COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tuxanuva 75 mg, 110 mg and 150 mg, hard capsules (dabigatran etexilate mesilate)

NL/H/5270/001-003/DC

Date: 11 March 2025

This module reflects the scientific discussion for the approval of Tuxanuva 75 mg, 110 mg and 150 mg hard capsules. The procedure was finalised on 3 October 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
DVT	Deep Vein Thrombosis
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
NVAF	Non-valvular Atrial Fibrillation
PE	Pulmonary Embolism
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TIA	Transient Ischemic Attack
TSE	Transmissible Spongiform Encephalopathy
VTE	Venous Thromboembolic Events

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Tuxanuva 75 mg, 110 mg and 150 mg hard capsules, from Stada Arzneimittel AG.

The product is indicated for:

Tuxanuva 75 mg
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.

Tuxanuva 110 mg
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.

Tuxanuva 150 mg
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.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Pradaxa 75 mg, 110 mg and 150 mg hard capsules, which has been registered in the EEA via a centralised procedure (EU/1/08/442) since 18 March 2008.

The concerned member states (CMS) involved in this procedure were Croatia, Czechia and Poland.

II. QUALITY ASPECTS

II.1 Introduction

Tuxanuva 75 mg is a capsule with a white opaque cap imprinted “MD” and white opaque body imprinted “75” with black ink, containing a blend of white to light yellow coloured pellets and light yellow coloured granulate. The capsule is 17.50 ± 0.40 mm in size. It contains as active substance 75 mg of dabigatran etexilate mesilate.

Tuxanuva 110 mg is a capsule with a white opaque cap imprinted “MD” and white opaque body imprinted “110” with black ink, containing a blend of white to light yellow coloured pellets and light yellow coloured granulate. The capsule is 19.40 ± 0.40 mm in size. It contains as active substance 110 mg of dabigatran etexilate mesilate.

Tuxanuva 150 mg is a capsule with a white opaque cap imprinted “MD” and white opaque body imprinted “150” with black ink, containing a blend of white to light yellow coloured pellets and light yellow coloured granulate. The capsule is 21.50 ± 0.40 mm in size. It contains as active substance 150 mg of dabigatran etexilate mesilate.

The excipients are:
Capsule content - tartaric acid (E334), hypromellose, talc, hydroxypropylcellulose (E463), croscarmellose sodium, magnesium stearate (E470b).
Capsule shell - titanium dioxide (E171), hypromellose.
Black printing ink - shellac (E904), propylene glycol (E1520), black iron oxide (E172), potassium hydroxide (E525).

The capsules are packed in oriented polyamide/aluminium/desiccant (OPA/Alu/desiccant) polyethylene-aluminium/polyethylene (PE-Alu/PE) blisters or 120 ml and 150 ml high-density polyethylene (HDPE) bottles with a child-resistant closure and a silica gel desiccant.

II.2 Drug Substance

The active substance is dabigatran etexilate mesylate (INN), an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is achiral and is soluble in pH 1.2. aqueous media, but insoluble in aqueous media above pH 3. Forced degradation have shown the substance to be sensitive towards acid and base hydrolyses, but

stable under photolytic degradation conditions. For this product, a single polymorphic form is consistently produced.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process is described in five stages of branched synthesis, comprising nine steps (eight synthetic and a final purification/salification step). There are four starting materials and four isolated intermediates. The process is made with standard chemical transformation steps, amide formation steps, nitro to amine reduction, intra-molecular cyclisation, and hydrolyses/carbamate formation. Final purification step convert base drug substance to the corresponding mesilate salt. Micronisation is possible, depending on customer´s requirements, but sufficient description is provided. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and ICH. Batch analytical data demonstrating compliance with this specification have been provided for three normal and one micronised batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 48 months (both micronised and non-micronised) when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. For the development of the dissolution study, a slightly larger basket apparatus has been selected for the Dabigatran etexilate capsules 150 mg as these are size "0" and because sporadic dissolution results were blamed on slow disintegration, due to the capsules not being able to move freely in the standard pharmacopoeial basket apparatus. The provided justification is deemed acceptable for the selection of the basket for the QC method. The discriminatory nature of the QC dissolution methods has been demonstrated.

