Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Apixaban

Proprietary Product Name: Eliquis

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

November 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
$AUC_{0\text{-}inf}$	Area under the curve from time 0 to infinity
AXA	Anti-factor Xa activity
BD	Twice daily
BMS	Bristol-Myers Squibb
BMS-562247	Apixaban
BMS-730823	Major metabolite of apixaban
BUN	Blood urea nitrogen
CBC	Complete blood cell count
CI	Confidence interval
CIAC	Central Independent Adjudication Committee
CK	Creatine kinase
CL	Clearance
CL_{NR}	Non-renal clearance
CL_R	Renal clearance
CrCl	Creatinine clearance
CRF	Case report form
CRNMB	Clinically relevant non-major bleeding
CUS	Compression ultrasound
D5W	5% dextrose in water
DAE	Discontinuation due to adverse event

Abbreviation	Meaning
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Board
DVT	Deep vein thrombosis
F	Bioavailability
F1.2	Prothrombin fragment F1.2
FSH	Follicle-stimulating hormone
FXa	Factor Xa
GCP	Good Clinical Practice
Hb	Haemoglobin
HCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
ICAC	Independent Central Adjudication Committee
ICH	International Conference on Harmonization
INR	International normalized ratio
IVRS	Interactive Voice Response System
k_a	Absorption rate constant
LMWH	Low molecular weight heparin
MB	Major bleeding
MedDRA	Medical Dictionary for Regulatory Activities
mPT	Modified prothrombin time
NSAID	Nonsteroidal anti-inflammatory drug
PD	Pharmacodynamic(s)
PE	Pulmonary embolism
p-gp	p-glycoprotein
PK	Pharmacokinetic(s)
PLS	Perfusion lung scan
QD	Once daily

Abbreviation	Meaning
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SMC	Study Management Committee
SSRI	Selective serotonin reuptake inhibitor
TAT	Thrombin-antithrombin III complex
TEAE	Treatment emergent adverse event
TC	Treatment compliance
UFH	Unfractionated heparin
ULN	Upper limit of normal
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
WBC	White blood cell
WOCBP	Women of childbearing potential
%CV	Coefficient of variability expressed as a percentage
%DEV	Percentage deviation from the nominal value

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	15 May 2015
Date of entry onto ARTG	21 July 2011 (2.5 mg) and 2 May 2013 (5 mg)
Active ingredient:	Apixaban
Product name:	Eliquis
Sponsor's name and address:	Bristol-Myers Squibb Australia Pty Ltd 4 Nexus Court, Mulgrave Victoria 3170
Dose form:	Film coated tablet
Strengths:	2.5 mg and 5 mg
Container:	Blister packs
Pack sizes:	2.5 mg: 10, 14, 20, 30, 60 or 100 tablets 5 mg: 14, 20, 56, 60, 100, 112, 120 or 168 tablets
Approved therapeutic use:	*Eliquis is Indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adult patients.* *Eliquis is indicated for the prevention of recurrent DVT and PE in adult patients.*
Route of administration:	Oral (PO)
Dosage:	*Treatment of DVT and PE* The recommended dose of Eliquis is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. *Prevention of Recurrent DVT and PE* The recommended dose of Eliquis is 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE.
ARTG numbers:	193474 (5 mg) and 172244 (2.5 mg)

Product background

This AusPAR describes the application by Pfizer Australia Pty Ltd, on behalf of Bristol-Myers Squibb Australia Pty Ltd (the sponsor), to extend the indications of Eliquis® (apixaban) to include the treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Currently Eliquis is approved for the following:

> *Eliquis is indicated for the prevention of venous thromboembolic events in adult patients who have undergone elective total hip or total knee replacement surgery.*
>
> *Eliquis is indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.*

The sponsor has proposed the following new indications:

> *Eliquis is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).*
>
> *Eliquis is indicated for the prevention of recurrent DVT and PE.*

The sponsor has also proposed a new pack size of 28 x 5 mg tablets, presented in a seven day/night blister pack.

Apixaban is an oral, reversible, direct and highly selective inhibitor of factor Xa (FXa). It does not require antithrombin III for antithrombotic activity and inhibits free and clot bound FXa and prothrombinase activity. It inhibits thrombin generation and thrombus development. Although it has no direct effect on platelet aggregation it inhibits platelet aggregation induced by thrombin. Studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that caused negligible prolongation of prothrombin time and bleeding time in rabbits and dogs but more than two fold increases in prothrombin time and bleeding time in rats.

Venous thromboembolic disease is relatively common. Based on Australian Institute of Health and Welfare (AIHW) hospital separation data, in 2008 there were an estimated 14,716 cases of VTE (70 cases per 100,000 Australians); 5,466 in males and 9,250 females.[1] Of those 43% of the VTE events occurred in people aged 15 to 64 years, 22% were aged 65 to 74 years, 24.1% were aged 75 to 84 years and 10.7% were aged ≥ 85 years. VTE had an estimated cost of $1.72 billion (0.15% of Gross Domestic Product (GDP)). The authors of the report note their estimate of the prevalence of disease was conservative and lower that the estimates per 100,000 population in the United Kingdom (UK) (1.5 times higher) and the USA (4 times higher).

Rivaroxaban (Xarelto, Bayer Australia Pty Ltd), another FXa inhibitor is also registered in Australia for the '*Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for the prevention of recurrent DVT and PE.*'

There are no current recommendations for laboratory monitoring for subjects taking the new oral anticoagulant medications. These drugs have been developed and approved without laboratory monitoring to guide dose adjustment, to predict subjects at risk of thrombosis/thromboembolism or bleeding, or to assist in the management of bleeding emergencies, overdose and the situations where subjects may require emergency surgeries or procedures. There has been considerable local and international interest in this issue and the sponsor was requested to comment on the evidence it holds regarding

[1] The burden of venous thromboembolism in Australia; report by Access Economics Pty Ltd for The Australia and New Zealand Working Party on the Management and Prevention of Venous Thromboembolism <https://www.deloitteaccesseconomics.com.au/uploads/File/The%20burden%20of%20VTE%20in%20Australia.pdf>

the utility of laboratory monitoring, and possible therapeutic dose (or anti FXa range). The sponsor indicated that it was unable to identify threshold levels of apixaban exposure or anti FXa that would predict efficacy or safety outcomes to define a therapeutic range, and that it did not have any clinical evidence to support routine laboratory monitoring. It noted other regulatory agencies had requested the provision of similar information. To date no agency has recommended routine laboratory monitoring for apixaban or required a study to define and/or validate a therapeutic range. The issue of laboratory monitoring of patients taking the new oral anticoagulants has been discussed by the Advisory Committee on the Safety of Medicines (ACSOM) and is a subject of consideration by the TGA.

The following guidance relate to the application:

- EMA Guideline on clinical investigation of medicinal products for the treatment of venous thromboembolic disease (CPMP/EWP/563/98).
- Guideline on Clinical Investigation Of Medicinal Products For Prophylaxis Of High Intra- And Post-Operative Venous Thromboembolic Risk (CPMP/EWP/707/98).
- Guideline on Clinical Investigation Of Medicinal Products For The Prophylaxis Of Venous Thromboembolic Risk In Non-Surgical Patients (CPMP/EWP/6235/04).
- Points To Consider When Switching Between Superiority And Non-Inferiority (CPMP/EWP/482/99).

Regulatory status

Apixaban was first approved in Australia in July 2011 for the indication:

> *Eliquis is indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip or total knee replacement surgery.*

It was approved in 2013 for the indication:

> *Eliquis is indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.*

At the time the TGA considered this application, Apixaban had also been approved internationally in the European Union (EU), USA and Canada (for see details below in Table 1).

Table 1: International regulatory status

Approval date	Approval date	Indications
EU	18 May 2011	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.

Approval date	Approval date	Indications
USA	28 December 2012	Eliquis® (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Eliquis is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery. Eliquis is indicated for the treatment of DVT. Eliquis is indicated for the treatment of PE. Eliquis is indicated to reduce the risk of recurrent DVT and PE following initial therapy.
Canada	16 December 2011	Eliquis (apixaban) is indicated for: • the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective knee or hip replacement surgery. • the prevention of stroke and systemic embolism in patients with atrial fibrillation. • the treatment of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE.
New Zealand	27 June 2013	Eliquis is indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip or total knee replacement surgery. Eliquis is indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with at least one additional risk factor for stroke.
Switzerland	26 August 2011	Prevention of venous thromboembolic events in adult patients who have undergone elective hip or knee replacement surgery. Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation.
Singapore	24 December 2012	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.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

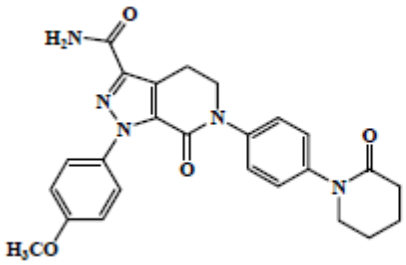
Introduction

The application and the supporting data relating to the proposed additional labels and consequential changes to the PI have been assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA.

Drug substance (active ingredient)

Apixaban is prepared in a purely synthetic multiple step process. It is achiral and of the Biopharmaceutics Classification System (BCS) Class III (high solubility low permeability).[2] Apixaban has the following structural formula (Figure 1):

Figure 1: Chemical structure of apaxiban



Quality summary and conclusions

Notwithstanding the acceptability of the new indications and associated dosing regimens, there are no outstanding issues with respect to the labelling and PI and Consumer Medicine Information (CMI) aspects.

III. Nonclinical findings

Introduction

In support of the proposed changes, the sponsor submitted a series of pharmacological and pharmacokinetics studies.

[2] The BCS is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

Nonclinical assessment and conclusion

Activated charcoal reduced exposure to apixaban in dog and rat studies. The use of activated charcoal also resulted in an increased excretion of apixaban in faeces at the expense of urine. Based on the findings, the sponsor suggests a putative role for activated charcoal in the management of apixaban overdose in humans.

A haemodialysis study in dogs demonstrated that apixaban is dialyzable, resulting in lower (but not statistically significant) peak plasma concentrations (C_{max}) values during dialysis but no effect on plasma exposure (area under the plasma concentration versus time curve (AUC)). A more extensive study needs to be conducted before any clinical significance can be concluded.

No P-glycoprotein (P-gp) inhibition by apixaban was observed for concentrations up to 54.7 μM.

The major excretory pathways for unchanged and metabolised apixaban included urine, faeces and bile in rats (WT, Pgp-KO and BCRP- breeds) and dog. The excretion studies also indicated that intestinal excretion and enteroenteric recirculation are facilitated by intestinal efflux transporters.

While no specific nonclinical studies pertaining to the efficacy of apixaban on DVT and PE were submitted; the sponsor notes that efficacy was demonstrated in the two pivotal phase three clinical studies.

The newly submitted nonclinical data raised no new safety concerns.

There are no nonclinical objections to the proposed extension of indications.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The sponsor provides the following information in the Clinical Overview:

> '*PE is the most serious complication of DVT, as the embolised blood clot lodges in the lung vasculature and obstructs blood flow through the lungs. This reduces oxygenation of the blood and increases mechanical strain on the heart, leading to cardiopulmonary compromise, which has a high risk of death. If a large thrombus acutely obstructs the pulmonary vasculature, sudden death is a common outcome, with approximately 300,000 deaths reported annually in the US, a number that exceeds that of deaths from myocardial infarction (MI) (170,000/year) and stroke (158,000/year)*'
>
> *In comparison with subjects who have experienced a provoked VTE (e.g. after surgery). 'The rate of recurrent VTE is higher in unprovoked VTE, 10% reported after 1 year compared to only 1% after 1 year in provoked VTE.'*
>
> *In studies for the indication of prevention of recurrent DVT and PE 'Subjects who discontinued active anticoagulant treatment (placebo arm) experienced symptomatic VTE recurrence rates of 7.1% (EINSTEIN EXT) and 8.8% (AMPLIFY EXT) over 12 months of study duration.'*

The sponsor has summed up the clinical rationale in the Clinical Overview with:

'Because bleeding is an important barrier to the use of long-term anticoagulation therapy for prevention of recurrent VTE in patients with unprovoked VTE, there remains an unmet medical need for this large group of patients.

For VTE treatment, apixaban has demonstrated efficacy that was non-inferior to enoxaparin/warfarin, and bleeding across all categories (unlike with rivaroxaban) that was significantly less frequent, including a 69% risk reduction in MB. In preventing a recurrent DVT or PE, apixaban was markedly superior to placebo in subjects with both unprovoked and provoked VTE, with a minimal increase in bleeding for the 2.5 mg BD dose compared to placebo.

The data from the apixaban VTE treatment clinical development program has demonstrated that it fills the recognized unmet medical need for treating and preventing recurrent VTE.'

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

- Five clinical pharmacology studies, including five that provided pharmacokinetic data and one that provided pharmacodynamic data.
- There were three studies evaluating the taste properties of oral formulations over a two year period (Study CV185061, Study CV185083 and Study CV185105)
- One population pharmacokinetic/ pharmacodynamic analyses.
- Two pivotal efficacy/safety studies.
- One dose-finding study.

Paediatric data

The submission did not include paediatric data.

A Paediatric Investigation Plan has been approved in the EU. The plan provides for pharmacokinetic, efficacy and safety studies in the paediatric population. There is also provision for a liquid formulation. However, the studies in children have been deferred until May 2015 at the earliest.

In the USA, the sponsor has full waivers for the following indications:

- Stroke prevention in non-valvular atrial fibrillation.
- VTE prevention in hip or knee replacement surgery.

