28 May 2020
EMA/322602/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Apixaban Accord

International non-proprietary name: apixaban

Procedure No. EMEA/H/C/005358/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AEs	Adverse events
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASMF	Active Substance Master File
AUC	Area under the plasma concentration versus time curve
BCS	Biopharmaceutics Classification System
BMI	Body mass index
CFU	Colony Forming Units
CK	Creatine kinase
CL/F	Apparent total clearance after oral administration
CLcr	Creatinine clearance
CLR	Renal clearance
Cmax	Peak plasma concentration
Cmin	Minimum plasma concentration
CRNM	Clinically relevant non-major
DOACs	Direct oral anticoagulants
DSC	Differential Scanning Calorimetry
DVT	Deep vein thrombosis
ESRD	End-stage renal disease
FXa	Factor Xa
GI	Gastrointestinal
GC	Gas Chromatography
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INR	International Normalized Ratio
IR	Infrared
KF	Karl Fischer titration

LMWH	Low-molecular weight heparin
LDPE	Low density polyethylene
MAA	Marketing Authorization Application
mPT	Modified prothrombin time
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
NOACS	Non-vitamin K antagonist oral anticoagulants
NSAIDs	Nonsteroidal anti-inflammatory drugs
NVAF	Non-valvular atrial fibrillation
Ph. Eur.	European Pharmacopoeia
PCC	Prothrombin complex concentrates
PE	Pulmonary embolism
P-gp	Permeability glycoprotein
PP	Polypropylene
PPCP	Polypropylene copolymer
PT	Prothrombin time
PVC	Polyvinyl chloride
PVdC	Polyvinylidene chloride
QbD	Quality by design
SM	Starting material
SmPC	Summary of product characteristic
t1/2	Half-life
TIA	Transient ischemic attack
Tmax	Time to reach peak plasma concentration
TSE	Transmissible Spongiform Encephalopathy
UF	Unfractionated
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet

VKA	Vitamin K antagonist
VTE	Venous thromboembolism
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 1 June 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Apixaban Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 April 2019.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indications:

For 2.5 mg:

Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or 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 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 (see section 4.4 for haemodynamically unstable PE patients).

For 5 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 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 (see section 4.4 for haemodynamically unstable PE patients).

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is

composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Eliquis instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Eliquis film-coated tablets 2.5mg and 5mg
- Marketing authorisation holder: Bristol-Myers Squibb/Pfizer EEIG
- Date of authorisation: 18/05/2011

- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/11/691

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Eliquis film-coated tablets 2.5mg and 5mg
- Marketing authorisation holder: Bristol-Myers Squibb/Pfizer EEIG
- Date of authorisation: 18/05/2011
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/11/691

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Eliquis film-coated tablets 5mg
- Marketing authorisation holder: Bristol-Myers Squibb/Pfizer EEIG
- Date of authorisation: 18/05/2011
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number: EU/1/11/691
- Bioavailability study number: 0310-16

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Alar Irs

The application was received by the EMA on	1 June 2019
The procedure started on	20 June 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	9 September 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	24 September 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 October 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 January 2020
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	2 March 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 March 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	26 March 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	13 May 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Apixaban Accord on	28 May 2020

2. Scientific discussion

2.1. Introduction

Apixaban Accord film-coated tablets 2.5mg and 5mg MAAs have been submitted according to the Article 10.1 of Directive 2001/83/EC, as amended (i.e. generic application) containing the same active substance in the same pharmaceutical form and strengths as the reference product. The reference product is Eliquis 2.5mg film-coated tablets, marketed by Bristol-Myers Squibb/Pfizer EEIG, that was first approved in the European Union on 18/05/2011 via centralised procedure (EU/1/11/691).

The drug substance is apixaban. The Pharmacotherapeutic group: antithrombotic agents, direct factor Xa inhibitors, ATC code: B01AF02

Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development. Preclinical studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that preserved haemostasis.

The indications sought for Apixaban Accord are the same as those for the reference product.

Apixaban Accord is indicated for:

2.5 mg:

- Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery (for 2.5mg strength only).
- 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 (see section 4.4 for haemodynamically unstable PE patients).

5 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 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 (see section 4.4 for haemodynamically unstable PE patients).

The product is a subject to medical prescription.

The maximum daily dose of apixaban is 20mg when taken orally. The posology and duration of treatment depend on the specific indications according to the SmPC. The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding.

Apixaban must not be used in patients who are actively bleeding, or who have liver disease which leads to problems with blood clotting and an increased risk of bleeding. The medicine must also not be used in

patients with conditions putting them at risk of major bleeding, such as an ulcer in the gut, or in patients being treated with other anticoagulant medicines except in specific circumstances.

