2020-DABI0291-PK-04 and 2020-DABI0291-PK-03), in line with the Dabigatran etexilate hard capsule 75 mg, 110 mg and 150 mg product-specific bioequivalence guidance EMA/CHMP/805498/2016, and literature data on clinical pharmacology, efficacy and safety, which is considered appropriate and relevant for a generic application.

The bioequivalence studies were as follows:

- an Open Label, Balanced, Randomized, Single-Dose, Two-Treatment, Two-Sequence, Four-Period, Full Replicate crossover Oral Bioequivalence Study of Dabigatran etexilate 150 mg Hard Capsule of Laboratorios Liconsa S.A., Spain and PRADAXA® (Dabigatran etexilate 150 mg hard capsules) 150 mg Hard Capsule of Boehringer Ingelheim International GmbH, Binger Str. 173 D-55216 Ingelheim am Rhein, Germany in Healthy, Adult, Human Subjects Under Fasting Conditions.

- an Open Label, Balanced, Randomized, Single-Dose, Two-Treatment, Two-Sequence, Four-Period, Full Replicate crossover Bioequivalence Study of Dabigatran etexilate 150 mg Hard Capsule of Laboratorios Liconsa S.A., Spain and PRADAXA (Dabigatran etexilate 150 mg hard capsules) 150 mg Hard Capsule of Boehringer Ingelheim International GmbH, Binger Str. 173 D-55216 Ingelheim am Rhein, Germany with multiple day Pre-treatment with a Proton Pump Inhibitor in Healthy, Adult, Human Subjects Under Fasting Conditions.

The Applicant has stated that the study has been conducted in compliance with GCP and GLP requirements. Apart of the investigators listed in the CSR, details of other persons involved in the assessment of protocol deviations have been provided. The outcome of the GCP inspections listed and monitoring reports for the BE studies 2020-DABI0291-PK-04 and 2020-DABI0291-PK-03 have been submitted.

The test product is an immediate release formulation, therefore single-dose studies are considered appropriate. In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 01 – January 2010) and with the Dabigatran etexilate hard capsules 75 mg, 110 mg and 150 mg product-specific bioequivalence guidance (EMA/CHMP/805498/2016), the studies have been conducted with the highest strength, which is adequate for drugs with linear pharmacokinetic and low solubility. According to the SmPC of the reference product, dabigatran capsules can be taken with or without food. Thus, the BE studies under fasting condition are adequate

as it is considered the most sensitive condition to detect potential differences between formulations. The replicate study design is acceptable as, taking into account the high intra-subject variability, it provides the possibility to widen the confidence interval for C_{max}. Moreover, the request for widened interval was specified in the clinical trials protocols.

In addition to the single dose study under fasting conditions, the Applicant performed a supplemental single dose study under fasting conditions in subjects pre-treated with pantoprazole a proton pump inhibitor, which is in accordance with Dabigatran etexilate hard capsules 75 mg, 110 mg and 150 mg product-specific bioequivalence guidance (EMA/CHMP/805498/2016).

In conclusion, the designs of the studies are in line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 01 – January 2010) and with the Dabigatran etexilate hard capsules 75 mg, 110 mg and 150 mg product-specific bioequivalence guidance (EMA/CHMP/805498/2016), and therefore are considered appropriate.

The sampling period was sufficient, and the sampling schedule and wash-out period were adequate taking into account the t_{max} and mean terminal $t_{1/2}$. Since AUC_{0-t} covers at least 80% of $AUC_{0-\infty,}$ the sampling schedule covers the plasma concentration time curve long enough, except for one subject in study 2020-DABI0291-PK-04, i.e., Subject 61 after Dabigatran Test administration in period 2 and two subjects in study 2020-DABI0291-PK-03, i.e., Subject 27 after Dabigatran Reference administration in period 3 and Subject 5 after Dabigatran Test administration in period 3.

Certificate of analysis of the Test and Reference products have been provided. The population was chosen according to the guidelines.

Bioanalytical method had satisfactory performance and was adequately validated for quantification of free dabigatran in plasma. As the EMA product specific guidance for dabigatran etexilate does not make a specific recommendation about analysing free (non-conjugated dabigatran) or total dabigatran (non-conjugated and conjugated dabigatran) for a bioequivalence study, the quantitation in plasma only of free dabigatran and not of total dabigatran also is considered acceptable.

The pharmacokinetic methods applied were appropriate for a single-dose study.

Three statistical analyses have been conducted for both studies: one for the assessment of the bioequivalence including the group effect in the ANOVA model, another to estimate the intra-subject CV (what is named incorrectly as reference scaled average bioequivalence) and another final analysis with the conventional ANOVA model. The results presented for both studies are based on the average bioequivalence analysis with the standard bioequivalence criteria proposed for the primary pharmacokinetic endpoints C_{max} and AUC_{0-t}, i.e. the 90% confidence intervals for geometric least square mean ratios of ln-transformed C_{max} and AUC_{0-t} of dabigatran should fall within 80.00-125%, although the bioequivalence criteria could been widened for C_{max} as the intra-subject variability of the Reference product for C_{max} was found to be greater than 30%. However, although according to the guidance the bioequivalence criteria could have been widened for C_{max}, the 90% confidence interval, which was 90.37%-104.22% for study 20-VIN-0032, and, respectively, 80.23%-96.71% for study 20-VIN-0033, fell within the conventional acceptance criterion of 80.00-125.00%.

