LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Avassan
(apixaban)

SE/H/2402/02/DC

This module reflects the scientific discussion for the approval of Avassan. The procedure was finalised on 2024-12-04. 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 Avassan, 5 mg, Film-coated tablet.

The active substance is apixaban. 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 Avassan, 5 mg, Film-coated tablet, 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 PL and RO as concerned member states (CMS). The application for Avassan with strength 2,5 mg was not found approvable since a major objection on strength biowaiver was not resolved. On day 199 of the procedure the 2.5 mg strength was withdrawn from the application.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Eliquis 2,5 mg, Film-coated tablet authorised in the Union since 2011, with Bristol-Myers Squibb/Pfizer EEIG as marketing authorisation holder.

The reference product used in the bioequivalence study is Eliquis 5 mg, Film-coated tablet from BG with Bristol-Myers Squibb/Pfizer EEIG as marketing authorisation holder.

Potential similarity with orphan medicinal products
N/A

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 apixaban are well known. As apixaban is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

The applicant has included information regarding impurities in the drug substance in the non-clinical overview. **This non-clinical issue is considered resolved.**

Environmental Risk Assessment (ERA)
Since Avassan 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 Avassan from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one single-dose bioequivalence study in the fasted state comparing Avassan, 5 mg, tablet, with the reference product Eliquis, 5 mg, film-coated tablet.

Pharmacokinetic properties of the active substance
Absorption: Apixaban has an oral bioavailability of 50 %. Following an oral dose of apixaban maximal plasma concentrations occur at approximately 3-4 hours.

The pharmacokinetics of apixaban is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.

Linearity: The pharmacokinetics of apixaban is linear within the dose range 2.5-10 mg.

Elimination: The terminal half-life is approximately 12 hours.

Study C21200– 5 MG, FASTING
Methods
This was a single-dose, two-way crossover study conducted in 42 healthy volunteers, comparing apixaban, 5 mg, tablet with Eliquis, 5 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of apixaban 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 study was conducted between 2021-11-11and 2021-12-30.

Results

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

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for apixaban, n=42.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1858.620 ± 367.2260**	**214.567 ± 44.1533**	**1.75 (0.50-4.50)**
Reference	**1717.657 ± 397.5767**	**188.583 ± 49.4771**	**3.50 (1.00-5.00)**
***Ratio (90% CI)**	**109.20 (104.06 - 114.60)**	**115.08 (107.98 -122.64)**	**-**

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%.

Discussion and overall conclusion

The bioequivalence study and its 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) and the EMA product-specific bioequivalence guidance (EMA/CHMP/291499/2018). The bioanalytical methods were adequately validated.

From a pharmacokinetic point of view, it is sufficient to establish bioequivalence with only one strength as the pharmacokinetics of apixaban is linear between 2.5 mg and 10 mg. For drugs with linear pharmacokinetics the bioequivalence study should in general be conducted at the highest strength. The highest strength has been studied which is in accordance with guideline recommendations.

Based on the submitted bioequivalence study, Avassan, 5 mg, tablet, is considered bioequivalent with Eliquis, 5 mg, film-coated tablet.

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 Avassan.

The submitted Risk Management Plan, version 0.3 signed 3rd December 2024 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.

Part II Safety specification

The summary of safety concerns is based on the reference medicinal product Eliquis[1].

Summary of safety concerns	
Important identified risks	• **Bleeding**
Important potential risks	• **Liver injury** • **Potential risk of bleeding or thrombosis due to overdose or underdose**
Missing information	• **Use in patients with severe renal impairment**

Part III Pharmacovigilance Plan

On-going and planned additional pharmacovigilance activities from RMP Part III.3:

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
Specific adverse reaction follow-up questionnaires for:
- Bleeding
- Spontaneous reports of liver injury events

The proposed routine pharmacovigilance activities are in line with the reference product and considered acceptable.

Part V Risk minimisation measures
Please see section VII.3.

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

Conclusion RMP assessment
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.

The submitted Risk Management Plan, version 0.3 signed 3rd December 2024 is considered acceptable.

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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.

Part V Risk minimisation measures

V.2. Additional Risk Minimisation Measures

Summary of Product Characteristics (SmPC) of Apixaban provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL) for patients.

This medicine has also special conditions and restrictions for its safe and effective use called **additional risk minimisation measures:**

- *Prescriber Guide* to minimize the risks of **bleeding and medication errors** and
- *Patient Alert Card (provided in each medicine pack)* to minimize the risks of **bleeding.**

V. USER CONSULTATION

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.
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

Selected 'parent' leaflets (Name of the product)	Indicate elements used as a basis for bridging, e.g. key safety messages, design/layout, device etc.	Route of authorization of parent package leaflet, Procedure number (CAP/NAP) /proof of approval.*
Eliquis 2.5 mg and 5 mg film-coated tablets	Content including key safety messages	E MEA/H/C/002148, EPAR
Esomeprazole 20 mg and 40 mg gastro-resistant capsules, hard	Design/layout	NL/H/4120/001-002/DC, Public Assessment Report

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, Avassan, is found adequate. There are no objections to approval of Avassan, 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)

Details of proposed additional risk minimisation activities
The MAH shall ensure that all physicians who are expected to prescribe apixaban are provided with the following educational material:
• Summary of Product Characteristics
• Prescriber Guide
• Patient Alert Cards

Key Elements of the Prescriber Guide:
• Details of populations potentially at higher risk of bleeding
• Recommended doses and guidance on the posology for different indications
• Recommendations for dose adjustment in at risk populations, including renal or hepatic impairment patients
• Guidance regarding switching from or to Apixaban treatment
• Guidance regarding surgery or invasive procedure, and temporary discontinuation
• Management of overdose situations and haemorrhage
• 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 that they are taking Apixaban if they need to have any surgery or invasive procedure.

Key Elements of the Patient Alert Card:
• 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 that they are taking Apixaban if they need to have any surgery or invasive procedure.

VII. APPROVAL

The decentralised procedure for Avassan, 5 mg, Film-coated tablet was positively finalised on 2024-12-04.

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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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