Good clinical practice

Good Clinical Practice (GCP) appears to have been adhered to for all the clinical studies reported in the submission.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
	Bioequivalence - Single dose	Study B0661007
		Study CV185111
	Food effect	Study B0661019
		Study CV185091
PK interactions	Prasugrel	CV185073
Population PK analyses	Target population	Study PMAR-00312

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

The submission contained data relating to the development of a liquid formulation as part of a Paediatric Investigation plan. The data indicate that the liquid formulation is suitable for both oral and nasogastric administration and is bioequivalent to the commercially available tablets. Food affects the bioavailability of the potential liquid formulation and this should be considered should there be an application to register that formulation. The bioavailability of the 5 mg tablet also appears to be decreased by food and this should be considered along with any other data the Sponsor has previously submitted with regard to that formulation.

Apixaban bioavailability was unaltered by concomitant prasugrel.

The population PK study described the following covariate effects:

- Administration of apixaban in the evening resulted in a 46% decrease in absorption rate constant (k_a) relative to administration in the morning or afternoon.
- Apparent total renal clearance following oral administration (CL_R/F) accounted for approximately 42% of the total clearance and increased with increasing creatinine clearance rate (cCrCL) up to a breakpoint of 150 mL/min with a linear relationship.
- Non-renal clearance following oral administration (CL_{NR}/F) was reduced in older (for example, a 40 year old and 80 year old male VTE treatment subject would have 11% higher and 7% lower CL_{NR}/F relative to a reference VTE treatment male subject who is 60 years old; resulting in 7% higher and 4% lower CL/F, respectively.
- Female subjects had 22.3% lower CL_{NR}/F relative to male subjects, resulting in a 13% lower CL/F.
- Asian race and concomitant use of strong or moderate CYP3A4/p-gp inhibitors resulted in decreases of 16.8% and 20.3% in CL/F, respectively.
- The effect of baseline body weight on apparent total volume of distribution following oral administration (V_c/F) was less than directly proportional, with a 24% reduction for a 50 kg subject and a 20% increase for a 120 kg subject relative to the reference subject with a body weight of 85 kg.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 2 shows the studies relating to each pharmacodynamic topic.

Table 2. Submitted pharmacodynamic studies.

PD Interactions	Prasugrel	CV185073
Population PD and PK-PD analyses	Target population	Study PMAR-00312

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

The sponsor has developed a valid model to explain the plasma concentration response relationship for apixaban in the dose range proposed for the treatment of VTE and prevention of recurrent VTE. This model has been used to generate the data presented in Table 1 of the Product Information document. The data generated in Table 1 are a product of both the model and the patient characteristics. Hence there would be expected to be some variability in the distributions of the parameters, especially since they are presented at median, 5th and 95th centiles. However, there was less variability in the pharmacodynamic outcome variables. In the opinion of the clinical evaluator, the data as presented in Table 1 is preferable to a version that did not give an indication of the variability.

The sponsor has also demonstrated no clinically relevant PD interaction with prasugrel at the dose ranges used in clinical practice.

Dosage selection for the pivotal studies

Study CV185017 was an open label, randomised, parallel group Phase II study in subjects with acute proximal or extensive calf-vein thrombosis, comparing three dose levels of apixaban with conventional therapy (LMWH or fondiparinux and VKA). The study was conducted at 64 centres in 11 countries from December 2005 to February 2007.

Evaluator's conclusions on dose finding for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)

There are some issues with the dose finding study. The definition of symptomatic PE was not included in the protocol. The comparator group included subjects treated with tinzaparin, which is not available in Australia. However, in the opinion of the clinical evaluator, these issues do not detract from the value of the study as a dose finding study.

All three dosing apixaban regimens had similar efficacy. For convenience of dosing, the 20 mg once daily would have been the most advantageous dosing regimen to take into Phase III. However, this would have been a different dosing strategy compared to the dosing regimens for the currently approved indications (once daily as opposed to twice daily).

The dosing regimen actually taken into the Phase III study was: Apixaban 10 mg twice daily for 7 days, then 5 mg twice daily; placebo warfarin and enoxaparin.

Efficacy

Studies providing efficacy data

Two pivotal efficacy/safety studies were submitted:

- Study CV185056 investigating the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and
- Study CV185057 investigating the prevention of recurrent DVT and PE.

Evaluator's conclusions on efficacy

For treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)

Non-inferiority was demonstrated for apixaban in comparison with conventional treatment according to the predefined criteria. There were 59 events in the apixaban population and 71 in the enoxaparin/warfarin. The relative risk (RR) (95% confidence interval (CI)) for the primary efficacy outcome measure in the per-protocol population was 0.6611 (0.4243 to 1.0301) with the upper 95% CI being <1.8 (the criterion for non-inferiority. In the primary efficacy population (used as a sensitivity analysis) the RR (95% CI) was 0.8390 (0.2965 to 1.1802), and the risk difference (95% CI) was -0.0044 (-0.0128 to 0.0040). The secondary outcome measures were also supportive for similar efficacy of apixaban and conventional treatment.

The study design conformed to EMA guidance.

The study population included appropriate at-risk groups and also included elderly subjects. The comparator treatment was the accepted standard of care and dosing for enoxaparin was within commonly accepted treatment guidelines (Clexane® Australian approved Product Information). However, some treatment guidelines preferentially recommend 1.5 mg/kg once daily for the initial management of DVT and PE (New Zealand Formulary and the British National Formulary). The clinical evaluator does not consider that this would have affected the results of the trial. The warfarin dosing recommendations and the proportion of subjects within therapeutic international normalized ratio (INR) in the warfarin group (61%) was consistent with other clinical trials in this population and with the general population of patients treated with warfarin in Australia.[3] The outcome measures were in accordance with guidance.[4] The margin for non-inferiority was clinically relevant and was adhered to in the analysis. The statistical procedures were appropriate. The subgroup analysis was extensive and included clinically relevant groupings. The non-inferiority margin (the upper 95% CI for the RR being <1.8 and a risk difference <0.035) was clinically meaningful (representing a <80% increase in risk), and the results were comfortably within this margin (the upper 95% CI being 1.0301, that is, <4% increase in risk and <0.5% increase in incidence).

In the opinion of the clinical evaluator, the inclusion of the Kaplan Meier plot for time to first DVT or PE or VTE related death in the PI is appropriate because it presents primary outcome measure in a manner that informs prescribers of the magnitude, timing and durability of the treatment effect.

[3] Dignan R, Keech AC, Gebski VJ, Mann KP, Hughes CF; Warfarin SMART Investigators. Is home warfarin self-management effective? Results of the randomised Self-Management of Anticoagulation Research Trial. Int J Cardiol. 2013 Oct 15;168(6):5378-84.
[4] CPMP/EWP/6235/04 Guideline On Clinical Investigation Of Medicinal Products For The Prophylaxis Of Venous Thromboembolic Risk In Non-Surgical Patients.

For prevention of recurrent DVT and PE

Both apixaban treatment regimens were superior to placebo with no apparent difference in efficacy between the apixaban doses. There were 19 events in the apixaban 2.5 mg group, 14 in the 5 mg and 77 in the placebo. In addition, there were 13 imputed events in the apixaban 2.5 mg group, 20 in the 5 mg and 19 in the placebo. The RR (95% CI) compared to placebo for apixaban 2.5 mg was 0.3283 (0.2225 to 0.4844) and for apixaban 5 mg was 0.3615 (0.2475 to 0.5281). The Risk difference (95% CI) compared to placebo was -0.0779 (-0.1032 to -0.0526) for apixaban 2.5 mg and -0.0740 (-0.0997 to -0.0482) for apixaban 5 mg. All these hypothesis tests were significant to p <0.0001. The secondary efficacy outcome measures were also supportive of superiority.

The study design conformed to EMA guidance.

The study population included appropriate at-risk groups and also included elderly subjects. The comparator treatment was placebo which is appropriate because 'no treatment' is an accepted standard of care. The outcome measures were in accordance with guidance. The statistical procedures were appropriate. The subgroup analysis was extensive and included clinically relevant groupings.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- Major or clinically relevant non major bleeding (CRNMB) during the treatment period
- Adverse events (AEs), laboratory tests, vital signs and electrocardiograms (ECGs).

Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety alone as the primary outcome.

Dose-response and non-pivotal efficacy studies

The dose-response study provided safety data, as follows:

- Major and CRNMB.
- AEs, clinical laboratory evaluations and vital signs.

Other studies evaluable for safety only

Clinical pharmacology studies provided:

- AEs, clinical laboratory tests and ECGs

Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety alone as the primary outcome.

Patient exposure

In Study CV185017 there were 128 subjects exposed to apixaban 5 mg twice daily, 133 to 10 mg twice daily and 124 to 20 mg once daily, for up to 12 weeks.

In Study CV185056 there were 2676 subjects exposed to apixaban, with 244 exposed for more than 172 days. The median duration of exposure was 168 days.

In Study CV185057 there were 840 subjects exposed to apixaban 2.5 mg twice daily; with 58 (6.9%) exposed for >367 days and the median exposure was 360 days. There were 811 subjects exposed to apixaban 5 mg twice daily; with 38 (4.7%) exposed for >367 days and the median exposure was 360 days.

Safety issues with the potential for major regulatory impact

Bleeding related adverse events

In Study CV185017 bleeding AEs were reported in 15 (11.7) % subjects in the 5 mg twice daily group, 17 (12.8%) in the 10 mg twice daily, 13 (10.5%) in the 20 mg once daily and 24 (19.0%) in the Long-term low-molecular-weight heparin (LMWH)/ vitamin K antagonist (VKA) group. Adjudicated bleeding events were reported in 14 (10.9) % subjects in the 5 mg twice daily group, 17 (12.8%) in the 10 mg twice daily, 13 (10.5%) in the 20 mg once daily and 20 (15.9%) in the LMWH/VKA group. Adjudicated major bleeding events were reported in one (0.8) % subjects in the 5 mg twice daily group, none (0.0%) in the 10 mg twice daily, one (0.8%) in the 20 mg once daily and none (0.0%) in the LMWH/VKA group. There was one major bleeding episode in the 5 mg group (bloody pleural effusion), one in the 20 mg (intracerebral bleed) and none in the LMWH/VKA. There were no reports of intraocular haemorrhage. Major bleeding or CRNMB was reported in 11 (8.6) % subjects in the 5 mg twice daily group, six (4.5%) in the 10 mg twice daily, nine (7.3%) in the 20 mg once daily and 10 (7.9%) in the LMWH/VKA group. The event rate (95% CI) for major bleeding or CRNMB was 8.6 (4.4 to 14.9) % for 5 mg twice daily, 4.5 (1.7 to 9.6) % for 10 mg twice daily, 7.3 (3.4 to 13.3) % for 20 mg once daily and 7.9 (3.9 to 14.1) % for LMWH/VKA. The most common bleeding related AEs were haematuria, haematoma and epistaxis.

In Study CV185056, bleeding AEs were reported in 415 (15.5%) subjects in the apixaban group and 695 (25.8%) in the enoxaparin/warfarin. The commonest bleeding related AEs were: epistaxis 77 (2.9%) subjects in the apixaban group and 146 (5.4%) in the enoxaparin/warfarin; contusion, 49 (1.8%) subjects in the apixaban group and 97 (3.6%) in the enoxaparin/warfarin; haematuria, 46 (1.7%) subjects in the apixaban group and 106 (3.9%) in the enoxaparin/warfarin; menorrhagia 38 (1.4%) subjects in the apixaban group and 30 (1.1%) in the enoxaparin/warfarin; and haematoma 35 (1.3%) subjects in the apixaban group and 76 (2.8%) in the enoxaparin/warfarin. Superiority was achieved for apixaban over standard enoxaparin/warfarin treatment in adjudicated major bleeding: RR (95% CI) 0.3070 (0.1728 to 0.5452) p <0.0001. There were three subjects with intracranial bleeds in the apixaban group and six in the enoxaparin/warfarin. There were no subjects with intraocular bleeds in the apixaban group and two in the enoxaparin/warfarin. There were six subjects with gastrointestinal bleeds in the apixaban group and 17 in the enoxaparin/warfarin.

In Study CV185057, bleeding AEs were reported in 99 (11.8%) subjects in the apixaban 2.5 mg group, 124 (15.3%) in the apixaban 5 mg, and 78 (9.4%) in the placebo. The commonest bleeding AE was epistaxis: 13 (1.5%) subjects in the apixaban 2.5 mg group, 29 (3.6%) in the 5 mg and eight (1.0%) in the placebo. Gastrointestinal bleeds were reported in 22 (2.6%) subjects in the apixaban 2.5 mg group, 29 (3.6%) in the 5 mg and 13 (1.6%) in the placebo. There were no reports of intracranial haemorrhage. There were two reports of intraocular haemorrhage in the apixaban 2.5 mg group, none in the 5 mg and one in the placebo. In the follow-up period bleeding treatment-emergent AEs (TEAEs) were reported in six (0.7%) subjects in the apixaban 2.5 mg group, six (0.7%) in the apixaban 5 mg, and nine (1.1%) in the placebo.

Neurological and cardiovascular events of special interest

In Study CV185056, neurological AEs were reported in 70 (2.6%) subjects in the apixaban group and 85 (3.2%) in the enoxaparin/warfarin. The most commonly reported

neurological AE was paraesthesia, reported in 20 (0.7%) subjects in the apixaban group and 40 (1.5%) in the enoxaparin/warfarin. Other events of special interest were uncommon and there was no significant increase in relative risk for any of the events.

In Study CV185057 neurological TEAEs were reported in 23 (3.0%) subjects in the apixaban 2.5 mg group, 21 (2.6%) in the apixaban 5 mg, and 26 (3.1%) in the placebo. There was no increase in the risk of thrombotic events or thrombocytopenia with apixaban.

Post-marketing data

No post-marketing data were included in the submission.