Since this is an abridged application claiming essential similarity to the reference product, no new clinical and non-clinical studies have been undertaken with the exception of one BE study (see Clinical Aspects section of this report).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 2.5 mg or 5 mg of apixaban as active substance.

Other ingredients are: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulphate, magnesium stearate, Opadry II Yellow (2.5 mg strength only), Opadry II Pink (5mg strength only).

The components of Opadry are: hypromellose, lactose monohydrate, titanium dioxide, triacetin, iron oxide yellow (Opadry Yellow), iron oxide red (Opadry Pink).

As described in section 6.5 of the SmPC, the product is available in PVC/PVdC/Aluminium blisters, PVC/PVdC/Aluminium perforated unit dose blister and HDPE bottles with polypropylene child resistant/continues threaded closure.

2.2.2. Active substance

General information

The chemical name of apixaban is 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide corresponding to the molecular formula $C_{25}H_{25}N_5O_4$. It has a relative molecular mass of 459.50 g/mol and the following structure:

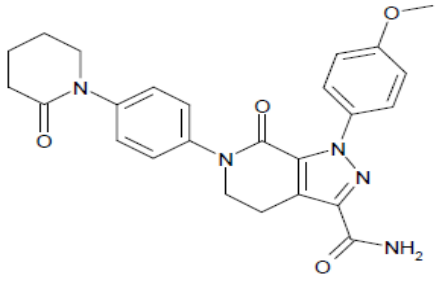


Figure 1: Apixaban structure

The chemical structure of apixaban was adequately elucidated by a combination of elemental analysis (C, H and N) and spectral data [IR, UV, ^{1}H-NMR, ^{13}C-NMR and MS (direct infusion, electrospray +)]. The solid state properties of the active substance were measured by XRPD and DSC.

Apixaban is a white to pale yellow non-hygroscopic crystalline powder, soluble in chloroform, sparingly soluble in dimethylsulfoxide and insoluble in water. Apixaban is a non-ionisable compound, so its solubility is not affected by changes in pH.

Apixaban is an achiral molecule. Polymorphism has been observed for apixaban; there are 13 forms reported in literature. The manufacturer consistently manufactures the same polymorphic form of apixaban. Stability of the polymorphic form has been adequately demonstrated. Polymorphism is controlled by an XRPD analysis test included in the active substance specification of both the ASMF holder and the applicant.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory. One active substance manufacturer is proposed together with an alternative manufacturer of a named intermediate.

Apixaban is synthesized in three main stages using well-defined starting materials with acceptable specifications. The suitability of the two proposed starting materials (SM), and their control strategies has been sufficiently demonstrated during the procedure in response to a major objection (MO). Following another MO asking the ASMF to address the carry-over of a specific impurity with mutagenic potential, the applicant presented a detailed genotoxic discussion in line with ICH M7; the data provided confirm the effective purge of potential genotoxic impurities.

The same specifications are applied for the named intermediate manufactured by both manufacturers. In response to a MO asking the ASMF holder to discuss the carry-over of impurities originating from the intermediate and the proposed starting materials, the ASMF holder revised its control strategy, including those impurities with mutagenic potential.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been updated during the procedure and are now considered adequate.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. In this regard, during the procedure the ASMF holder updated the Applicant`s part of the ASMF with a revised control strategy for impurities with genotoxic potential in line with ICH M7 Guideline as requested by the CHMP in a MO.

The ASMF holder and the applicant have included additional tests to control the residual level of potential nitrosamines derivatives in the final active substance.

No changes of the manufacturing process have been described in the manufacturing process development of the active substance.

Apixaban is packed in double low density polyethylene bags contained in polyethylene drums. The polyethylene bags comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: description, solubility, identification (IR, HPLC, XPRD), loss on drying (Ph.Eur.), sulphated ash (Ph.Eur.), related substances (HPLC), assay (HPLC), , residual solvents (GC), nitrosamines derivatives (HPLC-MS) and particle size (Malvern).

Impurities limits have been set in line with ICH Q3A guidance.

During the procedure, the ASMF holder and the applicant have included in the active substance specification tests to control the residual level of two additional solvents and, following the provision of the nitrosamine risk assessment, limit tests for two potential nitrosamines derivatives potentially arising from the SM. The relevant sections of the restricted and open part of the ASMF have been updated satisfactorily. The limit for nitrosamines derivatives has been set based on the maximum daily dose in line with ICH M7.

