LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Dabigatran Etexilate Viatris
(dabigatran etexilate mesilate)

SE/H/2315/01-03/DC

This module reflects the scientific discussion for the approval of Dabigatran Etexilate Viatris. The procedure was finalised on 2023-12-21. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Dabigatran Etexilate Viatris, 75 mg, 110 mg, 150 mg, capsule, hard.

The active substance is dabigatran etexilate mesilate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Dabigatran Etexilate Viatris, 75 mg, 110 mg, 150 mg, capsule, hard, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant, Vale Pharmaceuticals Ltd, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI and SK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Pradaxa, 75 mg, 110 mg or 150 mg, capsule, hard, authorised in EU since 2008, 2008 or 2011 (as an extension), respectively, with Boehringer Ingelheim International GmbH as marketing authorisation holder.

The reference product used in the bioequivalence studies is Pradaxa, 150 mg, capsule, hard, from DE with Boehringer Ingelheim International GmbH as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indications proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of dabigatran etexilate are well known. As dabigatran etexilate is a widely used, well-known active substance, no further studies are required, and the applicant provides none. An overview based on literature review is, thus, appropriate.

Ames test data for the impurity N-Nitroso-dabigatran shows that the impurity is non-mutagenic in either the absence or presence of rat or hamster S9 mix. As such, an impurity threshold calculation approach based on TTC (1.5ug/d limit) is acceptable (instead of the ADI approach).

Environmental Risk Assessment (ERA)
Since Dabigatran Etexilate Viatris is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Dabigatran Etexilate Viatris from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two single-dose bioequivalence studies comparing Dabigatran Etexilate Viatris (Dabigatran Etexilate) with the reference product Pradaxa.

Pharmacokinetic properties of the active substance
Absorption: After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran, which is the active form in plasma. The cleavage of the prodrug dabigatran etexilate by esterase-catalysed hydrolysis to the active principle dabigatran is the predominant metabolic reaction. The absolute bioavailability of dabigatran following oral administration was approximately 6.5%. After oral administration in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterised by a rapid increase in plasma concentrations with C_{max} attained within 0.5 and 2.0 hours post administration.

Food does not affect the bioavailability of dabigatran etexilate but delays the time to peak plasma concentrations by 2 hours. There are no restrictions with respect to food in the SmPC of the originator.

Linearity: Dabigatran C_{max} och AUC increased linearly within the dose range 10 to 400 mg.

Elimination: Plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of 11 hours in healthy elderly subjects. After multiple doses a terminal half-life of about 12-14 hours was observed. The half-life was independent of dose.

Study DABI-CAZ-1012 / SYNCD-003-22 (FASTING)
Methods
This was a single-dose, four-period, two-sequence, crossover replicate study conducted in 60 healthy volunteers, comparing Dabigatran Etexilate, 150 mg, hard capsules with Pradaxa, 150 mg, hard

capsules under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of free dabigatran (non-conjugated) and total dabigatran (non-conjugated plus conjugated dabigatran after complete alkaline cleavage of dabigatran glucuronides) were determined with LC-MS/MS methods. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 02-Jun-2022 and 26-Jun-2022.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 and 2 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for free dabigatran, test n=116, reference n=117.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1529.152 ± 488.1053**	**186.730 ± 61.6881**	**2.00 (1.00-3.50)**
Reference	**1477.497 ± 593.1032**	**176.885 ± 73.3111**	**2.00 (1.00-4.00)**
***Ratio (90% CI)**	**107.06 (99.02-115.76)**	**109.34 (100.79-118.63)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for total dabigatran, test n=116, reference n=117.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1550.886 ± 467.4608**	**188.678 ± 59.9868**	**2.00 (1.33-3.00)**
Reference	**1487.343 ± 563.1987**	**177.453 ± 69.3381**	**2.00 (1.00-3.00)**
***Ratio (90% CI)**	**107.23 (99.33-115.76)**	**109.49 (101.04-118.65)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study DABI-CAZ-1013 / SYNCD-002-22 (pre-treatment with a PPI)
Methods
This was a single-dose, four-period, two-sequence, crossover replicate study conducted in 60 healthy volunteers, comparing Dabigatran Etexilate, 150 mg, hard capsules with Pradaxa, 150 mg, hard capsules under fasting conditions after pre-treatment with a proton pump inhibitor (pantoprazole 40 mg b.i.d for 4 days). Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of free dabigatran (non-conjugated) and total dabigatran (non-conjugated plus conjugated dabigatran after complete alkaline cleavage of dabigatran glucuronides) were determined with LC-MS/MS methods. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 20-Jun-2022 and 18-Jul-2022.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 3 and 4 below.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for free dabigatran, n=118.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	958.717 ± 463.4791	106.970 ± 49.3591	2.50 (1.33-5.00)
Reference	876.912 ± 399.6587	100.194 ± 46.3939	2.50 (1.33-5.00)
*Ratio (90% CI)	108.01 (97.98-119.07)	105.75 (95.79-116.74)	-

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for total dabigatran, n=118.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	1014.245 ± 503.3508	115.386 ± 55.3501	2.00 (1.33-4.00)
Reference	924.876 ± 429.4628	107.507 ± 52.4292	2.00 (1.33-5.00)
*Ratio (90% CI)	108.40 (98.06-119.84)	106.76 (96.60-117.99)	-

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strengths of 75 mg and 110 mg.

