LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Dabigatran etexilate Liconsa
(dabigatran etexilate mesilate)

SE/H/2215/01-03/DC

This module reflects the scientific discussion for the approval of Dabigatran etexilate Liconsa. The procedure was finalised on 2024-06-26. 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 Liconsa, 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 Liconsa, 75 mg, 110 mg and 150 mg, capsule, hard, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC.

The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and the following countries as concerned member states (CMS): BE, ES, FI, LU, PT.

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

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

Potential similarity with orphan medicinal products
Not applicable

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 mesilate are well known. As dabigatran etexilate mesilate is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since the product applied for in this application 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 from a non-clinical point of view concerning Dabigatran etexilate Liconsa.

IV. CLINICAL ASPECTS

Pharmacokinetics
Bioequivalence
To support the marketing authorisation application, the applicant has conducted two bioequivalence studies comparing the test product Dabigatran etexilate, 150 mg, hard capsules with the reference product Pradaxa 150 mg, hard capsules. Both studies were single-dose studies under fasting conditions, but one included a multiple day pre-treatment with the proton pump inhibitor (PPI) pantoprazole.

Pharmacokinetic properties of the active substance
After oral administration, dabigatran etexilate is rapidly and completely converted into dabigatran, which is the active form in plasma. Dabigatran C_{max} och AUC increase linearly within the dose range 10 to 400 mg. Food does not affect the bioavailability of dabigatran etexilate but delays the time to peak plasma concentrations by 2 hours. Plasma concentrations of dabigatran show a biexponential decline with a mean terminal half-life of 11 hours. The half-life is independent of dose.

Study 2020-DABI0291-PK-04 (*without* PPI pre-treatment)
The study was an open label, randomised, single-dose, two-treatment, two-sequence, four-period, fully replicate crossover study under fasting conditions, conducted in 140 healthy volunteers, comparing Dabigatran etexilate, 150 mg, hard capsules, manufactured by Chemo India Formulations Pvt., Ltd., Hyderabad, India with Pradaxa, 150 mg, hard capsules, by Boehringer Ingelheim International GmbH, from the German market. The study was conducted between 15 March 2021 and 19 June 2021.

Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of dabigatran were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for dabigatran, n=253 (test product), n= 252 (reference product).

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	1352.2 ± 628.5	155.3 ± 72.9	2.250 (1.00 – 5.00)
Reference	1359.0 ± 599.6	155.8 ± 67.8	2.250 (1.00 - 4.50)
***Ratio % (90% CI)**	97.34 (91.09 - 104.02)	97.05 (90.37 - 104.22)	–
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 2020-DABI0291-PK-03 (*with* PPI pre-treatment)
The study was an open label, randomised, single-dose, two-treatment, two-sequence, four-period, fully replicate crossover study under fasting conditions, conducted in 96 healthy volunteers, comparing Dabigatran etexilate, 150 mg, hard capsules, manufactured by Chemo India Formulations Pvt., Ltd., Hyderabad, India with Pradaxa, 150 mg, hard capsules, by Boehringer Ingelheim International GmbH, from the German market. Pantozol 40 mg tablets, by Takeda GmbH, were administered in day 4, 3, 2 and 1 prior to the scheduled day of investigational product dosing (day 0), as well as along with the investigational product on day 0. The study was conducted between 20 July 2020 and 06 November 2020.

Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of dabigatran were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for dabigatran, n=168 (test product), n= 176 (reference product).

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	852.1 ± 441.2	94.3 ± 51.0	2.250 (1.25 - 4.50)
Reference	928.6 ± 427.5	101.5 ± 48.6	2.250 (1.25 - 5.00)
***Ratio % (90% CI)**	87.19 (80.14 - 94.86)	88.08 (80.23-96.71)	–
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%.

Biowaiver for the 75 mg and 110 mg strengths
A biowaiver was sought for the additional strengths of 75 mg and 110 mg, with reference to compliance with the conditions for biowaiver of additional strengths according to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr).

Discussion and overall conclusion

The bioequivalence studies were in accordance with the requirements of the product-specific bioequivalence guidance for Dabigatran etexilate hard capsule (EMA/CHMP/805498/2016), which says that bioequivalence studies should be performed in the fasted state, both with and without PPI pre-treatment (as the solubility of dabigatran etexilate is pH dependent, so PPIs might affect the bioavailability differently depending on the formulation).

Also, the bioequivalence studies and their 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). The bioanalytical methods were adequately validated.

Hence, based on the submitted bioequivalence studies, Dabigatran etexilate 150 mg hard capsule is considered bioequivalent with Pradaxa 150 mg hard capsule.

Absence of studies with the additional strengths of 75 mg and 110 mg is considered 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 as plasma AUC of dabigatran increases in a dose-proportional manner. Also, the biowaiver of the lower strengths is in accordance with the product-specific bioequivalence guidance for Dabigatran etexilate hard capsule (EMA/CHMP/805498/2016).

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 Liconsa.

Safety specification

The MAH has submitted the same RMP for all procedures included in this report. The MAH has submitted version 5.0 RMP dated 2023-05-07 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	• Haemorrhage
Important potential risks	• None
Missing information	• Paediatric patients with renal dysfunction (eGFR<50ml/min)

Pharmacovigilance Plan

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.

Risk minimisation measures

Routine risk minimisation is suggested for all safety concerns except for haemorrhage where they suggest a prescriber guide for HCP and a patient alert card as aRMM. For details about the conditioned aRMM, please refer to section VI below.

The Summary of the RMP is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 5.0 signed 2024-05-07 for all procedures are **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

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.

The results 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Dabigatran etexilate Liconsa, is found adequate. There are no objections to approval of Dabigatran etexilate Liconsa 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 ratio is considered positive, and Dabigatran etexilate Liconsa, 75 mg, 110 mg, 150 mg, capsule, hard 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

Not applicable

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:

- Physician educational material:
  - The Summary of Product Characteristics
  - Guide for healthcare professionals (prescriber guide)

- The Prescriber Guide should contain the following key safety messages:
  - Details of populations potentially at higher risk of bleeding.
  - Information on medicinal products that are contraindicated, or which should be used with

caution due to an increased risk of bleeding and/or increased dabigatran exposure.
- Contraindication for patients with prosthetic heart valves requiring anticoagulant treatment.
- Recommendation for kidney function measurement.
- Recommendations for dose reduction in at risk populations.
- Management of overdose situations.
- The use of coagulation tests and their interpretation.
- That all patients should be provided with a Patient alert card and be counselled about:
  - Signs or symptoms of bleeding and when to seek attention from a health care provider.
  - Importance of treatment compliance.
  - Necessity to carry the Patient alert card with them at all times.
  - The need to inform Health Care Professionals about all medicines the patient is currently taking.
  - The need to inform Health Care Professionals that they are taking Dabigatran etexilate if they need to have any surgery or invasive procedure.
  - An instruction how to take Dabigatran etexilate.

- <u>The patient information pack:</u>
  - Patient information leaflet
  - Patient alert card

- <u>The Patient Alert Card should contain the following key safety messages:</u>
  - Signs or symptoms of bleeding and when to seek attention from a healthcare provider
  - Importance of treatment compliance
  - Necessity to carry the patient alert card with them at all times
  - The need to inform Health Care Professionals about all medicines they are currently taking
  - The need to inform Health Care Professionals that they are taking Dabigatran if they need to have any surgery or invasive procedure.

VII. APPROVAL

The decentralised procedure for Dabigatran etexilate Liconsa, 75 mg, 110 mg, 150 mg, capsule, hard was positively finalised on 2024-06-26.

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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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