Confirmation of polymorphic purity and particle size distribution are included in the active substance specification as these are considered critical material attributes, as they impact the solubility of the active substance.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines with the exception of the in-house test of residual solvents, which were introduced during the procedure. The applicant is recommended to provide additional validation data (linearity, precision) for the in-house test of residual solvents. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on 4 pilot scale batches, and 2 production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 pilot scale and 2 production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 48 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on samples of the active substance. Results on stress conditions both in the solid and aqueous state on samples of the active substance were provided.

Only stability indicating parameters (description, loss on drying, assay, impurities) were tested. The analytical methods used were the same as those used for release testing and were stability indicating.

All tested parameters were within the specification limits under long term and accelerated conditions. Slight degradation was observed only under acidic, basic and oxidising stress conditions in solution.

Additional XRPD stability data from 3 validation batches of the active substance for up to 36 months under long term conditions has been provided confirming the stability of the desired polymorphic form of apixaban.

Since the submission includes data from stability studies on fewer than three production scale batches, the stability commitment has been amended to indicate that the studies will be continued through the proposed re-test period and an additional commercial scale batch will be placed on long term stability study through the proposed re-test period.

Additional stability data at release and after 47 months of storage under long-term storage conditions have been provided during the review, demonstrating that the particle size of the active substance is not affected by storage.

In line with internal policy -procedures, the applicant has fixed a one-year re-test period for the active substance.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the retest period of 60 months, with no special storage conditions, when stored in the proposed container, as proposed by the ASMF holder.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Apixaban film-coated tablets are available in two strengths (2.5 mg and 5 mg) both strengths have the same qualitative core composition and their formulation is dose proportional. The composition of the two strengths and the film coating agent Opadry has been given is outlined

Ingredients are: Apixaban, anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulphate, magnesium stearate, Opadry II Yellow (2.5 mg strength only), Opadry II Pink (5 mg strength only).

The components of Opadry are: hypromellose, lactose monohydrate, titanium dioxide, triacetin, iron oxide yellow (Opadry Yellow), iron oxide red (Opadry Pink).

The aim of the pharmaceutical development was to develop a stable, bioequivalent generic version of the reference product, Eliquis® (Apixaban) film-coated tablets 2.5 mg and 5 mg.

The formulation of Apixaban Accord is qualitative identical to the formulation of the reference medicinal product. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. Opadry II yellow (2.5 mg) and pink (5 mg) used in the coating are not described in any Pharmacopoeia, but all the individual ingredients (hypromellose, lactose monohydrate, titanium dioxide, triacetin, iron oxide yellow and iron oxide pink) are either described in Ph.Eur. or NF. Functionality related characteristics of excipients lactose, microcrystalline cellulose, croscarmellose sodium and magnesium stearate have been discussed. For all the mentioned excipients a specification for particle size distribution has been set; for magnesium stearate, specific surface area is also controlled. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. A series of binary active substance-excipient compatibility studies were performed and the results demonstrated good compatibility.

The choice of excipients is justified and their functions explained. The formulation used during clinical studies is the same as that intended for marketing.

Apixaban is considered to be a BCS Class III compound (high solubility and low permeability). It is freely soluble across the physiological pH. Apixaban is a non-ionisable compound, so its solubility is not affected by changes in pH. The polymorphic form and particle size may affect its performance *in vivo*. XRDP data on one batch of both strengths of finished product at release and stored for 6 months at 40°C/75%RH have been provided confirming that the polymorphic form of the active substance remains unchanged in the finished product during storage.

Pharmaceutical development of the finished product contains QbD elements. The formulation and manufacturing development have been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. A risk analysis was performed in order to define critical process steps and process parameters that may have an influence

on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The following critical quality attributes (CQA) were defined: tablet average weight, identification, dissolution, related substances, assay, content uniformity, microbial limits, elemental impurities and polymorphism. Assay, dissolution, content uniformity and related substances were identified as CQAs that can be impacted by the formulation and/or process variables and have been discussed in detail in the pharmaceutical development. Excipient levels of croscarmellose sodium, sodium lauryl sulphate and magnesium stearate have been optimised to give a dissolution profile similar to the one of the reference product.

The manufacturing process selected is dry mixing and direct compression. Blending and lubrication time were optimised to ensure the desired blend uniformity. Blending and lubrication have been adequately identified as critical process parameters. The impact of lubrication time and hardness on dissolution were also investigated and it was concluded that within the proposed range neither had a significant impact.

The dissolution studies performed with the paddle apparatus using 5mg batches of the reference and test products, including batches used in the bioequivalence study, showed similar dissolution profiles, with at least 80% dissolved in 45 minutes, between the test and reference product and for the reference product in all investigated media (50 rpm in 0.1N HCl, pH 4.5 acetate buffer and phosphate buffer pH 6.8, and 75 rpm in phosphate buffer pH 6.8 phosphate buffer).

