COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Apixaban 1A Pharma 2.5 mg and 5 mg, film-coated tablets
(apixaban)

NL/H/5037/001-002/DC

Date: 23 March 2023

This module reflects the scientific discussion for the approval of Apixaban 1A Pharma 2.5 mg and 5 mg, film-coated tablets. The procedure was finalised on 14 July 2021. 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
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
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Apixaban 1A Pharma 2.5 mg and 5 mg, film-coated tablets, from 1A Pharma GmbH.

The 2.5 mg and 5 mg strength products are indicated for:

- 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 ischaemic attack (TIA); age ≥75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

The 2.5 mg strength product is also indicated for:

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

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 Eliquis 2.5 mg and 5 mg film-coated tablets, marketed by Bristol-Myers Squibb/Pfizer EEIG, which has been authorized in the European Union via the centralised procedure since 18 May 2011 (EMEA/H/C/002148).

The concerned member state (CMS) involved in this procedure was Austria.

II. QUALITY ASPECTS

II.1 Introduction

Apixaban 1A Pharma 2.5 mg is a yellow, round, biconvex, film coated tablet, debossed “AX” on one side and “2.5” on the other side containing 2.5 mg apixaban.
Apixaban 1A Pharma 5 mg is a pink, oval, biconvex, film coated tablet, debossed with “AX” on one side and “5” on the other side, containing 5 mg apixaban.

The excipients for both strengths are:
Tablet core - lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulphate and magnesium stearate
Film coat – hypromellose, hydroxypropyl cellulose, macrogol 6000, titanium dioxide (E171), yellow iron oxide (E172) and (for 5 mg only) red iron oxide (E172).

The two tablet strength cores are dose proportional.

The tablets are packed in Aluminium-PVC/PVdC blisters or Aluminium-PVC/PVdC perforated unit dose blisters.

II.2 Drug Substance

The active substance is apixaban, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The active substance is practically insoluble in water. It exhibits polymorphism. The polymorphic form produced by the active substance manufacturer corresponds to the N-1 form.

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

An eight-step synthesis is described for the active substance. No heavy metal catalysts are used. No Class 1 solvents are used. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents. 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 in-house specification, which includes tests for description, identification, residue on ignition, loss on drying, assay, related substances, residual solvents, particle size distribution and microbiological quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scale batches.

Stability of drug substance

Stability data on the active substance have been provided for three commercial scale batches in accordance with applicable ICH guidelines at 25°C/65% RH (48 months) and 40°C/75% RH (6 months). Based on the data submitted, a retest period could be granted of 48 months 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. The choice of excipients is justified and their functions explained. Apixaban 1A Pharma is a generic form of the marketed

tablet named Eliquis. The manufacture and composition of the bio-batches used in bioequivalence studies is similar to the marketed product. Comparative dissolution profiles at pH levels 1.2, 4,5 and 6.8 have been provided to support a biowaiver for the 2.5 mg strength. The media and testing time points are in accordance with the recommendations for a biowaiver of an additional strength. The biowaiver is acceptable from a chemical-pharmaceutical point of view. The possibility to administer the product through a nasogastric tube has been demonstrated in line with the applicable EMA quality Q&A.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The film-coated tablets are manufactured by direct compression. Process validation data on the product have been presented for three batches per strength and per drug product manufacturer, in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the Ph. Eur. requirements. 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 colour and appearance, identification, uniformity of dosage units, water activity, assay, related substances (impurities), dissolution testing and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Release and shelf-life requirements are identical except for water activity, assay, and total impurities. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three full scaled batches per strength and per production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for full scale batches per strength and per product manufacturer, stored at 25°C/60% RH (36 and 3 months) and 40°C/75% RH (6 and 3 months). The stability was tested in accordance with applicable European guidelines. The results show no out of specifications or trends at the tested storage conditions. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 3 years. This medicinal product does not require any special storage condition.

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

Scientific data and/or certificates of suitability issued by the EDQM for lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of

Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated. No other substances are of ruminant animal origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Apixaban 1A Pharma 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 Apixaban 1A Pharma 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 Eliquis, 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

Apixaban 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 bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Apixaban 1A Pharma 5 mg, film-coated tablets (1A Pharma GmbH, the Netherlands)

was compared with the pharmacokinetic profile of the reference product Eliquis 5 mg film-coated tablets, (Bristol-Myers Squibb/Pfizer EEIG, UK).