Bioequivalence studies were carried out with the 150 mg and 75 mg strengths. Dissolution profiles in support of the results obtained in the bioequivalence study do not support the results obtained in the bioequivalence study, as no similarity is shown. In accordance with the Guideline on the Investigation of Bioequivalence, the Applicant has provided an acceptable discussion on the reasons for the discrepancy between the results obtained in the *in vitro* dissolution study, and the *in vivo* bioequivalence study.

A bracketing approach was used for the biowaiver of strengths for the 110 mg strength. Comparative dissolution data were obtained under the same conditions for all strengths in pH 2.0, 4.5 and 6.8 media. The modified basket was used due to the size of the 150 mg strength (see above) and pH 2.0 was used due to the instability of the drug substance at pH 1.2. Similarity of the dissolution profiles of the 150 mg (biobatch) and 110 mg strength was shown by bootstrapping in all three media. Similarity of the dissolution profiles of the 75 mg (biobatch) and 110 mg strength was shown by bootstrapping at pH 4.5 and pH 6.8. At pH 2.0, similarity could not be shown by bootstrapping and the dissolution profiles were compared visually. The dissolution profile of the 110 mg strength fell between the profiles of the 75 mg and 150 mg strengths, especially in the early timepoints. Using the bracketing approach, the biowaiver of strengths can be granted for the 110 mg strength.

As a paediatric indication has been included in the SmPC, the suitability of the formulation for children was addressed. The capsules are intended for children aged eight years and older who are able to swallow the capsules whole. The capsule sizes of the proposed product are the same as those of the reference product and no concerns with the safety of the excipients have been identified.

Manufacturing process

The manufacturing process includes the following steps: preparation of seal coated tartaric acid pellets blend, preparation of dabigatran blend, and capsule filling. Process validation data on the product have been presented for three batches per strength in accordance with the relevant European guidelines. The data demonstrates that the proposed manufacturing process is able to consistently produce batches which are in compliance with the proposed in-process control and finished product specifications.

Control of excipients

The excipients in the capsule fill all comply with Ph. Eur., supplied by additional controls for microbial quality and particle size distribution where needed. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification (active substance and colourants), average blend fill mass, average mass of filled capsules, uniformity of dosage units, water determination, disintegration time, dissolution, assay, related substances, microbial enumeration test and tests for specified microorganism. The release and shelf life limits are identical. The residual solvents used in the manufacturing process, are controlled as per ICH as in-process control. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. A risk evaluation on the presence of

nitrosamines in the drug product was carried out and tests for an impurity have been included in the drug substance and drug product specification. Based on the results of confirmatory testing, controls for nitrosamines originating from secondary amines in the API synthesis are not necessary.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches of each capsule strength from the proposed production site has been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three commercial scale batches stored at 25°C/ 60% RH (36 months), at 30°C / 65% RH (12 months) (150 mg only) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability study demonstrated that the finished product is not sensitive to light. On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions are "Store below 30°C" (blister) and "Store below 30°C. Store in the original package in order to protect from moisture" (bottle).

In-use stability data have been provided demonstrating that the product remains stable for 60 days following first opening of the container, when stored below 30 °C and in the original package in order to protect from moisture.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Tuxanuva has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Tuxanuva is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Pradaxa which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Dabigatran etexilate mesilate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Dabigatran etexilate capsules 75 mg, 150 mg without pre-treatment of pantoprazole and 150 mg with pre-treatment of pantoprazole (MSN Laboratories Private Limited, India) were compared with the pharmacokinetic profile of the reference product Pradaxa® 75 mg and 150 mg hard capsules (Boehringer Ingelheim International GmbH, Germany). The inclusion of a BE study with pre-treatment with pantoprazole is in accordance with the product specific guidance of the EMA for dabigatran etexilate.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

The free dabigatran measurement, which measures the main active metabolite of the pro-drug dabigatran etexilate mesilate, will be leading for the outcome of the BE studies according to the bioequivalence guideline of the EMA.

Biowaiver

The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all

strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),

d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Bioequivalence studies

Study 1: 150 mg dabigatran without pre-treatment of pantoprazole under fasted conditions

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, fully replicate crossover, open label bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 20 - 43 years. Each subject received a single dose (150 mg) of one of the two dabigatran formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were four dosing periods, separated by a washout period of 10 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.33, 3.67, 4, 5, 6, 8, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable.