The developed QC dissolution method is in line with Ph. Eur. requirements. To assess the discriminatory power of the dissolution method, two batches of Apixaban tablets 5 mg manufactured with different active substance particle size were studied. Apixaban tablets 5 mg manufactured with coarser active substance particle size showed significantly slower drug release rate and failed to meet finished product dissolution specification. Therefore, it was concluded that the selected dissolution method has sufficient discrimination power to identify the difference in formulation of Apixaban tablets.

To further substantiate the discriminatory power of the dissolution method and tighten the dissolution limits, in response to concerns raised during the procedure, the applicant investigated the dissolution of two batches of the finished product manufactured with different hardness, one with hardness higher than the one validated and one with acceptable hardness. The finished product with higher hardness (outside the process validation range) compared showed slower drug release and failed to comply with the new dissolution specification. The discriminatory power of the dissolution method has been satisfactorily demonstrated. The dissolution specification limit was updated during the procedure.

A bioequivalence study was performed with the 5 mg tablets showing bioequivalence between the high strength of the test and reference product. Details on the bioequivalence studies conducted can be found in Module 5 of this report. A bio-waver for the 2.5 mg strength has been adequately justified and agreed in line with the requirements of the Guideline on the Investigation of Bioequivalence (both strengths are manufactured by the same manufacturer using the same manufacturing process, the qualitative composition of is the same, the composition of the both strengths quantitatively proportional, the *in-vitro* dissolution profile is similar under identical conditions for the additional strengths and apixaban demonstrates linear pharmacokinetics over the therapeutic dose range).

In-use stability studies with crushed 5 mg tablets demonstrate that the product is stable for up to 4 hours in the mediums proposed in the SmPC (i.e. water, 5% dextrose in water, apple juice and apple sauce). No significant change in assay or impurities was observed and the level of all impurities remained below

specification limits in all investigated mediums. The data further support the suitability of the administration of the crushed and suspended tablets in water and in 5% dextrose via a nasogastric tube.

Apixaban film-coated tablets are packed in PVC/PVdC-Aluminium blisters and/or HDPE bottles with polypropylene child resistant/continued threaded closure, and/or polypropylene copolymer (PPCP) container as a transportation package. The material complies with Ph. Eur. and EC requirements. Child-resistance properties of the HDPE container with PP closure system have been demonstrated. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 5 main steps: co-sifting of excipients, blending, lubrication, compression, film-coating and packaging. The process is considered to be a standard manufacturing process.

Appropriate control specifications for the intermediates have been provided. The validation of the manufacturing process has been presented for three commercial scale batches of each tablet strength. It has been demonstrated that the manufacturing process is capable of producing finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, average weight of tablet, identification (HPLC, UV), water (KF – Ph. Eur.), resistance to crushing of tablets (Ph. Eur.), dissolution (by HPLC), uniformity of dosage units (content uniformity, HPLC – Ph.Eur.), assay and related substances (HPLC) and microbial examination (Ph. Eur.).

Specification limits for the identified impurity and total impurities has been tightened during the procedure in line with batch data. The proposed specification is now considered adequate. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The reference standards used are the same as used for the active substance testing and are considered suitable for use.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment on the potential presence of nitrosamine impurities originating from the active substance, the excipients, process equipment, cleaning agents and packaging materials has been provided. No risk has been identified. The company has committed to provide additional batch analysis data to confirm the conclusions of performed investigations on the potential presence of nitrosamine impurities in the Apixaban Accord 2.5/5 mg film-coated tablets prior to commercialization of the drug product. The applicant is recommended to provide batch analysis data from 6 pilot scale batches or 3 production scale batches confirming the absence of nitrosamines in the finished product prior to its commercialisation (REC 2). As both strengths of the finished product batches are manufactured from the same bulk data can be provided from either or both strengths.

Batch analysis results are provided for 3 production scale batches for both tablet strengths confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 production scale batches of both tablet strengths stored for up to 36 months (packed in blisters) and for up to 24 months (packed in HDPE bottles), under long term conditions (25ºC / 60% RH), and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Bulk stability data from 2 production scale batches of both finished product strengths stored for up to 12 months under long term conditions (25ºC / 60% RH) packed in a PPCP container, used for bulk storage and transportation, and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

In-use stability data (open bottle) from one production scale batch of each tablet strengths stored under long term conditions (25ºC / 60% RH) in a HDPE bottle for up to 90 days were provided.