Evaluator's conclusions on safety

Apixaban has a similar adverse effects profile to enoxaparin/warfarin but appears to have a decreased risk of bleeding related AEs with the dose regimen intended for the proposed new indications. Overall in Study CV185056, TEAEs were reported in 1795 (67.1%) subjects in the apixaban group and 1923 (71.5%) in the enoxaparin/warfarin. Death was reported in 37 (1.4%) subjects in the apixaban group and 44 (1.6%) in the enoxaparin/warfarin. Serious AEs (SAEs) were reported in 417 (15.6%) subjects in the apixaban group and 410 (15.2%) in the enoxaparin/warfarin.

In comparison with placebo, when used for prevention of recurrent DVT and PE, apixaban had a similar overall rate of AEs in comparison with placebo but there were more bleeding related AEs with apixaban and more VTE with placebo. In Study CV185057, TEAEs were reported in 596 (71.0%) subjects in the apixaban 2.5 mg group, 542 (66.8%) in the apixaban 5 mg, and 606 (73.4%) in the placebo. Death was reported for three (0.4%) subjects in the apixaban 2.5 mg group, four (0.5%) in the apixaban 5 mg, and ten (1.2%) in the placebo. SAEs were reported in 112 (13.3%) subjects in the apixaban 2.5 mg group, 107 (13.2%) in the apixaban 5 mg, and 158 (19.1%) in the placebo. DVT was reported as a SAE for three (0.4%) subjects in the apixaban 2.5 mg group, nine (1.1%) in the 5 mg and 40 (4.8%) in the placebo; and PE was reported as a SAE for five (0.6%) subjects in the apixaban 2.5 mg group, three (0.3%) in the 5 mg and 20 (2.4%) in the placebo.

Bleeding related AEs occurred at a lesser frequency with apixaban, using the dosing regimen intended for treatment of DVT and pulmonary embolism PE, in comparison with enoxaparin/warfarin. In Study CV185056, bleeding AEs were reported in 415 (15.5%) subjects in the apixaban group and 695 (25.8%) in the enoxaparin/warfarin. Superiority was achieved for apixaban over standard enoxaparin/warfarin treatment in adjudicated major bleeding: RR (95% CI) 0.3070 (0.1728 to 0.5452) p <0.0001.

There was clearly an increased risk of bleeding related AEs in comparison with placebo, but this risk was less than the increased risk of VTE in the placebo group.

In the opinion of the clinical evaluator, the pattern of bleeding related adverse events is consistent with that observed with the currently approved indications for apixaban.

The sponsor has stated in the PI that no dose adjustment is required in the elderly. This statement is supported by the data.

First round benefit-risk assessment

First round assessment of benefits

Benefits for treatment DVT and PE

Non-inferiority was demonstrated for apixaban in comparison with conventional treatment according to the predefined criteria. There were 59 events (symptomatic, recurrent VTE [nonfatal DVT or nonfatal PE] or VTE-related death) in the apixaban population and 71 in the enoxaparin/warfarin. The RR (95% CI) for the primary efficacy outcome measure in the per-protocol population was 0.6611 (0.4243 to 1.0301) with the upper 95% CI being <1.8 (the criterion for non-inferiority). In the primary efficacy population the RR (95% CI) was 0.8390 (0.2965 to 1.1802), and the risk difference (95% CI) was -0.0044 (-0.0128 to 0.0040). The secondary outcome measures were also supportive for similar efficacy of apixaban and conventional treatment.

Benefits for prevention of recurrent DVT and PE

Both apixaban treatment regimens were superior to placebo with no apparent difference in efficacy between the apixaban doses. There were 19 events (symptomatic, recurrent VTE [nonfatal DVT or nonfatal PE] or all-cause death) in the apixaban 2.5 mg group, 14 in the 5 mg and 77 in the placebo. In addition, there were 13 imputed events in the apixaban 2.5 mg group, 20 in the 5 mg and 19 in the placebo. The RR (95% CI) compared to placebo for apixaban 2.5 mg was 0.3283 (0.2225 to 0.4844) and for apixaban 5 mg was 0.3615 (0.2475 to 0.5281). The Risk difference (95% CI) compared to placebo was -0.0779 (-0.1032 to -0.0526) for apixaban 2.5 mg and -0.0740 (-0.0997 to -0.0482) for apixaban 5 mg. All these hypothesis tests were significant to p <0.0001. The secondary efficacy outcome measures were also supportive of superiority.

The sponsor has chosen the lower dose regimen to be recommended in clinical practice. In the opinion of the clinical evaluator this is appropriate as it minimises exposure to apixaban without compromising efficacy.

First round assessment of risks

When used for the treatment of DVT and PE apixaban has a similar adverse effects profile to enoxaparin/warfarin but appears to have a decreased risk of bleeding related AEs with the dose regimen intended for the proposed new indications. Overall, in Study CV185056, TEAEs were reported in 1795 (67.1%) subjects in the apixaban group and 1923 (71.5%) in the enoxaparin/warfarin. Death was reported in 37 (1.4%) subjects in the apixaban group and 44 (1.6%) in the enoxaparin/warfarin. SAEs were reported in 417 (15.6%) subjects in the apixaban group and 410 (15.2%) in the enoxaparin/warfarin.

In comparison with placebo, when used for prevention of recurrent DVT and PE, apixaban had a similar overall rate of AEs in comparison with placebo but there were more bleeding related AEs with apixaban and more VTE with placebo. In Study CV185057, TEAEs were reported in 596 (71.0%) subjects in the apixaban 2.5 mg group, 542 (66.8%) in the apixaban 5 mg, and 606 (73.4%) in the placebo. Death was reported for three (0.4%) subjects in the apixaban 2.5 mg group, four (0.5%) in the apixaban 5 mg, and ten (1.2%) in the placebo. SAEs were reported in 112 (13.3%) subjects in the apixaban 2.5 mg group, 107 (13.2%) in the apixaban 5 mg, and 158 (19.1%) in the placebo. DVT was reported as a SAE for three (0.4%) subjects in the apixaban 2.5 mg group, nine (1.1%) in the 5 mg and 40 (4.8%) in the placebo; and PE was reported as a SAE for five (0.6%) subjects in the apixaban 2.5 mg group, three (0.3%) in the 5 mg and 20 (2.4%) in the placebo.

The previously identified risks with apixaban are bleeding related AEs and potentially hepatic AEs. Other than these risks, the profile of AEs indicated by the PI and from Study CV185057 is similar to that of placebo. With regard the proposed new indications:

- Bleeding related AEs occurred at a lesser frequency with apixaban, using the dosing regimen intended for treatment of DVT and pulmonary embolism PE, in comparison with enoxaparin/warfarin. In Study CV185056, bleeding AEs were reported in 415 (15.5%) subjects in the apixaban group and 695 (25.8%) in the enoxaparin/warfarin. Superiority was achieved for apixaban over standard enoxaparin/warfarin treatment in adjudicated major bleeding: RR (95% CI) 0.3070 (0.1728 to 0.5452) p <0.0001.
- When used for the prevention of recurrent DVT and PE, there was clearly an increased risk of bleeding related AEs in comparison with placebo but this risk was less than the increased risk of VTE in the placebo group.

The risks of intracranial, gastrointestinal and intraocular bleeds appear to be similar to that identified in the RMP.

Elevation of liver enzymes and hepatic AEs appear to occur at a lesser rate than for warfarin. However, it is not clear whether these AEs are more common with apixaban than with placebo. In the opinion of the clinical evaluator, it is appropriate that liver injury should remain an Important Potential Risk in the Risk Management Plan (RMP).

Although not identified in the clinical data, issues that may arise in clinical practice include lack of practical laboratory methods for monitoring effect, lack of an antidote to reverse effect in an emergency, lack of guidelines for switching to alternative treatments, and the potential for decreased adherence to a twice daily dosing regimen compared to a once daily regimen.

First round assessment of benefit-risk balance

The benefit-risk balance of Eliquis (apixaban), given the proposed usage, is favourable. For the treatment of DVT and PE, apixaban has similar efficacy to enoxaparin/warfarin but a lower risk of bleeding related AEs. For the prevention of recurrent DVT and PE, the reduction in DVT, PE and all-cause death with apixaban more than compensates for the increased risk of bleeding related AEs. The extended treatment of recurrent VTE is justified by the reduction in risk of DVT and PE in the treated population.

First round recommendation regarding authorisation

The clinical evaluator has no objection to the approval of Eliquis (apixaban) for the following additional indications:

> *Eliquis is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).*
>
> *Eliquis is indicated for the prevention of recurrent DVT and PE.*

However, there are some subgroups of patients not included in the pivotal studies to whom the results could not be extrapolated. Consideration should be given to excluding these patients from treatment with apixaban. These patients include: haemodynamically unstable patients, patients with massive PE, patients with multiple DVT/PE or patients with an underlying pro-coagulant disorder.

Clinical questions

Pharmacokinetics

1. With regard to the effect of food on the bioavailability of the 5 mg tablet demonstrated in Study CV185111, does the sponsor have any additional information that demonstrates no effect of food on the bioavailability of this formulation?

Pharmacodynamics

2. Please provide summary tabulations for the results of activated partial thromboplastin time (aPTT) from Study CV185073. The tabulations should include mean, median, standard deviation (SD), minimum, maximum, for Day 1, Day 6 and for change from baseline for each of the study groups.

Efficacy

3. Were the formulations of apixaban and comparator used in the pivotal studies the same as those available in Australia?
4. What proportion of patients in Study CV185057 with DVT also had a PE?
5. Please clarify and list the symptoms used to define symptomatic DVT and PE.
6. Please explain why apixaban should not undergo routine, initial or intermittent laboratory monitoring either by plasma concentration monitoring or by using anticoagulation assays such as anti-factor Xa for the proposed indications or populations:
    a. Discuss if there are any special circumstances/populations where laboratory monitoring could be beneficial, such as the peri-operative setting, acute coronary syndrome (where interventions such as Percutaneous coronary intervention (PCI or the administration of thrombolytic agents are under consideration), in the event of bleeding or recurrent thrombosis, elderly patients, deteriorating hepatic or renal function, when parenteral anticoagulants are considered, concomitant use of potentially interacting medications, in the event of overdose or to assess possible poor compliance?
    b. Discuss whether new patients or patients switching to apixaban could benefit from laboratory monitoring.
    c. Discuss whether any changes to the PI are proposed as a result of the above?
7. Has there been any modelling or analysis of apixaban plasma concentrations or anticoagulation assay results in the proposed indications or populations to:
    a. Investigate the potential role for any laboratory monitoring?
    b. Investigate a potentially improved efficacy and/or safety profile for apixaban, or dose adjustment?
    c. If there has been any modelling or analysis undertaken for the above questions, please submit the reports to the TGA.
8. Have there been any discussions with the FDA, EMA or Health Canada regarding the laboratory monitoring of apixaban in relation to the new indications proposed?
9. Are there any clinical trials completed, underway or being proposed or discussed for apixaban that include laboratory monitoring as part of the study design, for example trials that compare monitored apixaban with unmonitored apixaban or with warfarin?
10. Is the sponsor proposing to include further information in the Product Information for apixaban regarding plasma concentrations, or anticoagulant activity that may be associated with an increased risk of bleeding, or regarding a therapeutic range, or any form of laboratory monitoring in relation to the proposed indications?

Safety

11. In Study CV185056 did any of the four subjects in the apixaban group with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN) and total bilirubin >2 times the ULN on the same date fulfil the criteria for Hy's Law? What other medical conditions or concomitant treatments would have explained these abnormalities in these individual subjects?
12. Please provide an update on the progress of the drug development program for the antidote.

Second round evaluation of clinical data submitted in response to questions

Details of the sponsor's responses and the clinical evaluator's comments on these responses are detailed in Attachment 2 Extract from the Clinical evaluation report.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of apixaban in the proposed usage are unchanged from those identified in the First round evaluation.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of apixaban in the proposed usage in addition to those identified in in the First round evaluation are: drug induced liver injury. The additional data submitted in response to the TGA's request for further information included one case of drug induced liver injury. In the opinion of the clinical evaluator, transient elevation of liver enzymes should be listed as an important identified risk for all indications of apixaban. It is also appropriate that liver injury remains an Important Potential Risk.

Second round assessment of benefit-risk balance

The risk-benefit balance remains the same as that stated in in the First round evaluation. The benefit-risk balance of Eliquis (apixaban), given the proposed usage, is favourable. For the treatment of DVT and PE, apixaban has similar efficacy to enoxaparin/warfarin but a lower risk of bleeding related AEs. For the prevention of recurrent DVT and PE, the reduction in DVT, PE and all-cause death with apixaban more than compensates for the increased risk of bleeding related AEs. The extended treatment of recurrent VTE is justified by the reduction in risk of DVT and PE in the treated population.

Second round recommendation regarding authorisation

The clinical evaluator has no objection to the approval of Eliquis (apixaban) for the following additional indications:

> *Eliquis is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).*
>
> *Eliquis is indicated for the prevention of recurrent DVT and PE.*

However, there are some subgroups of patients not included in the pivotal studies to whom the results could not be extrapolated. Consideration should be given to excluding these patients from treatment with apixaban. These patients include: haemodynamically

unstable patients, patients with massive PE, patients with multiple DVT/PE or patients with an underlying pro-coagulant disorder.

V. Pharmacovigilance findings

Risk management plan

For this submission the sponsor has provided the apixaban EU-RMP (version 12, document date 21 October 2013 with data lock point 17 May 2013) and an Australia specific annex (ASA) (version 5, document date 17 March 2014). This format replaces the Core Company RMP (CCRMP) evaluated for the last submission for the non-valvular atrial fibrillation (NVAF) indication.

The evaluator notes that provision of the EU-RMP and ASA is the TGA's preferred option as described in the RMP Questions and Answers document.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 3.