Dabigatran may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of dabigatran. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

40 subjects enrolled in the study. 2 subjects did not turn up for multiple period check-ins and were therefore excluded. 4 subjects did not check in for two or less periods. 36 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of free dabigatran, 150 mg under fasted conditions.

Treatment N = 36	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	1620.0 ± 666.7	1667.9 ± 690.4	169.6 ± 65.9	2.25 (1.00 – 3.33)
Reference	1568.8 ± 707.8	1616.5 ± 728.7	164.5 ± 71.7(	2.25 (1.25 – 3.33)
***Ratio (90% CI)**	1.09 (0.97 – 1.21)	1.08 (0.97 - 1.20)	1.08 (0.97 – 1.21)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 2: 150 mg dabigatran with pre-treatment with pantoprazole under fasted conditions

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, fully replicate crossover, open label bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 20 - 43 years. In each period, four days prior to drug administration, all subjects were given pre-treatment with pantoprazole (Pantoprazole 40 mg GR tablets) twice daily at 12 hours interval with 240 mL water. On drug administration, each subject received a single dose (150 mg) of one of the two dabigatran formulations, co-administered with one dose of Pantoprazole 40 mg GR tablet. The dabigatran tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were four dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.33, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 8, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

40 subjects enrolled in the study. 40 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of free dabigatran, 150 mg under fasted conditions.

Treatment N = 40	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	1162.4 ± 493.8	1192.5 ± 505.3	124.3 ± 54.1	2.33 (1.00 – 4.33)
Reference	1128.40 ± 499.55	1157.2 ± 507.1	118.8 ± 58.6	2.33 (1.00 – 4.33)
***Ratio (90% CI)**	1.05 (0.94 – 1.17)	1.05 (0.95 - 1.16)	1.08 (0.96 – 1.21)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 3: 75 mg dabigatran under fasted conditions

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, fully replicate crossover, open label bioequivalence study was carried out under fasted conditions in 44 healthy male subjects, aged 19 - 44 years. Each subject received a single dose (75 mg) of one of the two dabigatran formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were four dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.33, 3.67, 4, 5, 6, 8, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable.

Dabigatran may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of dabigatran. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used ibn this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

44 subjects enrolled in the study. Two subjects did not turn up to multiple check-in periods and were therefore excluded. 42 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of free dabigatran, 75 mg under fasted conditions.

Treatment N = 42	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	761.540 ± 314.374	786.609 ± 318.119	88.087 ± 35.469	2.00 (1.00 – 3.33)
Reference	791.665 ± 261.476	815.332 ± 263.720	90.830 ± 28.849	2.13 (1.25 – 4.00)
***Ratio (90% CI)**	0.92 (0.83 – 1.02)	0.92 (0.84 – 1.01)	0.94 (0.85 – 1.03)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies 1 - 3:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Dabigatran etexilate capsules, 75 mg and 150 mg, with and without pre-treatment of pantoprazole, is considered bioequivalent with Pradaxa, 75 mg and 150 mg, with and without pre-treatment of pantoprazole.

The results of Study 1 and 2 with 150 mg formulation can be extrapolated to the other strength 110 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 Tuxanuva.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Haemorrhage
Important potential risks	None
Missing information	• Patients aged 0 to 2 years who were born prematurely [1]

	• Paediatric patients with renal dysfunction (eGFR <50ml/min)[1]

[1] these safety concerns are only valid in countries where the paediatric indication is approved.

The member states agreed that routine pharmacovigilance activities are sufficient for the risks and areas of missing information.

It is considered that additional risk minimisation measures are necessary for the safe and effective use of the product. The educational material contains the following key elements:

- The SmPC
- 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 (only for adult indications)
    - Management of overdose situations
    - The use of coagulation tests and their interpretation
- All patients should receive 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 the medicinal product if they need to have any surgery or invasive procedure.
    - An instruction how to take the medicinal product.

The MAH shall provide an educational pack for each therapeutic indication, targeting all physicians who are expected to prescribe/use Tuxanuva. This educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Tuxanuva 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.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Pradaxa. No new clinical studies were conducted. The MAH demonstrated through two bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 language used for the purpose of user testing the PL was English.

The test consisted of: a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The results show that the PL 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

Tuxanuva 75 mg, 110 mg and 150 mg hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Pradaxa 75 mg, 110 mg and 150 mg hard capsules. Pradaxa is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Tuxanuva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 October 2023.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-