Samples were tested for appearance, assay, impurity/degradants, dissolution, water content, and microbial quality (tested yearly at long-term studies). Identification, average weight of tablet and uniformity of dosage units for apixaban tablets are only tested at release since they are not stability-indicating tests. All results were within specification limits. The analytical procedures used are stability indicating.

In addition, one batch per strength was exposed to light as defined in the ICH Q1B Guideline on Photostability Testing of New Drug Substances and Products. Data showed no significant change in description, assay or degradation products of apixaban, concluding that the finished product is not sensitive to light.

Forced degradation studies on one batch of the 5 mg strength were performed by exposing the finished product to acid, base, oxidation by peroxide, extreme moisture and heat, UV and metal ion oxidation (solution of Cu (II) and Fe (III)). The possible degradation products were identified and the stability indicating power of the HPLC analytical method was confirmed.

Based on satisfactory bulk stability data, 12 months storage period is assigned for the bulk tablets stored in the PPCP container. Tablets are to be repacked in to blisters within 12 months from the date of bulk packing into PPCP containers.

The start of shelf life of the finished product is being considered from the date of dispensing materials for the manufacture of the finished product, which is more stringent than the requirements stated in guideline CPMP/QWP/072/96.

Based on available stability data, the proposed shelf-life of 36 months with no special storage conditions as stated in the SmPC (section 6.3) are acceptable for the product packaged in PVC/PVDC-Aluminium blisters and HDPE bottles.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of

ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical and pharmaceutical aspects

Information about the synthesis process and the control mechanisms for the active substance is provided in the supporting ASMF. The initially raised MOs regarding the proposed starting materials, the disclosed level of details of the route of synthesis as well as the carry-over of impurities and the control strategy for the potentially genotoxic impurities have been adequately addressed. The company is recommended to perform additional validation data (linearity, precision) for the in-house tests for residual solvents.

Risk assessment on nitrosamines has been provided. Based on the presented data, it can be concluded that no risk has been identified. Nevertheless, the applicant is recommended to provide batch analysis data from 6 pilot scale batches or 3 production scale batches confirming the absence of nitrosamines in the finished product prior to its commercialisation.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. In line with ICH Q2 (R1) requirements, the applicant is recommended to provide additional validation data (linearity, precision) for the in-house tests for residual solvents.
2. The applicant is recommended to provide batch analysis data from 6 pilot scale batches or 3 production scale batches of the finished product confirming the absence of nitrosamines in the finished product prior to its commercialisation.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is 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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been

discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Apixaban Accord manufactured by Accord Healthcare S.L.U. is considered unlikely to result in any significant increase in the combined sales volumes for all apixaban containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

The non-clinical overview is based on published literature data. This is acceptable since apixaban is well known active substance and essential similarity is claimed to the reference product. There are no new non-clinical studies performed in support of the proposed application hence the presented Non-clinical Overview is considered sufficient for this type of MAA.

2.3.4. Conclusion on the non-clinical aspects

There are no objections to approval of Apixaban Accord from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for tablets containing apixaban. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of apixaban based on published literature. The SmPC is in line with the SmPC of the reference product.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

GCP

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

A request for a waiver of a bioequivalence study for Apixaban Accord 2.5 mg was submitted by the applicant according to the following general requirements [Ref: Guideline on the Investigation of Bioequivalence, Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/Corr**]:

a) All the strengths i.e. 2.5 mg and 5 mg of proposed pharmaceutical products are manufactured by the same manufacturer i.e. Intas Pharmaceutical Limited using the same manufacturing process,

b) The qualitative composition of the Apixaban film-coated tablets 2.5 mg is same as that of apixaban film-coated tablets 5 mg.

c) The composition of the all strengths i.e. 2.5 mg and 5 mg are quantitatively proportional i.e. the ratio between the amount of each excipient to the amount of active substance(s) is same among 2.5 mg and 5 mg strengths.

d) The in-vitro dissolution profile is similar under identical conditions for the additional strengths i.e. 2.5 mg and the strength of batch used in the bioequivalence studies i.e. 5 mg (see **Dissolution conditions** and **Table 5**).

e) Apixaban demonstrates linear pharmacokinetics over the therapeutic dose range.