Table 3: Summary on Ongoing safety concerns

Important identified risk (VTE prevention, AF, VTE Treatment and Prevention of Recurrent VTE)	• Bleeding
Important identified risk (VTE prevention)	• Transient elevation of liver tests
Important potential risk (AF, VTE Treatment and Prevention of Recurrent VTE)	• Liver Injury
Missing information	• Paediatrics • Pregnant or lactating women • Severe hepatic impairment • Severe renal impairment • Black/African American population • Hip fracture surgery • AF with valvular disease • Patients with prosthetic heart valve • Haemodynamically unstable PE patients • Non-Caucasian and non-Asian ethnicity • Off-label use

The ASA includes additional safety concerns not listed in the EU-RMP as follows:

Important potential risks	• GI Bleeding in those ≥ 80 years for AF • Ocular bleeding in those ≥ 80 years for AF
Missing information	• Management of severe bleeding • Use in the very elderly (≥75 years) for VTEp • Overdose/Coagulation monitoring

The above safety concerns were included in the ASA based on TGA requirements resulting from previous evaluations. The sponsor has provided the following statement in the ASA regarding these additions:

> *The sponsor wishes to clarify that it does not consider these additions to represent activities that are necessary to ensure patient safety and proper use of the product based on available evidence.*

Pharmacovigilance plan

Routine pharmacovigilance is proposed to monitor the specified important identified and potential risks and missing information. Two drug utilisation studies are ongoing in Sweden and the Netherlands. No other additional pharmacovigilance activities are proposed.

Risk minimisation activities

The proposed risk minimisation plan includes routine activities (product labelling) to mitigate the specified risks. A patient and healthcare professional educational program is proposed as additional risk minimisation for the important identified and potential risks.

Reconciliation of issues outlined in the RMP report

Table 4 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the RMP evaluator and the evaluation of the sponsor's responses.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety	No specific response provided.	Not applicable (n/a).

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.		
2. It is noted that a dose reduction from 5 mg twice daily to 2.5 mg twice daily is recommended for the non-valvular atrial fibrillation (NVAF) indication in patients with at least two of the following: ≥ 80 years, body weight ≤ 60 kg or serum creatinine ≥ 133 µmol/L. No dose reduction is recommended for the proposed indications in these situations. This disparity is highlighted to the Delegate.	*In discussing the recommendation for appropriate dosing, evaluation of the population receiving therapy is of critical importance. Venous Thromboembolism (VTE) and Non-Valvular Atrial Fibrillation (NVAF) are different clinical situations, with different patient populations that lead to different risk-benefit considerations. As justified below, the sponsor maintains that the posology should match what was studied in our program because a highly favourable benefit-risk profile was demonstrated in both trials with this posology and because of the clinical importance of not under dosing patients with active clots and/or a high risk of recurrent VTE.*	Notwithstanding the justification provided, the disparity in dose reduction instructions between indications is subject to approval by the Delegate.
3. The approved VTE prevention indication specifies for use in an adult population only. It is highlighted to the Delegate that this qualification is missing in the proposed indications even though there exists potential for off-label use in a paediatric population and apixaban is not recommended for paediatric use.	*The sponsor has updated the Product Information to specify the use in adult population only.*	This is acceptable from a RMP standpoint.
4. The sponsor is requested to confirm why the important identified risk *Transient elevation of liver tests* still remains only attributed to the VTE prevention indication. It is noted the following statement appears in the EU-RMP. *Typically transient, asymptomatic, perioperative*	*Please note the statement from the RMP that is quoted in the question above should read 'Typically transient, asymptomatic, ~~perioperative~~ elevations of LFTs were reported, with most elevations resolving on blinded study drug or after discontinuation for the AF and VTE treatment Phase 3 studies'. The error will be corrected.*	The sponsor's justification is not accepted. This recommendation is maintained to the Delegate and supported by a separate recommendation in the second round clinical evaluation report. Currently 'liver function test abnormal' is listed in the PI as an adverse event

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
elevations of LFTs were reported, with most elevations resolving on blinded study drug or after discontinuation for the AF and VTE treatment Phase 3 studies. Given this statement it is recommended that the identified risk *Transient elevation of liver tests* is amended to incorporate all indications.	The sponsor has provided justification against incorporating all indications for the identified risk 'transient elevation of liver tests', arguing that such transient elevations were considered to be related to surgical factors.	related to the VTE prophylaxis indication. The delegate may wish to consider altering PI statements as appropriate based on this recommendation.
5. Similarly for missing information *Use in the very elderly (≥75 years) for VTEp* the sponsor should provide a justification as to why this risk should not incorporate all indications.	The sponsor has provided the requested justification.	The sponsor's justification is acceptable from a RMP standpoint.
6. No specific pharmacovigilance activities relating to the proposed indications are detailed in the EU-RMP or in the ASA. The sponsor is requested to confirm whether they intend to undertake any post-marketing studies such as a patient registry or other surveillance of the product's safety in the populations proposed for registration.	*The sponsor confirms there is no intention to undertake any post-marketing studies such as a patient registry or other surveillance of the product's safety in the populations proposed for registration that would be in addition to standard Pharmacovigilance practices.*	The sponsor's response is noted.
7. The sponsor is requested to detail if they plan on conducting a PFP for the DVT/PE indications if approved.	*The sponsor is not planning to conduct a PFP for the DVT/PE treatment indications.*	The sponsor's response is noted.
8. The educational materials (Prescriber Guide, On-line Learning Module and Patient Alert Card) should be updated to include information specific to the proposed indications. The updated versions of these materials should be provided to the TGA for	*The Patient Alert Card will be updated to include information specific to the DVT/PE indications if approved.* *The sponsor will not be updating the On-line learning Module content to include information specific to the proposed indications because its content is identical to the Prescriber Guide,*	The TGA notes the sponsor's commitments to provide any updated educational materials to the TGA prior to launch. The evaluator takes this response to mean that the on-line module will be no longer available and the Prescriber guide

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
review.	*which will be updated, and the Prescriber Guide will be available on-line. This will avoid duplication of tools.* *The sponsor commits to providing the updated Prescriber Guide and Patient Alert Card to the TGA for review upon completion of the PI negotiations and prior to launch of the product for the approved indications.*	will be the primary educational tool for health professionals. If this is not the case, the sponsor should update the module in line with other educational materials to avoid disparity.
9. Regarding the Australian-specific missing information *Management of severe bleeding* and *Overdose and coagulation monitoring* the sponsor is requested to provide an update to the TGA on the development of an assay to effectively monitor the anticoagulation effect of apixaban.	The sponsor has provided the requested update. Development of an anti-Xa assay appears to be undergoing validation. According to the sponsor '*it is anticipated that most of the large coagulation diagnostic companies will have CE versions of these assays available by 2015-2016'*.	The sponsor's update is noted.
10. Similarly the sponsor should provide an update to the TGA on the development of an antidote to apixaban.	*The sponsor has referred the RMP evaluator to their response to a similar question asked by the clinical evaluator.* *In their response the sponsor has outlined their strategy for developing an antidote.*	The sponsor's approach to antidote development is acceptable from a RMP standpoint.
11. It was noted in the apixaban Periodic Safety Update Report (PSUR) (18 May 2013-17 November 2013) that the overdose section of the Company Core Data Sheet (CCDS) was updated to include the following text: *Hemodialysis is unlikely to be an effective means of managing apixaban overdose.* The sponsor should provide justification as to why this has not been translated to the overdose section of the proposed PI.	*The sponsor has updated the Product Information in line with the text approved with a previous submission on 16 June 2014.*	This is acceptable from a RMP standpoint subject to final consideration by the Delegate.
12. Co-administration of strong inducers of both CYP3A4 and P-gp may lead to reduced plasma	*The sponsor has updated the Product Information in line with the recommendation in the EU*	This is acceptable from a RMP standpoint subject to final consideration by the

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
concentrations of apixaban. This is particularly important where efficacy is imperative (that is, the proposed therapeutic indications). The related changes to the CCDS appear to have been incorporated into the proposed PI *interactions with other medicines* section. It is drawn to the Delegate's attention that perhaps this point should be made more clearly as a precautionary statement.	*product information.*	Delegate.
13. *Haemodynamically unstable PE patients* is a new item of missing information directly relating to the proposed indications. The approved US product label includes a related precaution. It is recommended that a similar precaution is included in the Australian PI as routine risk minimisation for the missing information *Haemodynamically unstable PE patients*. This should be appropriately reflected in the EU-RMP and/or ASA.	*The sponsor has updated the Product Information.*	This is acceptable from a RMP standpoint subject to final consideration by the Delegate.
14. The EU and US product labels include a precaution regarding temporary discontinuation of apixaban and the associated increased risk of thrombosis. The corresponding precaution in the Australian PI focuses more on the increased risk of stroke when transitioning from apixaban to warfarin. Consideration should be made for inclusion of similar advice to the EU Summary of Product Characteristics (SmPC) regarding temporary discontinuation in general.	*The sponsor has updated the Product Information in line with the recommendation in the US product information.*	This is acceptable from a RMP standpoint subject to final consideration by the Delegate.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
15. The proposed PI contains advice on switching between apixaban and other anticoagulants. It is noted that the US product label contains the following useful statement regarding measuring INR when switching from apixaban to warfarin: *Eliquis affects INR, so that INR measurements during coadministration with warfarin may not be useful for determining the appropriate dose of warfarin.* It is recommended that a similar statement is included in the Australian PI.	*The sponsor has updated the Product Information.*	This is acceptable from a RMP standpoint subject to final consideration by the Delegate.
16. Changes made to the PI in response to the evaluation process should be reflected in the Consumer Medicine Information (CMI) as appropriate.	*The sponsor provides an assurance that any changes made to the PI in response to the evaluation process will be reflected in the CMI.*	This is acceptable.

Summary of recommendations

It is considered that the sponsor's response to the TGA has not adequately addressed all issues identified in the RMP evaluation report. There is one outstanding issue. There are additional recommendations (see below).

Outstanding issues

RMP evaluation report

After considering the sponsor's response, the following recommendation is maintained from the RMP evaluation report:

- It is recommended that the identified risk '*Transient elevation of liver tests'* is amended to incorporate all indications.

This recommendation is supported by statements in the clinical evaluation report. Currently 'liver function test abnormal' is listed in the PI as an adverse event related to the VTE prophylaxis indication. The Delegate may wish to consider altering PI statements as appropriate based on this recommendation.

There are additional recommendations based on Advisory Committee on the Safety of Medicines (ACSOM) advice below.

Advice from ACSOM

Additional recommendations based on ACSOM advice

The ACSOM advised that the following safety concerns should be included for consideration in the RMP:

- patients with extremes of body weight, cancer-related venous thromboembolic events (VTE) and provoked VTE[5];
- patients requiring rapid reversal of effect (for example, semi-urgent surgery); and
- drug-drug interactions.

These are foreseeable clinical situations for which there is a paucity of information regarding apixaban treatment. Therefore the evaluator recommends that the above safety concerns are included in the RMP as missing information unless the sponsor can provide sufficient justification for not doing so. Pharmacovigilance and risk minimisation activities should be assigned to these items of missing information. At this time routine pharmacovigilance and risk minimisation would be considered sufficient. It is noted that the draft PI already includes information on the impact of body weight on apixaban exposure.

Additional information relating to ACSOM advice

On 19 December 2014 the TGA sought further information from the sponsor via a request relating to the following ACSOM advice:

> *The committee noted there is no published therapeutic range for apixaban plasma monitoring, or data that linked the pharmacokinetic (PK)/pharmacodynamic (PD) properties with safety or efficacy. The committee advised that it would be useful to request the sponsor to provide this information, as well as information on apixaban plasma levels in patients who experienced serious adverse events in the clinical trials.*

According to the response (dated 19 January 2015) the sponsor confirmed that '*PK and anti-FXa activity data were collected in a small subset of subjects at pre-determined visits and were not prospectively collected at the time of bleeding or clotting events in the Phase 3 studies submitted for the respective indications and there are no PK data available for post-marketing reports of these adverse events*'.

Further, regarding investigation of the potential role of laboratory monitoring, the sponsor stated that '*analyses have revealed a wide overlap in apixaban exposure and anti-FXa activity values for those who did and did not experience safety (a composite bleeding of major and clinically relevant non-major) or efficacy (VTE or VTE-related death) events…No discernable threshold levels could be identified that would predict better or worse safety or efficacy outcomes for individual patients. Thus, there is no evidence that adjusting doses of apixaban using apixaban plasma concentrations or anti-FXa activity would improve the efficacy/safety profile of apixaban for VTE Treatment patients*'.

The sponsor's response has been considered by the evaluator in the context of this application. It appears that the sponsor has confirmed that they do not currently hold evidence which demonstrates the effect of monitoring on the safety of the product.

[5] Provoked DVT or PE in a patient with an antecedent (within 3 months) and transient major clinical risk factor for venous thromboembolism (VTE) e.g. surgery, trauma, significant immobility (bedbound, unable to walk unaided or likely to spend a substantial proportion of the day in bed or in a chair), pregnancy or puerperium, or in a patient who is having hormonal therapy (oral contraceptive or hormone replacement therapy). National Institute for Health and Care Excellence (NICE) Clinical Guideline (CG144) (June 2012) <http://www.nice.org.uk/guidance/cg144/chapter/guidance>

Key changes to the updated RMP

EU-RMP (version 12, document date 21 October 2013, data lock point 17 May 2013) and Australian Specific Annex (version 5, document date 17 March 2014) has been superseded by:

> EU-RMP (version 13, document date 7 July 2014, data lock point 17 May 2013) and Australian Specific Annex (version 6, document date 13 November 2014).

Key changes from the version evaluated in the first round are summarised below.