In the protocol of study 20-VIN-0032, the ANOVA model to employ depended on the statistical significance of the group effect. However, according to the protocol of study 20-VIN-0033, the ANOVA model to employ should not depend on the p value of the group effect and the results obtained with the group effect included in the model should be considered for the regulatory decision. For this reason, the Applicant presented the results for the relevant analysis based on the ANOVA model with the group effect included in the model, in line with the protocol, that also demonstrated the bioequivalence. For all PK parameters, C_{max}, AUC_{0-t} and AUC_{0-inf}, the 90% CI were contained in the

standard bioequivalence range 80-125%. Significant p value was observed for Period(Group) and Formulation with no impact on the overall equivalence assessment.

For both studies, in the analysis of the intra-subject CV for reference scaled average bioequivalence three analyses have been conducted including observations only for the test, only for the reference and the sum of both. The Applicant clarified that only the analysis for evaluation of intra-subject CV of reference formulation was needed to be presented, according to the "Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1)" and the protocol.

For study 20-VIN-0033, it was also noted in the analysis for the so-called reference scaled average bioequivalence that the 90% CI reported for $LnAUC_{0-t}$ and Ln AUC_{0-inf} fails to show bioequivalence being 78.23 – 93.18% and 78.92 – 93.22% respectively; however, this analysis was not used for the demonstration of the bioequivalence. For study 20-VIN-0032 in the analysis for the so-called reference scaled average bioequivalence the 90% CI was reported only for C_{max}.

An exploratory analysis to assess if the group-by formulation is significant was conducted by the Applicant. For both studies, the observed p-values for this Group*Formulation interaction effect were found to be not statistically significant for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. As the Group*Formulation interaction was not found statistically significant, the groups' data can be combined.

Both formulations were well tolerated in the BE studies.

The Applicant requested biowaiver for Dabigatran etexilate hard capsule 75 mg and Dabigatran etexilate hard capsule 110 mg. To support the request, a justification and results of comparative dissolution tests have been provided. The *in vitro* dissolution tests comparing the *in vitro* dissolution similarity between additional strengths and the test bio-batch over physiological pH range were conducted.

The applicant selected the modified basket (24.5 mm) for 150 mg capsules that has the same specification as that of standard basket, except for the inner and outer diameter in order to allow free movement of the capsules during the dissolution test. The Applicant provided information to adequately justify the use of the different baskets for all the strengths (standard basket apparatus for the 75 mg and 110 mg capsules and modified basket for 150 mg capsules). The comparative release profiles of 150 mg strength in modified and standard baskets on 12 samples have been conducted and the results indicated that use of the modified basket does not alter the dissolution profile and has a lower variability.

Therefore, the use of different baskets for the similarity of dissolution profiles between the additional strengths and the test biobatch can be considered acceptable.

Because the RSD deviation of the products is not less than 20% for the first point and not less than 10% from second to last time point and more than one mean value of >85% was dissolved for any of the formulation, the requirements of the *Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1 – January. 2010)* regarding the calculation of the f2 similarity factor have not been fulfilled. Thus, the Applicant used the bootstrap analysis as alternative method to the f2 statistics.

The Applicant provided the complete output data of the Bootstrap f2 calculation with BootF2BCA software including all four different approaches for the 90% CI: normal approximation, basic bootstrap-t-CI, percentile CI and bias corrected and accelerated CI.

All the time-points for calculated f2 similarity factors have been included for f_2 estimation. An updated report has been also provided including the dissolution profiles of the batches manufactured in Laboratorios Licosa S.A (LC)* for each strenght vs the test biobatch 150 mg EB19028 manufactured at Chemo India Formulation in 3 different pH media (0.01N HCl (pH 2.0- release media), pH 4.5 and pH 6.8) without surfactant using the bootstrap methodology including the requested f2 with 90% CI by percentile method. The similarity of the dissolution profiles of the batched manufactured at Laboratorios Liconsa S.A versus the biobatch (150mg EB19028) manufactured at Chemo India

Formulation is considered demonstrated. Therefore the use of the additional manufacturing site Laboratorios Licosa S.A (LC) is considered acceptable

In summary, the results of the bioequivalence studies conducted with Dabigatran Etexilate 150 mg Hard Capsule of Chemo India Formulation can be extrapolated to the other strengths 75 mg and 110 mg, according to conditions in the BE Guideline.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence study(ies) Dabigatran Etexilate Leon Farma 150mg hard capsule is considered bioequivalent with PRADAXA (Dabigatran Etexilate 150 mg hard capsule).