Dissolution conditions

Apparatus	Paddle
Rotation speed	50 rpm (0.1N HCl, pH 4.5 Acetate buffer, pH 6.8 Phosphate buffer) and 75 rpm (in pH 6.8 Phosphate buffer; QC Medium)
Volume	900 ml
Dissolution media	HCl 0.1N
	pH 4.5 Acetate buffer
	pH 6.8 Phosphate buffer
Temperature	37 ± 0.5°C
Time Points	10, 15, 20, 30, 45 and 60 minutes
Units	12 units

Table 1 . Comparative dissolution data for Apixaban film-coated tablets 5 mg versus Apixaban film-coated tablets 2.5 mg

Apixaban tablets	Dissolution Medium	Time (minutes)						F2 Vs BE batch
		10	15	20	30	45	60	
Apixaban tablets 5mg B. No. T07222 (Test BE Batch)	0.1N HCl (at 50 rpm)	61	71	77	83	87	89	
	pH 4.5 Acetate buffer (at 50 rpm)	74	80	83	87	89	90	
	pH 6.8 Phosphate buffer (at 50 rpm)	70	76	79	83	86	88	
	pH 6.8 Phosphate buffer (at 75 rpm)	91	95	97	99	100	101	
	0.1N HCl (at 50 rpm)	54	66	72	79	85	88	65
	pH 4.5 Acetate buffer (at 50 rpm)	76	83	86	90	92	94	77

Apixaban tablets 2.5mg B. No. T07221	pH 6.8 Phosphate buffer (at 50 rpm)	69	76	80	84	87	89	94
	pH 6.8 Phosphate buffer (at 75 rpm)	89	94	96	98	99	100	*
Apixaban tablets 2.5mg B. No. T07223	pH 6.8 Phosphate buffer (at 75 rpm)	87	92	94	97	98	99	*
Apixaban tablets 2.5mg B. No. T07225	pH 6.8 Phosphate buffer (at 75 rpm)	91	94	96	99	99	100	*

* More than 85% dissolution was observed in 15 minutes for both products for which dissolution comparison is considered. Hence, f2 calculation is not considered necessary.

Clinical studies

To support the application, the applicant has submitted one (1) bioequivalence study, Study No. 0310-16

2.4.2. Pharmacokinetics

Methods

Study design

Study 0310-16 was an open-label, analyst-blinded, balanced, randomized, single oral dose, two-sequenced, two-period, two-treatment cross-over bioequivalence study in healthy, adult subjects under fasting conditions with a wash out period of 5 days between two administrations. In each period single oral dose of either test or reference product of apixaban 5 mg tablets was orally administered.

Test and reference products

Test Product: Apixaban tablets 5 mg by Intas Pharmaceuticals Limited, Matoda, India; batch No. T07222; manufacturing date: May 2016, expiry date: Apr 2018

Reference Product: Eliquis® 5 mg tablets by Bristol-Myers Squibb S.r.l, Loc. Fontana del Ceraso, 03012 Anagni (FR) Italy (MAH: Bristol-Myers Squibb/Pfizer EEIG, Uxbridge, Middlesex, UB8 1DH, UK); Lot No.: AAM3567 from UK market; expiry date: Feb 2019

Population studied

A total of 32 healthy male subjects (Asian race, aged 19 – 44 years, BMI 18.56 – 28.18 kg/m^2) were included in the study. Only non-smokers were allowed in this study.

31 subjects completed both study phases and were included in the pharmacokinetic and statistical analysis.

One subject was withdrawn from the study on the grounds of protocol non-compliance in Period-II.

Prior to check-in in Period-I, one subject discontinued from the study on his own accord and was replaced with next available volunteer.

Analytical methods

The plasma samples of subjects were analysed using a validated LC-MS/MS method over a concentration range of 0.252 ng/mL to 300.148 ng/mL for apixaban. A detailed description of the operative procedures and the validation process were provided.

In conclusion, the analytical method allowed a suitable investigation of the bioavailability of apixaban after oral administration.

Pharmacokinetic variables

Primary variables were C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

Secondary pharmacokinetic parameters determined were T_{max}, λz, $t_{½}$ and residual area %.

Statistical methods

The pharmacokinetic parameters were calculated from the plasma concentration vs. time profile by non-compartmental model for apixaban. Statistical comparison of the PK of the two formulations was carried out to assess the bioequivalence between test and reference formulations.

PK parameters for each individual were tabulated and graphically presented. Actual time-points of the sample collection are used for the calculation of PK parameters. All concentration values below the lower limit of quantification are set to zero for the pharmacokinetic and statistical calculations. Individual AUC parameters were calculated using the linear trapezoidal rule. ANOVA was performed on the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Non-parametric analysis of t_{max} was performed on untransformed data. ANOVA model included Sequence, Subject (Sequence), Formulation and Period as fixed effects

Criteria for conclusion of bioequivalence:

The 90% confidence intervals for the difference of means of ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for apixaban fell within acceptance range of 80.00 to 125.00% to conclude the test product was bioequivalent to the reference product under fasting conditions.