Table 5: Key changes to the EU-RMP and ASA

Summary of key changes between EU-RMP version 12/ASA version 5 and EU-RMP version 13/ASA version 6	
Safety specification	• Nil significant change
Pharmacovigilance activities	• Nil significant change
Risk minimisation activities	• Nil significant change
ASA	• Updated to reflect recent amendments to the Australian labelling document • Updated to list differences between the Australian and European labelling documents. • Updated to reflect additional risk minimisation measures for the different indications. • Updated to reflect completion of the five quarterly distribution reports

The evaluator has no objection to the above changes.

Suggested wording for conditions of registration

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

> *EU-RMP (version 13, document date 7 July 2014, data lock point 17 May 2013) and Australian Specific Annex (version 6, document date 13 November 2014) to be revised to the satisfaction of the TGA, must be implemented (see outstanding issues above).*

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The sponsor sought approval for a new pack size of 28 tablets for the apixaban 5 mg tablets in order to provide the 7 day dose of 10 mg twice daily recommended for the initial

treatment of DVT and/or PE. The quality evaluator had no objections to this additional presentation.

Nonclinical

The nonclinical evaluator did not have any objections to the proposed extension of indication. Five nonclinical studies were provided in the submission. Activated charcoal reduced apixaban in dog and rat studies and increased excretion of apixaban in the faeces at the expense of urine. In a dog study apixaban was dialyzable, lowered the C_{max} of apixaban (although not statistically significantly) but did not affect plasma AUC. Rat and dog studies demonstrated the major excretory pathways for unchanged and metabolised apixaban included urine, faeces and bile in rats and dog models. The excretion studies also indicated that intestinal and enteroenteric recirculation are facilitated by intestinal efflux transporters. There were no studies specifically studying the efficacy of apixaban in DVT or PE.

Clinical

The clinical evaluator has recommended approval for apixaban for the indication of:

> *Eliquis is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).*
>
> *Eliquis is indicated for the prevention of recurrent DVT and PE.*

The evaluator has recommended acceptance of the sponsor's dosage for the treatment of DVT and PE of:

> *The recommended dose of Eliquis is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily.*

The evaluator has also recommended acceptance of the sponsor's dosage for the prevention of recurrent DVT and PE of:

> *The recommended dose of Eliquis is 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE.*

The clinical dossier included the following data:

- 5 clinical pharmacology studies: 5 provided pharmacokinetic data and one provided pharmacodynamic data
- 3 studies evaluating the taste properties of oral formulations
- 1 population PK/PD analysis
- 1 Phase II study dose finding study
- 2 Phase III studies
- Integrated summaries of clinical pharmacology, efficacy and safety

Pharmacology

Apixaban is 50% bioavailable and exhibits linear pharmacokinetics across the approved dose range. The time to peak plasma concentration (T_{max}) is at 3 to 4 hours and it is 87% plasma protein bound. Apixaban is mainly metabolized by cytochrome P450 isozyme CYP3A4, is a substrate of P-glycoprotein and breast cancer receptor protein (BCRP). It is approximately 27% renally excreted, with the remainder from biliary and direct intestinal excretion and the half-life is about 12 hours.

The findings from the pharmacology studies are as follows:

- Three modified release 5 mg formulations compared with the approved 5 mg immediate release formulation did not demonstrate bioequivalence of two formulations, and the third, although bioequivalent did not behave as a modified release formulation.
- Studies of the taste properties of candidate oral formulations of apixaban revealed the unsweetened, unflavoured formulations were unpalatable. An orange flavoured solution was developed and the palatability of the solution after 1 and 2 years of storage was considered acceptable by the adult testers.
- A 5 mg dose of the oral solution and a crushed 5 mg tablet suspended in a 5% dextrose water solution when given by nasogastric tube were bioequivalent (ratio (90% CI) crushed tablet: oral solution for AUC_{0-inf} was 0.950[0.905 to 0.997]).
- Single 5 mg doses of an oral solution given by nasogastric tube or by mouth were bioequivalent (ratio (90% CI) nasogastric: oral 0.968 (0.9226 to 1.011) for $AUC_{0\ inf}$ and 0.953 (0.873 to 1.040) for C_{max}.
- Single 5 mg doses of the oral solution given with nasogastric feeds and in the fasted state were not bioequivalent (ratio (90% CI) fed: fasted for AUC_{0-inf} was 0.813 (0.766 to 0.863)). The bioavailability of a standard commercial 5 mg tablet was also reduced by food (AUC_{0-inf} reduced by 20%, C_{max} reduced by 15%).
- The apixaban exposures from a single 5 mg dose of the oral solution administered nasogastrically or orally by syringe when given with infant formula were equivalent but the C_{max} was decreased by 20% with nasogastric dosing.
- The oral bioavailability of apixaban was similar when co-administered with prasugrel given as a 60 mg loading followed by 10 mg daily for 4 days. Although the AUC was similar there was a 12% reduction in the C_{max} of prasugrel. However, 90% of subjects had more than 50% inhibition in platelet aggregation after the loading dose. There was no independent effect of apixaban on ADP-induced platelet aggregation and no effect of prasugrel on the anti-FXa activity of apixaban, INR or prothrombin time (PT).
- The population PK/PD modelling based on data from the clinical studies in this submission showed fractional renal clearance of about 42% of the total clearance and had a linear relationship with estimated CrCL. Total clearance did not vary greatly with age compared to the reference 60 year old subject. Females had a13% lower fractional clearance than males. Asian race resulted in a decrease of 16.8% CL/F and strong or moderate CYP3A4 or P-gp inhibitors resulted in a 20.3% Cl/F.
- The population PK/PD relationship was modelled and found that there was an apparent linear relationship between predicted plasma concentration and anti-FXa activity and that there was no statistically significant relationship between major bleeding and clinically-relevant non-major bleeding or VTE or VTE-related death.

Efficacy

Study 185017

This was a Phase II open-label, randomised, parallel group study in 520 subjects with a confirmed acute proximal or extensive calf-vein thrombosis but without symptomatic PE, comparing 5 mg BD, 10 mg BD and 20 mg once daily (QD) dose of apixaban with conventional therapy (LMWH or fondaparinux followed by vitamin K antagonist (VKA) (starting no longer that 48 hours after randomisation)). The LMWH doses could be tinzaparin 175 IU/kg once daily subcutaneously (SC), enoxaparin 1.5 mg daily SC or enoxaparin 1.0 mg/kg twice daily SC. Fondaparinux was dosed at 7.5 mg daily SC unless

body weight was < 50 kg (5 mg SC) or > 100 kg (10 mg SC). The apixaban subjects were blinded to the dose. There were 12 weeks of treatment followed by a 30 day follow-up.

Subjects were excluded if they were pregnant or breast feeding; had a thrombectomy, caval filter or use of a fibrinolytics agent to treat the current episode of DVT; more than 24 hours of pre-randomisation therapy with Unfractionated heparin (UFH), LMWH or fondaparinux or more than a single starting dose of VKA; active bleeding; creatinine clearance < 30 mL/min, impaired liver function test (LFT) (ALT>3 times ULN); use of VKA for indications other than DVT; use of aspirin > 165 mg /day; or uncontrolled hypertension or bacterial endocarditis. The use of a combination of clopidogrel (75 mg) and aspirin, or azole antifungals, human immunodeficiency virus (HIV) protease inhibitors or macrolide antibiotics were not permitted and were required to be discontinued 2 weeks before study participation. Premature discontinuations occurred in 13.1% of the 5 mg BD group, 9.0% of the 10 mg BD group, 16.4% of the 20 mg daily group and 7.8% of the LMWH/VKA group, mostly due to adverse events (5.6% overall, 6.4% in the apixaban groups).

The subjects were predominantly White (96.3%), male (62.1%), with a median age of 59 (interquartile range (IQR) 48.0 to 71.0) years (37.5% ≥ 65 years). The median duration of symptoms was 6.0 days (IQR 4 to 11) most DVTs were on the left side (5701%), were the first reported VTE event (75%), were unprovoked [were not associated with thrombophilic conditions (94.2%), had no active cancer (92.7%), had no trauma or surgery within 3 months in (78.3%)]. The DVT outcomes were measured by repeated bilateral compression ultrasound (CUS) and perfusion lung scan, and were centrally adjudicated. The study was not powered to detect differences between the study groups.

The primary efficacy endpoint was the composite of adjudicated symptomatic VTE (recurrent DVT, fatal or non-fatal PE) and deterioration (increase) of the thrombotic burden as assessed by repeat bilateral CUS and PLS. The results are presented in Table 6.

Table 6: Symptomatic VTE or deterioration of thrombotic burden, Study CV185017

Treatment	% (95% CI) with symptomatic recurrent VTE or deterioration	% difference from control group (LMWH / fondaparinux and VKA)	% (95% CI) improvement	% (95% CI) no change
Apixaban 5 mg BD	6.0 (2.4, 11.9)	1.7 (-4.4, 8.2)	76.1 (67.3, 83.5)	17.9 (1.5, 26.1)
Apixaban 10 mg BD	5.6 (2.3, 11.2)	1.4 (-4.6, 7.5)	81.6 (73.7, 88.0)	12.8 (7.5, 20.0)
Apixaban 20 mg QD	2.6 (0.5, 7.4)	-1.7 (-7.3, 3.6)	78.4 (69.9, 85.5)	19.0 12.3, 27.3)
LMWH / fondaparinux and VKA	4.2 (1.4, 9.6)	N/A	80.5 (72.2, 87.2)	15.3 (9.3, 23.0)

Key secondary outcomes were:

- Symptomatic DVT and
- Symptomatic PE (fatal or non-fatal) and
- Deterioration, improvement and no relevant change on proximal thrombus based on CUS (Table 7), and

- Deterioration, improvement and no relevant change on composite lung thrombus score based on PLS (Table 7).

Symptomatic recurrent VTE (recurrent DVT or fatal or nonfatal PI) occurred in 2.6%, 3.2%, 1.7%, 2.5% of the apixaban 5 mg BD/10 mg BD/20 mg QD and LMWH-VKA groups, respectively.

Table 7: Outcomes for proximal thrombus and composite lung thrombus score Study CV185017

Treatment	Outcome	Proximal thrombus on CUS	Composite lung thrombus score
Apixaban 5 mg BD	Improved	70.1%	40.2%
	Deteriorated	1.7%	3.4%
	no change	28.2%	24.8%
Apixaban 10 mg BD	Improved	72.0%	37.6%
	Deteriorated	2.4%	0.8%
	no change	23.2%	30.4%
Apixaban 20 mg QD	Improved	72.4%	38.8%
	Deteriorated	0.9%	0
	no change	25.9%	28.4%
LMWH / fondaparinux and VKA	Improved	65.3%	44.1%
	Deteriorated	1.7%	0%
	no change	30.5%	23.7%

Study CV 185056 (AMPLIFY)

This was a randomised, active controlled, parallel group, double blind, triple-dummy efficacy and safety study in 5395 adult subjects with acute symptomatic proximal DVT (the popliteal vein or a more proximal vein demonstrated by imaging with CUS; grey scale or colour Doppler, or ascending contrast venography) or acute symptomatic PE (segmental or more proximal branch intraluminal filling defect on spiral CT, intraluminal filling defect or sudden cut-off of vessels more than 2.5 mm in diameter on pulmonary angiogram or a perfusion defect of at least 75% with local normal ventilation on ventilation/perfusion lung scan) as adjudicated by a central committee.

The exclusion criteria were extensive and were aimed at excluding subjects who were pregnant or breast feeding, with risk factors for recurrence or bleeding, allergies, a serum creatinine of >221µmol/L, CrCl < 25 mL/min, ALT or AST > 2 times ULN and total bilirubin > 1.5 times ULN. Prohibited therapies included treatment of the current event for more than 2 days for fondaparinux of LMWH or VKA, or 36 hours for UFH by continuous infusion, aspirin > 165 mg/day, dual platelet therapy, other antithrombotic agents, glycoprotein IIb/IIIa inhibitors and strong inhibitors of CYP3A4.

The study treatments were apixaban 10 mg BD orally for 7 days, then 5 mg BD (plus placebo enoxaparin and warfarin) or enoxaparin 1 mg/kg 12 hourly until INR ≥ 2, warfarin dosed to target range 2.0 to 3.0 (plus placebo apixaban). Treatment was for 6 months, followed by a 30 day follow-up period.

Randomisation was via a centralised procedure in a 1:1 ratio and stratified by type of disease (symptomatic proximal DVT or PE with or without DVT) at baseline. Of the 5395 subjects randomised 5365 received at least one dose of study treatment (2676 received apixaban and 2689 received warfarin), and 4605 (2314 in the apixaban group and 2291 in the enoxaparin warfarin group) completed the study. The majority of discontinuations were due to death, AE or thrombotic event. The per-protocol population included 2257 in the apixaban group and 2235 in the enoxaparin/warfarin group.

The subjects were 58.7% male, with a median age of 58 years (IQR 46.0, 70.0) and were mostly White (82.7%). Renal function was normal (> 80 mL/min) in 64.5%, mildly impaired (50 < CrCL ≤ 80 mL/min) in 23.3% and moderately impaired (30 < CrCL ≤ 50 mL/min) in 5.7%. Most (89.8%) had unprovoked VTE (65.9% had no identified risk factor), 23.7% were smokers, 16.2% had a recurrent VTE, 2.5% had a history of a prothrombotic genotype and 2.7% had active cancer). The groups were similar for index event (66.6% proximal DVT) method of diagnosis of the index event (99.2% CUS for DVT and 87.9% spiral CT for PE), prior anticoagulant and antiplatelet use and for concomitant anticoagulant medications received during the study (overall 6.4% received a LMWH and 3.5% received a VKA).

Non-inferiority of the treatments was based on the upper 95% for the RR for difference between the two groups for the primary efficacy outcome using a stratified analysis of <1.8 and a risk difference of <0.035. Multiplicity was addressed using a hierarchical approach to hypothesis testing. The study was adequately powered to detect a difference for the primary outcome.