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.

Biowaiver

For the 2.5 mg strength, a biowaiver was granted because the following requirements were met, in accordance with 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.

Bioequivalence studies

Design

A blinded, randomised, single-dose, three-period, three-treatment, three-sequence crossover bioequivalence study was carried out under fasted conditions in 30 healthy male and female (26 male/ 4 female) subjects, aged 22-55 years. Each subject received a single dose (5 mg) of one of the three apixaban formulations. Reference 1 was Eliquis 5 mg film-coated tablets from the EU market, and reference 2 was Eliquis 5 mg film-coated tablet, purchased outside the EU. The results for reference 2 were therefore considered supportive and the results from comparison of the test product versus reference 1 were pivotal. The tablet was orally administered with 240 mL water after an overnight fast of at least ten hours. There were three dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, and 60 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

One subject dropped out in period I. Therefore, 29 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of apixaban, 5 mg, under fasted conditions.

Treatment N=29	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	1589 (±353)	1612 (±358)	165 (±37)	2,33 (1,00 – 4,50)
Reference 1	1603 (±294)	1631 (±298)	169 (±36)	2,45 (1,00 – 4,50)
***Ratio (90% CI)**	0.98 (0.94-1.03)	--	0.98 (0.92-1.04)	--

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products.
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, Apixaban 1A Pharma 5 mg is considered bioequivalent with Eliquis 5 mg (reference 1 and 2).

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).

The results from the 5 mg formulation can be extrapolated to the 2.5 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Apixaban 1A Pharma.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Bleeding
Important potential risks	• Liver disorders • Potential risk of bleeding or thrombosis due to overdose or underdose

Missing information	• Use in patients with severe renal impairment

The routine pharmacovigilance activities and routine risk minimisation measures are in line with the innovator product. Additional risk minimization measures include educational materials for healthcare professionals and patients. There is a prescriber guide regarding both important potential risks, and a patient alert card for the risk of bleeding.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Eliquis. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Eliquis (EMEA/H/C/002148) for the content and several Sandoz product PLs for layout and design (EMEA/H/C/1181-1183, AT/H/0350/DC, DE/H/1354-1356, NL/H/1170-1172, DK/H/300/01-02/II/18, SE/357,359, 361/01-04/R01, UK/H/2385-2387/001-004). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Apixaban 1A Pharma 2.5 mg and 5 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Eliquis 2.5 mg and 5 mg film-coated tablets. Eliquis is a well-known medicinal product with an established favourable efficacy and safety profile. Bioequivalence for the 5 mg strength has been shown to be in compliance with the requirements of the European guidelines . A biowaiver was granted for the 2.5 mg strength.

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 Apixaban 1A Pharma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 July 2021.

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
NL/H/5037/1-2/IA/001/G	Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a site where batch control/testing takes place Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	No Yes	11-11-2021	Approved	N/A
NL/H/5037/1-2/IA/002/G	Change in the name and/or address of the marketing authorisation holder	Yes	14-3-2022	Approved	N/A
NL/H/5037/1-2/IB/003	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product - Implementation of change(s) for which no new additional data are submitted by the MAH	Yes	21-7-2022	Approved	N/A
NL/H/5037/1-2/IA/004/G	Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a site where batch control/testing takes place Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product - Minor change in the manufacturing process. Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	No No No	1-11-2022	Approved	N/A
NL/H/5037/1-2/IA/005/G	Change in the name and/or address of: a manufacturer (including where relevant	No	14-12-2022	Approved	N/A

	quality control testing sites); or an ASMF holder; or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the technical dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or a manufacturer of a novel excipient (where specified in the technical dossier)				
	Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance - Up to 10-fold increase compared to the originally approved batch size	No			
	Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	No			
NL/H/5037/1-2/IA/006/G	Change in immediate packaging of the finished product - Change in type of container or addition of a new container - Deletion of an immediate packaging container that does not lead to the complete deletion of a strength or pharmaceutical form	Yes	14-12-2022	Approved	N/A
	Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	No			
	Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used))	No			

	- Change that does not affect the product information				