Results

Table 2. Pharmacokinetic parameters for apixaban (non-transformed values)

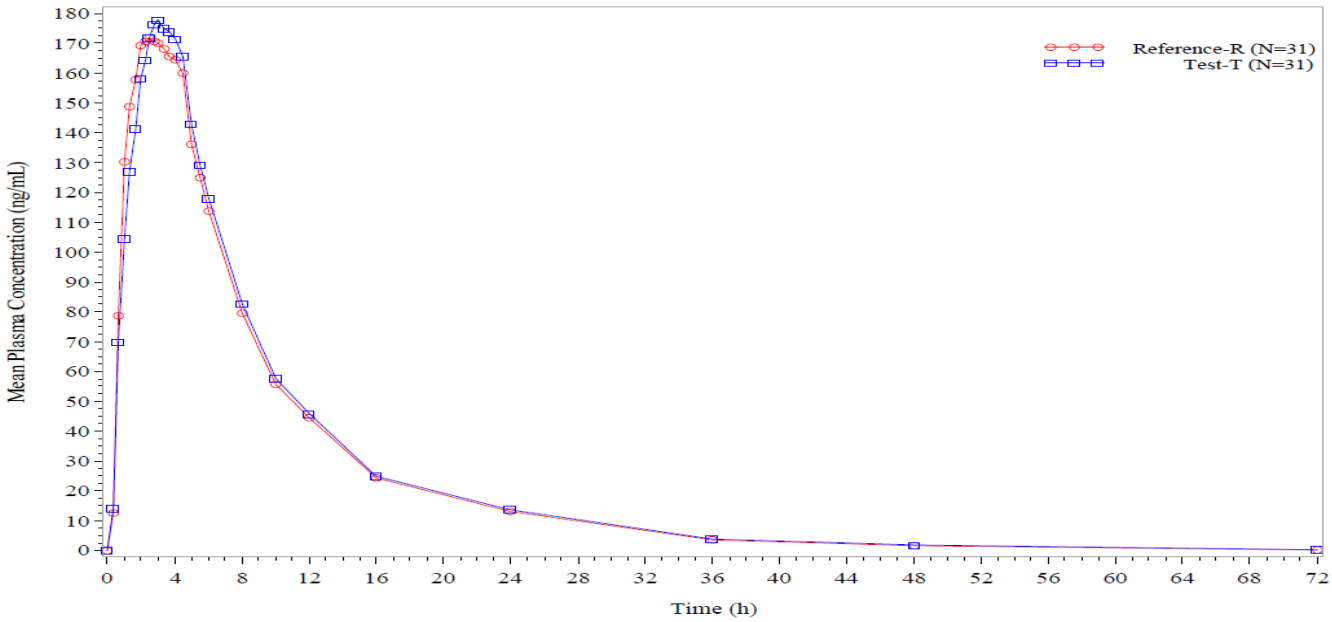
Pharmacokinetic parameter	**Test N=31**		**Reference N=31**	
	arithmetic mean **geometric mean**	**SD** **CV%**	**arithmetic mean** **geometric mean**	**SD** **CV%**
$AUC_{(0-72h)}$ (ng*h/mL)	**1707.893** 1670.691	± 359.5802 21.1%	**1683.108** 1648.415	± 340.4582 20.2%
$AUC_{(0-\infty)}$ (ng*h/mL)	1717.846 1680.635	± 360.3570 21.0%	1692.468 1657.902	± 340.4766 20.1%
C_{max} (ng/mL)	**189.046** 185.785	± 35.8055 18.9%	**187.740** 184.381	± 35.8139 19.1%

Pharmacokinetic parameter	Test N=31		Reference N=31	
	arithmetic mean **geometric mean**	**SD** **CV%**	**arithmetic mean** **geometric mean**	**SD** **CV%**
T_{max}* (h)	2.75	1.00 - 4.00	2.50	1.00 - 4.50
AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 3. Statistical analysis for apixaban (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals (%)	CV%*
$AUC_{(0-72h)}$	**101.4**	97.73 – 105.24	8.6
$AUC_{(0-\infty)}$	**101.4**	97.78 – 105.22	8.5
C_{max}	**100.8**	94.81 – 107.11	14.2
* estimated from the Residual Mean Squares			

Figure 2. Mean plasma concentration vs. time curve for apixaban after administration of Test and Reference formulations (5 mg) to healthy subjects (N=31).



Safety data

There were no adverse events during the conduct of the study. There were no clinically significant findings in the vital signs assessment or the laboratory tests in any of the subjects in the study.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

To support the application, the applicant has submitted a single dose crossover design bioequivalence study under fasting conditions to demonstrate essential similarity with the reference product Eliquis 2.5 mg and 5 mg film-coated tablets (manufactured by Bristol-Myers Squibb/Pfizer EEIG, UK). According to the SmPC of reference product, the pharmacokinetics of apixaban appears linear over the therapeutic dosage range. Apixaban can be taken without regard to food. Therefore, the selection of the highest dose, 5 mg, to be used in the bioequivalence study under fasting conditions is justified and in accordance to guidelines.