The primary efficacy outcome was the incidence of an adjudicated composite of symptomatic recurrent VTE (nonfatal DVT or nonfatal PE) or VTE-related death during the 6 months of therapy demonstrated non-inferiority:

- Event rate: apixaban (95% CI) 0.0226(0.0169, 0.0283), enoxaparin/warfarin 0.0269 (0.0208, 0.0331)
- RR (95% CI) in the primary efficacy population was 0.8390 (0.5965, 1.1802) (p <0.001 for non-inferiority, p=0.3128 for superiority)
- Risk difference (95% CI) was -0.0044 (-0.0128, 0.0040)

Consistent results were seen in the analysis in the per-protocol population. The time in therapeutic range (TTR) for INR 2.0 – 3.0 was 60.9%; INR was < 2.0 22.9% of the time and > 3.0 for 16.1% of the time. There was no centre TTR quartile by treatment interaction or index event stratum (PE or DVT) by treatment interaction. Comparative outcome events by baseline characteristic were shown.

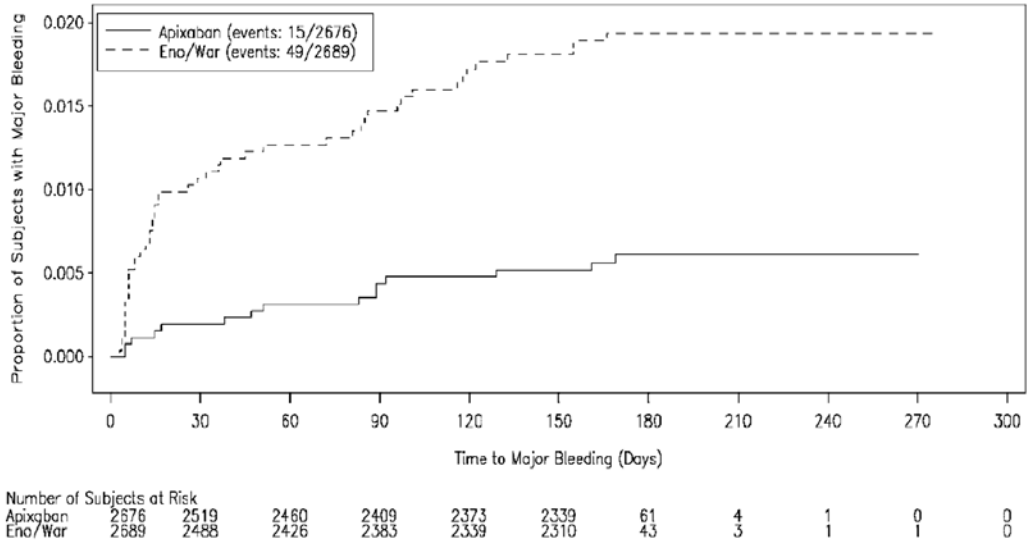
The results for the key secondary endpoints for the primary efficacy subjects were as follows:

- Recurrent symptomatic VTE and all-cause death: 84 episodes in the apixaban group, 104 in the enoxaparin/warfarin, RR (95% CI) 0.8151 (0.6146 to 1.0812), p = 0.1554.
- Event rate (95% CI) composite of recurrent symptomatic VTE and CV-related death: 0.0234 (0.0176 to 0.0292) in the apixaban group and 0.0292 (0.0228 to 0.0357) in the enoxaparin/warfarin.
- Event rate (95% CI) composite of recurrent symptomatic VTE, VTE-related death and major bleeding: 0.0280 (0.0216 to 0.0343) in the apixaban group and 0.0448 (0.0369 to 0.0527) in the enoxaparin/warfarin.
- Event rate (95% CI) symptomatic non-fatal DVT: 0.0084 (0.0049 to 0.0119) in the apixaban group and 0.0133 (0.0089 to 0.0177) in the enoxaparin/warfarin.
- Event rate (95% CI) symptomatic non-fatal PE: 0.0104 (0.0065 to 0.0142) in the apixaban group and 0.0095 (0.0058 to 0.0132) in the enoxaparin/warfarin.
- Event rate (95% CI) VTE-related death: 0.0046 (0.0020 to 0.0072) in the apixaban group and 0.0061 (0.0031 to 0.0091) in the enoxaparin/warfarin.
- Event rate (95% CI) CV-related death: 0.0058 (0.0028 to 0.0087) in the apixaban group and 0.0087 (0.0052 to 0.0123) in the enoxaparin/warfarin.

- Event rate (95% CI), all-cause death: 0.0157 (0.0109 to 0.0205) in the apixaban group and 0.0198 (0.0145 to 0.0251) in the enoxaparin/warfarin.
- Event rate (95% CI) composite of recurrent symptomatic VTE, myocardial infarction, stroke, CV-related death, major bleeding, CRNMB: 0.0699 (0.0602 to 0.0205) in the apixaban group and 0.1261 (0.0145 to 0.0251) in the enoxaparin/warfarin.

In the 30 day follow-up period event rates were similar between the treatment groups except for non-fatal PE which was more common in the enoxaparin/warfarin group: event rate (95% CI) 0.0007 (0.0000 to 0.0018) in the apixaban compared to 0.0033 (0.0012 to 0.0055) in the enoxaparin/warfarin, p = 0.0345. The Kaplan-Meier plots (Figure 2) suggested a comparative benefit of apixaban over enoxaparin/warfarin from 30 to 180 days.

Figure 2: Kaplan-Meier Plot for Major Bleeding During the Treatment Period – Treated Subjects, Study CV185056



Study CV185057 (AMPLIFY – EXT)

This was a randomised, double-blind, placebo-controlled, parallel group Phase III study of two dosage regimens of apixaban in comparison with placebo in 2482 adult subjects with symptomatic proximal DVT or PE that was either provoked or at risk of recurrence that had completed approximately 6 to 12 months of standard anticoagulant therapy or had completed an assigned CV185056 study treatment. Treatment was for 12 months with a 1 month follow-up period. Subjects were excluded if they were pregnant or breastfeeding, had a provoked VTE event without likely recurrence, > 12 months anticoagulation planned for the index event, active bleeding or high bleeding risk, subjects with cancer treated indefinitely with anticoagulation, subjects with LMWH or warfarin contraindicated, those with another reason for anticoagulation including multiple episodes of unprovoked DVT and prothrombotic genotypes, bacterial endocarditis or uncontrolled hypertension, thrombocytopenia, anaemia (defined as haemoglobin (Hb) <90 g/L), serum creatinine > 221 µmol/l; CrCL < 25 mL/min ALT or AST > 2 times ULN, total bilirubin (BR) > 1.5 times ULN. Prohibited therapies were the same as Study CV185056. Subjects were randomised on a 1:1:1 ratio to apixaban 2.5 mg BD, apixaban 5 mg BD or placebo within 7 days of discontinuation of treatment for the index event. Stratification was by index event type (DVT or PE ± DVT) and by previous treatment. The subjects were 57.4% male and 85.3% White, and a median (IQR) age of 58 (46.0, 68.0) with 67.0% < 65 years and 19.7% between 65 and 75 years. Approximately 70% had normal renal function, 21.6% had CrCL 50 < CrCL ≤ 80 mL/min. Of those, 2051 completed the study (726(86.4%)/684 (84.1%)/641(77.3%) in the 2.5 BD/5mg BD placebo). Prior VKAs were used by

64.3%/64.1%/62.7% of subjects in the apixaban 2.5 mg BD/apixaban 5 mg BD/ placebo groups, respectively, and prior antiplatelet agents in approximately 13% overall. Approximately 84% of subjects took one or more concomitant medications in the study. Approximately one third of the subjects in each treatment group had participated in Study CV185056 and approximately half of those had received apixaban. The diagnostic criteria for the index event were similar to Study CV185056.

The study had a 90% power with a level of significance of 0.05 to detect a RR of 0.4135 for the comparison of apixaban and placebo at 12 months. Of the 840/811/826 subjects randomised to the 2.5 mg BD/5 mg BD/placebo groups, respectively, 726/684/641 completed the study. Discontinuations due to DVT occurred in 0.6%/1.0%/6.9% subjects randomised to the 2.5 mg BD/5 mg BD/placebo groups, respectively, due to PE in 0.55%/0.2%/2.2% subjects randomised to the 2.5 mg BD/5 mg BD/placebo groups, respectively and due to bleeding in 1.0%/1.0%/0.4 subjects randomised to the 2.5 mg BD/5 mg BD/placebo groups, respectively.

The efficacy analysis was based on the ITT population with imputation of events for missing data. The primary efficacy outcome was the incidence of an adjudicated composite of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause death:

- **2.5 mg BD**: 32 events, event rate 0.0381 (0.0252, 0.0510), RR (95% CI) compared to placebo 0.3283 (0.2225, 0.4844), risk difference (95% CI) compared to placebo - .0779 (-0.1032, -0.0526)
- **5 mg BD**: 34 events, event rate 0.0418 (0.0281, 0.0556), RR (95% CI) compared to placebo 0.3615 (0.2475, 0.5281), risk difference (95% CI) compared to placebo -0.0740 (-0.097, -0.0482)
- **Placebo**: 96 events, event rate 0.1158 (0.0940, 0.01376).

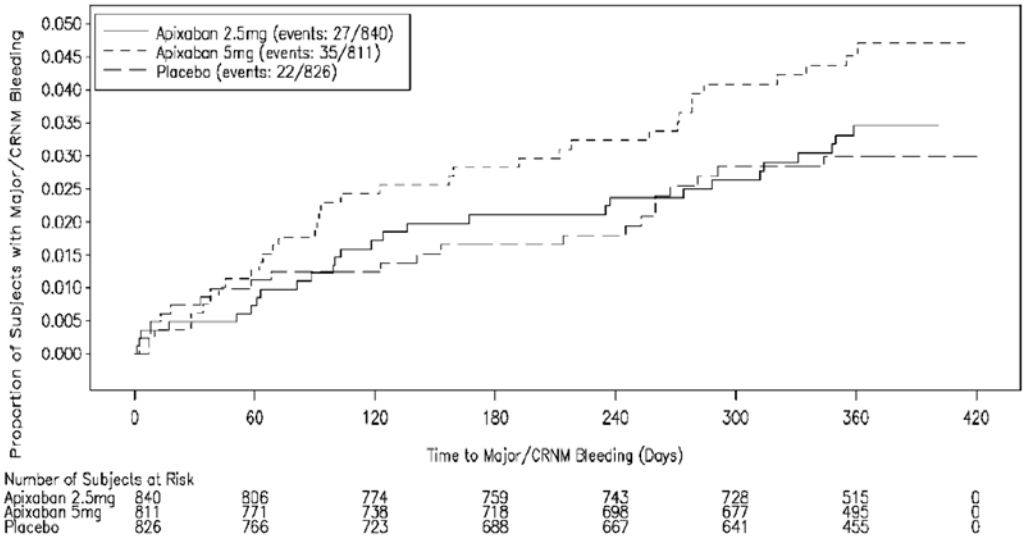
The results for the secondary efficacy outcomes were:

- Composite of recurrent symptomatic VTE or VTE-related death: event rate (95% CI) 0.0321 (0.0202 to 0.0441) for apixaban 2.5 mg, 0.0418 (0.0281 to 0.0556) for apixaban 5 mg and 0.1110 (0.0896 to 0.1324) for placebo. Risk difference (95% CI) versus placebo -0.0790 (-0.1035 to -0.0545) for apixaban 2.5 mg and -0.0691 (-0.0945 to -0.0437) for apixaban 5 mg, p <0.0001.
- Composite of recurrent symptomatic VTE or CV related death (with imputation): event rate (95% CI) 0.0167 (0.0080 to 0.0253) for apixaban 2.5 mg, 0.0172 (0.0083 to 0.0262) for apixaban 5 mg and 0.0881 (0.0688 to 0.1073) for placebo. Risk difference (95% CI) versus placebo -0.0715 (-0.0926 to -0.0504) for apixaban 2.5 mg and -0.0700 (-0.0912 to -0.0489) for apixaban 5 mg, p <0.0001.
- Symptomatic nonfatal DVT: event rate (95% CI) 0.0226 (0.0126 to 0.0327) for apixaban 2.5 mg, 0.0344 (0.0219 to 0.0470) for apixaban 5 mg and 0.0869 (0.0677 to 0.1060) for placebo. Risk difference (95% CI) versus placebo -0.0642 (-0.0858 to -0.0426) for apixaban 2.5 mg and -0.0523 (-0.0752 to -0.0294) for apixaban 5 mg, p <0.0001.
- Symptomatic nonfatal PE: event rate (95% CI) 0.0274 (0.0163 to 0.0384) for apixaban 2.5 mg, 0.0308 (0.0189 to 0.0426), for apixaban 5 mg and 0.0446 (0.0306 to 0.0587) for placebo. Risk difference (95% CI) versus placebo -0.0162 (-0.0337 to 0.0013) for apixaban 2.5 mg and -0.0127 (-0.0308 to 0.0054) for apixaban 5 mg, p >0.05.
- VTE related death: event rate (95% CI) 0.0202 (0.0107 to 0.0298) for apixaban 2.5 mg, 0.0295 (0.0179 to 0.0412) for apixaban 5 mg and 0.0314 (0.0195 to 0.0432) for placebo. Risk difference (95% CI) versus placebo -0.0113 (-0.0266 to 0.0039) for apixaban 2.5 mg and -0.0019 (-0.0185 to 0.0148) for apixaban 5 mg, p >0.05.