The results of studies 20-VIN-0032 [2020-DABI0291-PK-04] and 20-VIN-0033 [2020-DABI0291-PK-03] with 150 mg formulation can be extrapolated to the other strengths, i.e., 75 mg and 110mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 5. 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)

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

Table 6. 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	Routine Pharmacovigilance activities beyond adverse reactions reporting and signal detection: Adverse event follow-up form for adverse reaction Additional Pharmacovigilance activities: None

	or urgent procedures for situations of life threatening or uncontrolled bleeding. Additional risk minimisation measures: Prescriber guide and patient alert card.	
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

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 2.0 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of dabigatran etexilate hard capsules. The reference product Pradaxa is indicated for:

Pradaxa 75 mg hard capsules:

- Primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.
- Treatment of VTE and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.

Pradaxa 110 mg hard capsules:

- Primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total 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 ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.
- Treatment of VTE and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.

Pradaxa 150 mg hard capsules:

- 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.
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.
- Treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, two bioequivalence studies form the pivotal basis with an open label, balanced, randomised, single-dose, two-treatment, two-sequence, four-period, fully replicate cross-over study design and an open label, balanced, randomised, single-dose, two-treatment, two-sequence, four-period, fully replicate cross-over with multiple day pre-treatment study design. The studies designs are considered adequate to evaluate the bioequivalence of this formulation and were in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic methods applied are adequate.

The results presented for both studies are based on the average bioequivalence analysis with the standard bioequivalence criteria proposed for the primary pharmacokinetic endpoints C_{max} and AUC_{0-t}, i.e., the 90% confidence intervals for geometric least square mean ratios of ln-transformed C_{max} and AUC_{0-t} of dabigatran should fall within 80.00-125%.

The test formulation of Dabigatran etexilate Leon Farma 150 mg hard capsules met the protocol-defined criteria for bioequivalence when compared with the reference formulation Pradaxa 150 mg

hard capsules. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t} were all contained within the protocol-defined acceptance range of [range, e.g., 80.00 to 125.00%]. The point estimates and their 90% confidence intervals for the parameter C_{max} were all contained within standard acceptance range of [range, e.g., 80.00 to 125.00%], although according to the *Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1*, widening of the bioequivalence criteria has been proposed for C_{max} as the intra-subject variability of the Reference product for C_{max} was found to be greater than 30%. Thus, *Dabigatran etexilate Leon Farma 150 mg hard capsules* and Pradaxa 150 mg hard capsules can be confirmed as bioequivalent.

Based on the results of the comparative dissolution profiles with the Bootstrap f2 calculation with the methodology corresponding to 90% CI estimation based on the percentile bootstrap, the similarity of the dissolution profiles between the three different strengths (i.e. 75, 110 and 150mg) has been demonstrated in order to support the requested biowaiver and the use of two manufacturing sites. In conclusion, the results of the bioequivalence studies conducted with Dabigatran etexilate Leon Farma 150 mg hard capsules can be extrapolated to the other strengths, i.e., Dabigatran etexilate Leon Farma hard capsules 75 mg and Dabigatran etexilate Leon Farma hard capsules 110 mg, as the requirements set out in the Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1 are met.

Having considered the data submitted in the application and available on the chosen reference medicinal product, no additional risk minimisation activities are required beyond those included in the product information.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Dabigatran Etexilate Leon Farma is favourable in the following indication:

> Dabigatran etexilate Leon Farma 75 mg hard capsule
>
> Primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.
>
> Treatment of VTE and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.
>
> For age appropriate dose forms, see section 4.2.
>
> Dabigatran etexilate Leon Farma 110 mg hard capsule
>
> Primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total 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 ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.

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

Treatment of VTE and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.

For age appropriate dose forms, see section 4.2.

Dabigatran etexilate Leon Farma 150 mg hard capsule

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.

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

Treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.

For age appropriate dose forms, see section 4.2.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall provide an educational pack for each therapeutic indication, targeting all physicians who are expected to prescribe/use Dabigatran Etexilate Leon Farma. This educational pack is aimed at

increasing awareness about the potential risk of bleeding during treatment with Dabigatran Etexilate Leon Farma and providing guidance on how to manage that risk.

The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority prior to distribution of the educational pack. The educational pack must be available for distribution for all therapeutic indications prior to launch) in the Member State.

The physician educational pack should contain:

- The Summary of Product Characteristics
- Prescriber Guides
- Patient Alert Cards

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
- Dosing tables for the different dose forms (only for paediatric VTE)
- Recommendation for kidney function measurement
- Recommendations for dose reduction in at risk populations (only for adult indications)
- Management of overdose situations
- The use of coagulation tests and their interpretation
- That all patients/carers 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 Leon Farma if they need to have any surgery or invasive procedure.
- An instruction how to take Dabigatran Etexilate Leon Farma

The MAH shall also provide a patient alert card, the text of which is included in Annex III of the EPAR and in the package with the leaflet.