Overall study design was acceptable and in line with pharmacokinetic properties of apixaban. The BE study was conducted under standardised conditions. The sampling period was sufficient, the sampling time schedule and wash-out period were adequate taking into account the T-max and elimination half-life of apixaban. The sampling schedule reached up to 72 hours, however, the residual area was still evaluated and found to be lower than 20% for all subjects indicating that the duration of sampling was sufficient.

The population was chosen according to the guidelines. Bioanalytical method had satisfactory performance and was adequately validated. The pharmacokinetic and statistical methods applied were appropriate for a single dose study. The 90% confidence intervals for ln-transformed pharmacokinetic variables Cmax, AUC0-t and AUC0-∞ were within the conventional bioequivalence range of 80.00% to 125.00%.

The pharmacokinetic variables for apixaban were comparable between test and reference product. Both formulations were well tolerated in the study.

Additionally, the applicant has requested biowaiver for the 2.5 mg dosage strength. To support the request, a justification and results of comparative dissolution tests have been provided. The in vitro dissolution tests complimentary to the bioequivalence study comparing the in vitro dissolution similarity between additional strength and the test bio-batch over physiological pH range were conducted.

Comparative dissolution profiles demonstrated that the bio-batch and additional strength of test formulation were essentially similar over the physiological pH range. More than 85% of apixaban is dissolved within 15 minutes at pH 6.8 in Phosphate buffer at rotation speed of 75 rpm (QC media). Calculated similarity factors, f2 values suggest the similarity (50<f2 calculated<100) of dissolution profiles in 0.1N HCl and in buffers at pH 4.5 and 6.8 when 50 rpm rotation speed has been used. The applicant also included Bootstrap method based calculations for f2 to estimate the similarity between the dissolution profiles of the test and reference batches. As the computed lower bound of the confidence interval for f2 values were found to be more than 50 at pH 6.8 and in 0.1N HCl, the dissolution profiles are considered essentially similar. Thus, all criteria for a biowaiver according to the Guideline on the Investigation of Bioequivalence have been fulfilled.

2.4.6. Conclusions on clinical aspects

Based on the presented bioequivalence study Apixaban Accord 2.5mg and 5mg film-coated tablets are considered bioequivalent with Eliquis® 2.5 mg and 5 mg film-coated tablets (by Bristol-Myers Squibb/Pfizer EEIG, UK).

2.5. Risk management plan

Safety concerns

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	Severe renal impairment

Pharmacovigilance plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Safety concern	**Risk minimisation measures**
Bleeding	Routine risk minimisation measures: Sections 4.2, 4.3, 4.4, 4.5, 4.8, 4.9, 5.1 and 5.3 of Apixaban SmPC have information on this safety concern. Section 2, 3 and 4 of Apixaban PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: Prescribers Guide, Patient Alert Card
Liver injury	Routine risk minimisation measures: Sections 4.2, 4.4 and 4.8 of Apixaban SmPC have information on this safety concern. Section 4 of Apixaban PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Potential risk of bleeding or	Routine risk minimisation measures:

Safety concern	Risk minimisation measures
thrombosis due to overdose or underdose	Section 4.9 of Apixaban SmPC has information on this safety concern. Section 3 of Apixaban PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None
Severe renal impairment	Routine risk minimisation measures: Sections 4.2, 4.4, 4.9 and 5.2 of Apixaban SmPC have information on this safety concern. Section 2 and 3 of Apixaban PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Eliquis 2.5/5 mg film-coated tablets (Parent PIL 1) and Solifenacin succinate 5/10mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of apixaban tablets. The reference product Eliquis is indicated for:

For 2.5 mg:
Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or 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 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 (see section 4.4 for haemodynamically unstable PE patients).

For 5 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 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 (see section 4.4 for haemodynamically unstable PE patients).

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a two-period, two-treatment cross-over bioequivalence study in healthy, adult subjects under fasting conditions design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Apixaban Accord met the protocol-defined criteria for bioequivalence when compared with Eliquis. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Apixaban Accord is favourable in the following indications:

- Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery (2.5 mg tablets only).

- 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 (see section 4.4 for haemodynamically unstable PE patients).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

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 European Medicines Agency;
- 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.

Additional risk minimisation measures

The Marketing Authorisation Holder 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 Accord 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 Accord 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 Accord if they need to have any surgery or invasive procedure.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.