- CV related death: event rate (95% CI) 0.0202 (0.0107 to 0.0298) for apixaban 2.5 mg, 0.0295 (0.0179 to 0.0412) for apixaban 5 mg and 0.0350 (0.0225 to 0.0475) for placebo. Risk difference (95% CI) versus placebo -0.0145 (-0.0303 to 0.0012) for apixaban 2.5 mg and -0.0052 (-0.0223 to 0.0119) for apixaban 5 mg, p >0.05.
- All-cause death: event rate (95% CI) 0.0262 (0.0154 to 0.0370) for apixaban 2.5 mg, 0.0308 (0.0189 to 0.0426) for apixaban 5 mg and 0.0398 (0.0265 to 0.0531) for placebo. Risk difference (95% CI) versus placebo -0.0131 (-0.0303 to 0.0041) for apixaban 2.5 mg and -0.0085 (-0.0263 to 0.0094) for apixaban 5 mg, p >0.05.

The Kaplan-Meier indicated a sustained treatment effect during the 12 month treatment period (Figure 3).

Figure 3: Kaplan-Meier Plot for Major Bleeding During the Treatment Period – Treated Subjects, Study CV185057



In the follow-up period 0.5%/1.0%/0.4% in the apixaban 2.5 mg BD/5 mg BD/placebo groups, respectively, had symptomatic VTE (non-fatal DVT or non-fatal PE) or all-cause death. In the period 3 to 30 days after the last dose of study drug 0.95%/0.62%/0.12% of the 2.5 mg BD/5 mg BD/placebo groups reported nonfatal DVT, nonfatal PE, myocardial infarction or stroke.

Safety

A total of 4,712 subjects were exposed to apixaban during the clinical studies supporting this submission. The median duration of treatment was 168 days in Study CV185056 and 360 days in Study CV185057.

TEAEs

In Study CV185017 TEAEs were reported in 60.2% of the 5 mg BD group, 54.1% of the 10 mg BD group, 66.1% of the 20 mg QD group and 57.1 % of the LMWH-VKA group. The commonest TEAEs were headache (8.1%), pain in extremity (4.9%) and diarrhoea (4.2%). In Study CV185056 TEAEs were reported in 67.1% of the apixaban group and 71.5% of the enoxaparin/warfarin group. The commonest AE was headache reported in 6.3% of subjects in the apixaban group and 6.2% of the subjects in the enoxaparin/warfarin group. In Study CV185057 TEAEs were reported in 71.0% in the apixaban 2.5 mg BD group and 66.8% of the apixaban 5 mg BD group and 73.4% of the placebo group. DVT was the most commonly reported event (7.5% in the placebo group) (CER p 110).

Treatment related adverse events (TRAEs)

In Study CV185056 TRAEs were reported in 19.4% of subjects in the apixaban group and 30.3% in the enoxaparin/warfarin group. Epistaxis was the most common (2.4% and 4.6% for apixaban and enoxaparin/warfarin, respectively). In Study CV 185057 TRAEs were reported in 17.7%/17.9%/14.4% of the 2.5mg BD/5mg BD/placebo groups respectively. In Study CV185017 21.9%/21.8%/25.8%/26.2% reported TRAES in the 5mg/10mg/20mg/LMWH-VKA group. The most common event was headache (2.6%).

Deaths

In Study CV185056 deaths were reported in 1.4% and 1.6% of subjects in the apixaban and enoxaparin/warfarin groups respectively. Causes of death were similar between the two groups and there was not a predominance of any one system organ class. There were 2 fatal bleeding events in the apixaban group and 1 in the enoxaparin/warfarin group. In Study CV185057 deaths were reported for 0.4%/0.5%/1.2% of the 2.5 mg BD/5mg BD/placebo groups. Two of the 10 deaths in the placebo group were due to PE and there were 3 others reported as sudden death. In Study CV185017 one subject died (by suicide) during the treatment phase of the study, two others died in the follow-up phase; one from metastatic cancer and the other from a PE in the context of renal failure and testicular cancer. An additional 5 deaths occurred between 31-87 days, all with neoplastic disease.

SAEs

In Study CV185056 the commonest SAEs were PE reported in 0.9% of subjects in the apixaban group and 1.4% of subjects in the apixaban/warfarin group, followed by DVT (0.7% in the apixaban group and 1.2% in the enoxaparin warfarin group). In Study CV185057 SAEs were reported in 13.3%/13.2%/19.1% of the 2.5mg BD/5 mg BD/placebo groups. DVT as a SAE was reported for 0.34%/1.1%/4.8% 2.5mg BD/5 mg BD/placebo groups and PE as a SAE was reported for 0.6%/0.3%/2.4% 2.5mg BD/5 mg BD/placebo groups. In Study CV185017 SAEs were reported for 12.5%/8.3%/16.1%/12.2% for the 5 mg BD/10 mg BD/20 mg QD/LMWH/VKA. Dizziness was the commonest SAE in the apixaban groups (reported by 3 subjects, [0.8%]).

Discontinuations due to AEs

In Study 185056 discontinuations due to AEs occurred in 6.1% of apixaban subjects and 7.4% of enoxaparin/warfarin but no single event type occurred in ≥ 1% of the subjects. DVT was reported in 0.5%/0.9% and for PE 0.4%/0.6% for apixaban and enoxaparin/warfarin, respectively. Gastrointestinal haemorrhage leading to discontinuation occurred in 0.3%/0.6% apixaban and enoxaparin/warfarin, respectively. In Study CV185057 discontinuations due to AEs occurred in 8.0%/7.5%/16.2% of the 2.5 mg BD/5 mg BD/placebo groups. DVT occurred in 0.5%/1.0%/6.7% in the 2.5 mg BD/5 mg BD/placebo groups. PE occurred in 0.5%/0.2%/2.3% in the 2.5 mg BD/5 mg BD/placebo groups**.** In Study CV185017 discontinuations due to AEs occurred in 7.0%/4.5%/8.9%/4.0%. Vaginal haemorrhage and dizziness occurred in 0.5% of the apixaban group.

Bleeding events

In Study 185017, bleeding events were reported in 11.7%/12.8%/10.5%/19.0% of subjects in the 5 mg BD/10 mg BD/20 mg QD/ LMWH-VKA groups. Major bleeding events (see Definitions below) were infrequent with 1 in the 5 mg BD group (bloody pleural effusion) and 1 intracerebral bleed in the 20 mg QD group. Major bleeding/CRNMB (see Definitions below) grouped together was reported for 8.6%/4.5%/7.3%/7.9% in the 5 mg BD/10 mg BD/20 mg QD/ LMWH-VKA groups. The most common types of bleeding events were haematuria, haematoma and epistaxis. In Study CV185056 15.5% of the apixaban group and 25.8% of the enoxaparin/warfarin group reported bleeding AEs. The most common were epistaxis, contusion and haematuria.

Definitions of bleeding in pivotal studies.

Major bleeding *was defined as:*

Acute clinically overt bleeding accompanied by at least one of the following:

- *A decrease in haemoglobin of >20 g/L [>2 g/dL];*
- *A transfusion of >2 units of packed red blood cells or 1000 mL or more of whole blood;*
- *Bleeding that occurred in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or another critical organ (to be specified);*
- *Bleeding that was fatal.*

CRNM bleeding *was defined as acute clinically overt bleeding that did not satisfy any of the additional criteria required for the bleeding event to be defined as a major bleeding event and met at least one of the following criteria:*

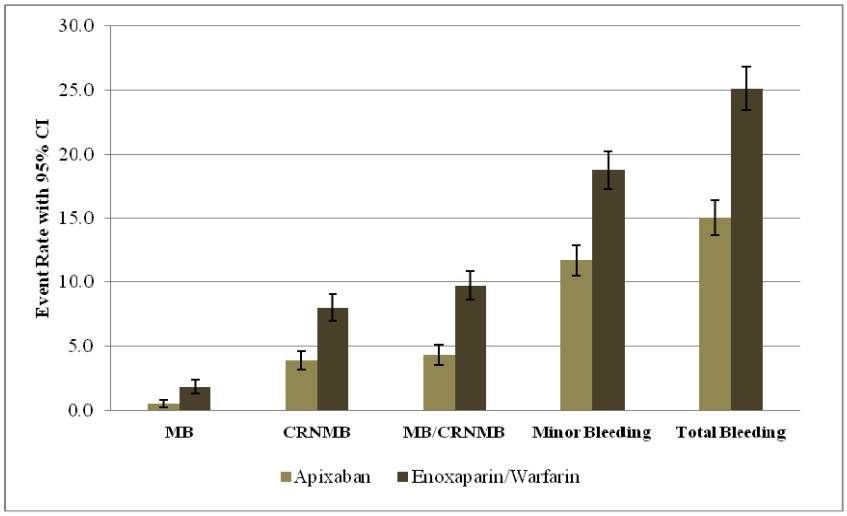
- *Any bleeding compromising haemodynamics;*
- *Any bleeding leading to hospitalisation;*
- *Subcutaneous hematoma larger than 25 cm^2, or 100 cm^2 if there was a traumatic cause;*
- *Intramuscular haematoma documented by ultrasonography;*
- *Epistaxis that lasted for more than 5 minutes, was repetitive (that is, two or more episodes of bleeding more extensive than spots on a handkerchief within 24 hours), or led to an intervention (for example, packing or electrocoagulation);*
- *Gingival bleeding occurring spontaneously (that is, unrelated to eating or tooth brushing) or lasting for more than 5 minutes;*
- *Haematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after instrumentation (such as catheter placement or surgery) of the urogenital tract;*
- *Macroscopic gastrointestinal hemorrhage, including at least one episode of melena or hematemesis, if clinically apparent with positive results on a faecal occult-blood test;*
- *Rectal blood loss, if more than a few spots on toilet paper;*
- *Haemoptysis, if more than a few speckles in the sputum and not occurring within the context of pulmonary embolism;*
- *Any other bleeding type considered to have clinical consequences for a subject such as medical intervention, the need for unscheduled contact (visit or telephone call) with a physician, temporary cessation of a study drug; or associated with pain or impairment of activities of daily life.*

Minor bleeding *was defined as an acute clinically overt bleeding event that did not meet the criteria for either a major bleeding event or a CRNM event.*

Fatal bleeding *was defined as a bleeding event that the ICAC determined was the primary cause of death or contributed directly to death*

Figure 4 (below) summarises the event rates for bleeding events in Study CV185056.

Figure 4: Summary of Adjudicated Bleeding Endpoints in Study CV185056

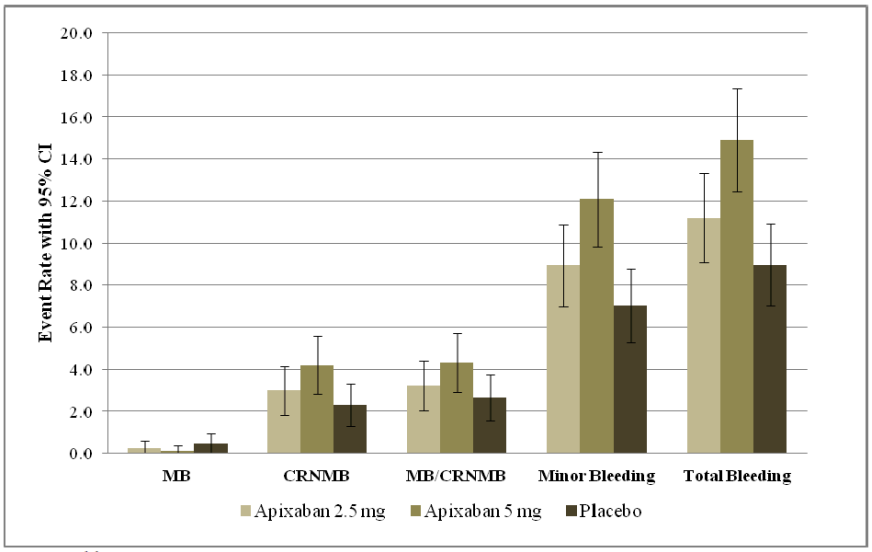


Source: Table 14.2.4.1, CV185056 CSR. MB=major bleeding, CRNMB=clinically relevant non-major bleeding, CI=confidence interval.

Major bleeding occurred in 0.6% of apixaban subjects and 1.8% of the enoxaparin/warfarin subjects (RR (95%CI) 0.0307 (0.1728, 0.5452); risk difference (95% CI) -0.0013(-0.0170, -0.0056; p<0.0001). Major bleeding/CRNMB occurred in 4.3% of the apixaban subjects and 9.7% of the enoxaparin/warfarin subjects (risk difference (95%CI) -0.0499 (-0.0632, -0.0366); p<0.0001). The most common site for major bleeding was gastrointestinal in both treatment groups (0.2% and 0.6% for apixaban and enoxaparin/warfarin respectively). Three subjects in the apixaban and 6 in the enoxaparin/warfarin group had intracerebral bleeding events. The difference in the incidence of major bleeding between apixaban and enoxaparin/warfarin was consistent in a centre-based TTR analysis.

In Study CV185057 11.8%/15.3%/9.4% in the 2.5 mg BD/5 mg BD/placebo groups had bleeding AEs with the most common epistaxis. Gastrointestinal bleeds occurred in 2.6%/3.6%/1.6% of the 2.5 mg BD/5 mg BD/placebo groups. Figure 5 (below) summarises the event rates for bleeding events in Study CV185057.

Figure 5: Summary of Adjudicated Bleeding Endpoints in Study CV185057



Source: Table 14.2.4.1, CV185057 CSR. MB=major bleeding, CRNMB=clinically relevant non-major bleeding, CI=confidence interval.