Discussion and overall conclusion

The bioequivalence studies and the statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr).

According to the product-specific bioequivalence guidance for Dabigatran etexilate hard capsule 75 mg, 110 mg and 150 mg (EMA/CHMP/805498/2016), bioequivalence studies should be performed in the fasted state, with administration of the 150 mg strength (as the substance has linear pharmacokinetics and low solubility). As proton pump inhibitors (PPIs) may affect the bioavailability of dabigatran differently depending on the formulation, an additional study under conditions of multiple day pre-treatment with a PPI, such as pantoprazole (40 mg b.i.d. for 4 days), should be conducted in addition to the regular study under fasting conditions.

The submitted studies are adequate and comply with the requirements for bioequivalence demonstration as stated in the product-specific bioequivalence guidance.

The bioanalytical methods were adequately validated.

Dabigatran etexilate is a prodrug. After oral administration and absorption, it is rapidly and completely converted to dabigatran, which is the active form in plasma. According to the product-specific bioequivalence guidance, the determining analyte should be the metabolite (dabigatran). In this application, two analytes were measured in the studies, free and total dabigatran (sum of non-conjugated and conjugated dabigatran) and bioequivalence assessment is based on both analytes.

Bioequivalence has been demonstrated for the highest strength in the fasted state as well as following pre-treatment with PPI in line with the recommendations in the product-specific bioequivalence guidance for dabigatran etexilate.

Absence of studies with the additional strengths of 75 mg and 110 mg is acceptable, as all conditions for biowaiver for additional strength(s), as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) are fulfilled and since the pharmacokinetics of dabigatran is linear between 75 mg and 150 mg.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Dabigatran Etexilate Viatris.

Part II Safety specification
The MAH has submitted the version 0.2 RMP dated 2023-05-17 and proposed the following summary of safety concerns:

Table 3: SVIII- 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)

The summary of safety concerns is in line with the latest approved summary of safety concern of the originator Pradaxa (RMP version number 41.1, date of final sign off: 14 September 2022). The important potential risk “Medication error due to complexity of reconstitution of and dosing with the oral solution (paediatric population below 1 year of age) is omitted which is acceptable since only capsules are applied for.

Part III Pharmacovigilance Plan
The pharmacovigilance plan is in line with the latest approved RMP of the originator Pradaxa (RMP version number 41.1, date of final sign off: 14 September 2022). Routine pharmacovigilance is suggested and in accordance with the originator the applicant has proposed follow-up questionnaires concerning haemorrhage, which is acknowledged. No additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested for all safety concerns except for haemorrhage where a prescriber guide for HCP and a patient alert card is suggested as aRMM. This is in line with the originator and is endorsed. For details about the conditioned aRMM, please refer to section VI.3 below.

Part VI Summary of the RMP
The summary of the RMP is endorsed.

Conclusion of RMP assessment
The submitted Risk Management Plan, version 0.2 signed 2023-05-17 is considered acceptable.

The 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 RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Pradaxa 75 mg hard capsules, EMEA/H/C/000829/X/0122/G regarding content and Duloxetine Mylan 30 mg hard gastro-resistant capsules, EMEA/ H/ C/003981 regarding layout.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Dabigatran Etexilate Viatris, is found adequate. There are no objections to approval of Dabigatran Etexilate Viatris, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**
  The educational material should contain a prescriber guide for HCP and a patient alert card for the patient as followed:

  The MAH shall provide an educational pack for each therapeutic indication, targeting all physicians who are expected to prescribe/use dabigatran. This educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with dabigatran 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 dosage forms (only for paediatric VTE)
• Recommendation for kidney function measurement
• Recommendations for dose reduction in at risk populations
• Management of overdose situations
• The use of coagulation tests and their interpretation
• That all patients/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 Viatris if they need to have any surgery or invasive procedure.
  • An instruction how to take Dabigatran Etexilate Viatris

The MAH shall also provide a patient alert card in each pack of the medicinal product, the text of which is included in Annex III.

The key safety messages is in line with Annex IID for Pradaxa and is acceptable.

VII. APPROVAL

The decentralised procedure for Dabigatran Etexilate Viatris, 75 mg, 110 mg, 150 mg, capsule, hard was positively finalised on 2023-12-21.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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