Major bleeding events occurred in 0.2%/0.1%/0.5% of the 2.5 mg BD/5 mg BD/placebo groups (apixaban not statistically significantly different from placebo). Major/CRNMB events occurred in 3.2%/4.3%/2.7% of the 2.5 mg BD/5 mg BD/placebo groups. Intraocular haemorrhage occurred in 2 subjects in the 2.5mg BD group and 1 subject in the placebo group. No intracranial bleeds occurred in the apixaban groups. In the follow-up period bleeding AEs were reported in 0.7%/0.7%/1.1% of the 2.5 mg BD/5 mg BD/placebo groups.

Liver injury

Elevated liver enzymes were reported in subjects in the three clinical studies. In Study 185056 6.1% (n=162) of the apixaban group and 11.5% (n=308) of the enoxaparin/warfarin group reported elevated liver enzymes. Of those 4 apixaban subjects (0.2%) had ALT or AST >3 times ULN and BR>2 times ULN on the same day and one had ALT>3 times ULN, BR>2 times ULN and ALP< 2 times ULN on the same date. The abnormality seen in the latter subject was considered by the sponsor to be related to apixaban. In Study CV185057 3.7%/3.0%/3.3% in the 2.5 mg BD/5 mg BD/placebo groups had elevated liver enzymes. ALT>3xULN was reported in 1.1%/0.6%/1.1% of the 2.5 mg BD/5 mg BD/placebo groups. There were no Hy's Law cases. In Study CV185017 no subject had AST >3xULN and BR>2 times ULN on the same day. ALT or AST >3 times ULN was reported for 5 subjects in the apixaban groups and 2 in the LMWH-VKA group.

The clinical evaluator also raised the issue of the safety of apixaban while breast feeding, based on the findings of a previously evaluated rat study in which it was concentrated in breast milk and that it is a substrate of the Breast Cancer Resistance Protein (BCRP) efflux transporter. A warning regarding breast feeding is included in the proposed PI. The ACPM will be asked to comment on its adequacy.

The summary of post-market data (Summary of Clinical Safety) was consistent with the known safety concerns for apixaban (bleeding events; PE/thrombosis/drug ineffective; hepatic events).

Risk management plan

The RMP evaluation unit has accepted the EU Risk Management Plan (version 13, document date 7 July 2014, data lock point 17 May 2013) and Australian Specific Annex (version 6, document date 13 November 2014).

The following were outstanding matters and should be followed up in sponsor's the Pre-ACPM Response:

- Revision of the Australia Specific Annex in accordance with the requirements of the RMP evaluator as outlined in the second round RMP Evaluation report.

Risk-benefit analysis

Delegate's considerations

Efficacy

The sponsor has relied on a single pivotal study (CV185056) to support its proposed indication for the treatment of VTE. This was a large study with over 2000 patients in each treatment arm that completed the study. The detection of new or recurrent VTE outcomes in Study CV185056 was event driven (clinical suspicion of an event followed by diagnostic radiology), and there was no routine radiological follow-up of the index event. This is study design is in accordance with TGA adopted EU guidelines. Apixaban was shown to be non-inferior to a combination of enoxaparin and warfarin for the composite endpoint of

symptomatic recurrent VTE or VTE-related death. The key secondary endpoints of the study were supportive of the findings, as were the individual components of the composite endpoints. In the dose finding study (CV185017) the DVT thrombotic burden, as measured by the proximal thrombus on CUS showed an improvement in 70 to 72% of subjects taking apixaban 5 mg BD or 10 mg BD. In this study the PE thrombotic burden, measured by the composite lung thrombus score improved in 38 to 40% of subjects. An increase in the thrombotic burden of DVT was shown in 1.7% on the 5 mg BD dose and 2.4% in the 10 mg BD dose, and for PE 3.4% and 0.8% for the 5 mg BD and 10 mg BD doses, respectively. The findings of this study support the indication for treatment of DVT and PE.

A single pivotal study (CV185057) demonstrated the superiority of 2.5 mg BD and 5 mg BD of apixaban over placebo in the prevention of the composite endpoint of symptomatic recurrent VTE or all-cause death. The efficacy was similar for both doses of apixaban. The key secondary composite endpoints supported the findings. The individual components of the composite endpoints did not all reach statistical significance for a risk reduction compared with placebo, although there was a reduction in relative risk of each event type compared with placebo. There was no clear efficacy advantage for the 5 mg BD dose over the 2.5 mg BD dose but the study was not designed for cross group comparisons. In both the pivotal studies the most common reason for discontinuation was lack of efficacy, although lack of efficacy was more common in the comparator arms.

Safety and RMP

A total of 4,712 subjects were exposed to doses of 2.5 mg BD to 20 mg QD in the clinical trials for apixaban for the proposed indications. The duration of exposure in the prevention study was only one year but this meets the recommendations from the TGA adopted EU guidelines. The primary safety concern with apixaban is bleeding events. There is no specific antidote but a candidate specific reversal agent is undergoing development. The risk of major bleeding and major bleeding plus clinical relevant non-major bleeding events reported was significantly lower with apixaban than enoxaparin/warfarin in the treatment study. The increased risk of bleeding in the prevention study was greater with apixaban than placebo as would be expected. The event rates were lower for major bleeding than in the treatment study for the same dose of apixaban but for the combination of major bleeding and CRNMB the frequency of events was the same. Major bleeding in both studies was less frequent than reported in the ARISTOTLE (2.13%) and AVERROES (1.41%) studies for stroke prevention in patients with atrial fibrillation.

Liver enzymes elevations had been previously noted in clinical studies and liver enzyme elevations are mentioned in the PI and the RMP. Elevations of liver enzymes were noted in both pivotal studies and in the Phase II study. Elevations of ALT>3 times ULN occurred in up to 3.7% of subjects taking apixaban but there was no obvious dose-dependent relationship in the dose-finding study and liver enzyme elevations were also seen in the comparator groups.

There was an increase in thromboembolic events in the period 3 to 30 days after the completion of Study CV185057 in the apixaban groups compared to the placebo group. The sponsor will be asked for comment.

Dose

The clinical evaluator has supported a dose of 10 mg BD initially followed by 5 mg BD for the prevention of VTE. The 10 mg BD initial dose is supported by the dose finding study in that approximately 82% had an improvement in their thrombotic burden and 5.6% deteriorated and 12.8% were unchanged, representing the best overall improvement of the doses tested. There was little difference between the major bleeding events between the groups and CRNMB was lowest in the 10 mg BD dose group. The dose finding study was for 12 weeks. It is reasonable for ongoing therapy to choose the 5 mg BD for ongoing

treatment as it was the lowest dose with acceptable efficacy. The clinical evaluator supported a dose of 2.5 mg BD for the prevention of recurrent VTE events. The 2.5 mg BD dose had a reduction in risk of VTE and lower risk of bleeding compared to the 5 mg BD dose. The composite endpoint of recurrent VTE or all-cause death was occurred in 3.8% of subjects (or 2.3% in the sensitivity analysis of adjudicated events without imputation) taking 2.5 mg BD apixaban, and 4.2% taking apixaban 5 mg BD (1.7% without imputation). The composite of major bleeding and CRNMB occurred in 3.2% of the apixaban 2.5 mg BD and 4.3% of the apixaban 5mg BD. There is a higher risk of non-fatal PE but a lower risk of VTE –related death in the 2.5 mg BD group and this is balanced against the bleeding risk.

Indication

The clinical evaluator supported the indications:

> *Eliquis is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).*
>
> *Eliquis is indicated for the prevention of recurrent DVT and PE.*

The proposed wording is consistent with the approved indication internationally for apixaban for the proposed indications and, although broader than the clinical trial populations, is considered acceptable. The proposed PI includes precautionary statements against the use of apixaban for haemodynamically unstable patients.

Data deficiencies

White men predominated as subjects in the studies. There were no patients with PE requiring interventions other than anticoagulation. Between 3% and 4% of the patients in each of the pivotal studies took non-study anticoagulants. As the outcome event numbers are small this may have had an impact on the results. The sponsor will be requested to comment.

Conditions of registration

The following are proposed as conditions of registration:

1. The EU-RMP (version 13, document date 7 July 2014 with data lock point 17 May 2013) and Australian Specific Annex (version 6, document date 13 November 2014) to be revised to the satisfaction of the TGA must be implemented.

Questions for the sponsor

The sponsor is requested to address the following issues in the Pre-ACPM Response:

1. Enteroenteric re-circulation of apixaban has been demonstrated in animal models for apixaban and activated charcoal has been demonstrated to reduce exposure in animals and humans. Does the sponsor plan to investigate the use of repeat dose activated charcoal?
2. The bioequivalence of the oral solution and crushed tablet has been demonstrated in studies included in this submission. Please indicate how the bioequivalence of the whole 5 mg tablet and the crushed 5 mg tablet has been identified.
3. The population PK derived fractional clearance for subjects of Asian race was decreased by 16.8%. Please indicate the reason the sponsor has not included this information in the relevant section of the PI?
4. During Studies CV185056 and CV185057 3 to 4% of subjects took non study anticoagulants. Please comment on the impact of these major protocol violations on the outcomes of the studies. In the response please include a comment on the impacts for safety as well as efficacy.

5. Please provide a justification for not including a precautionary statement against the use of apixaban in subjects with active cancer, similar to the one that appears in the SmPC.
6. The clinical evaluator was not satisfied with the response to the question about symptomatic DVT. Please indicate if the sponsor considered a DVT 'symptomatic' if it was proximal, regardless of the symptoms the subject complained of. If not, please identify what the sponsor considered 'symptomatic' in these subjects.
7. A larger proportion of patients reported thromboembolic events during days 3 to 30 after the completion of Study CV185057 in the apixaban groups compared to placebo. Please provide comment on whether there is a 'rebound' or withdrawal phenomenon in VTE patients.

Summary of issues

The primary issues with this submission are as follows:

1. Whether the study populations are representative of the subjects likely to receive apixaban for the proposed indication.
2. Whether placebo is a reasonable comparator for the prevention study.
3. Whether there should be dose adjustment for age and renal function.

Proposed action

The Delegate had no reason to say, at this time, that the application for apixaban (Eliquis) should not be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Does the committee consider the findings for the study populations are generalisable to the likely population?
2. Is the choice of comparator (placebo) reasonable for the prevention study?
3. The sponsor has proposed that there should not be any dose adjustment for age or renal function. Does the committee support this proposal?
4. Does the committee consider the precautionary statement about the Use in Lactation is adequate to convey the risks?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Executive summary

- **Study Populations Representative:** the study population included appropriate at risk groups and also included elderly subjects.
- **Placebo a Reasonable Comparator:** placebo is appropriate because 'no treatment' is an accepted standard of care in this patient population.
- **Dose Adjustment for Age and Renal Function:** the subgroup analysis results of age or renal function groups were consistent with the overall efficacy and safety results, with no indication of any clinically important treatment by subgroup interactions.

- **Precautionary Statement about Use in Lactation**: the current language in the Pregnancy and Lactation section of the PI sufficiently addresses the concern regarding the use of apixaban during breast feeding and provides clear guidance to patients and physicians.

As agreed with the Delegate by email on 11 March 2015, the responses to the RMP evaluation are addressed in the separate 'Sponsor's Response to Recommendations made in the Risk Management Evaluation Report' and will work with the TGA to finalise these before approval. An updated apixaban Australian Specific Annex will be provided to the TGA following confirmation of acceptability of the above after the ACPM meeting and the sponsor's discussion with the TGA.

As agreed with the Delegate by email on 11 March 2015, the responses for the *Questions to Sponsor* are provided in a separate appendix.

Changes have been made to the PI in response to recommendations from various evaluators and the Delegate.

ACPM's advice sought

1. *Does the committee consider the findings for the study populations are generalisable to the likely population?*

The sponsor concurs with the assessment of the clinical evaluator; the study population included appropriate at risk groups and also included elderly subjects.

For VTE treatment, apixaban has demonstrated efficacy that was non-inferior to enoxaparin/warfarin and bleeding across all categories that was significantly less frequent, including a 69% risk reduction in MB. In preventing a recurrent DVT or PE, apixaban was markedly superior to placebo in subjects with both unprovoked and provoked VTE, with a minimal increase in bleeding for the 2.5 mg BD dose compared to placebo. The data from the apixaban VTE treatment clinical development program has demonstrated that it fills the recognised unmet medical need for treating and preventing recurrent VTE. The populations studied in the clinical program are reflective of the patient populations for which the drug is being proposed (including but not limited to: DVT/PE ratio, special populations, provoked/unprovoked VTE).

2. *Is the choice of comparator (placebo) reasonable for the prevention study?*

As stated in the CER with which the sponsor concurs; the comparator treatment was placebo, which is appropriate because 'no treatment' is an accepted standard of care.

For this patient population it was determined that the risk of bleeding with a VKA would offset the potential benefit of continued anticoagulation (had reached clinical equipoise with respect to continuation or cessation of anticoagulant therapy), therefore placebo was considered the appropriate comparator for this study.

3. *The sponsor has proposed that there should not be any dose adjustment for age or renal function. Does the committee support this proposal?*

The sponsor submitted subgroup analysis results of age or renal function groups for both efficacy and safety endpoints and has reproduced the subgroup analysis results of the AMPLIFY study below.

The efficacy and safety results by the age and renal function groups were consistent across both subgroups, with no indication of any clinically important treatment by subgroup interactions. As shown below, the relative risk for major bleeding in the combined severe and moderate renal impairment patients was 0.53 (95% confidence interval: 0.18, 1.62) and similar to that seen in patients with mild renal impairment who would not require a dose reduction. For efficacy, there was no indication of a decreased benefit compared to standard of care. The subgroup analysis of age groups also showed that the RR was

consistent across different age groups (≤65 years, 65 to 75 years, and ≥75 years) for both major bleeding and VTE/VTE-related death. Therefore, the sponsor does not recommend a dose reduction based on age or renal function.

Figure 6: Forest Plot for Adjudicated VTE/VTE-related Death in Study CV185056 - Primary Efficacy Population

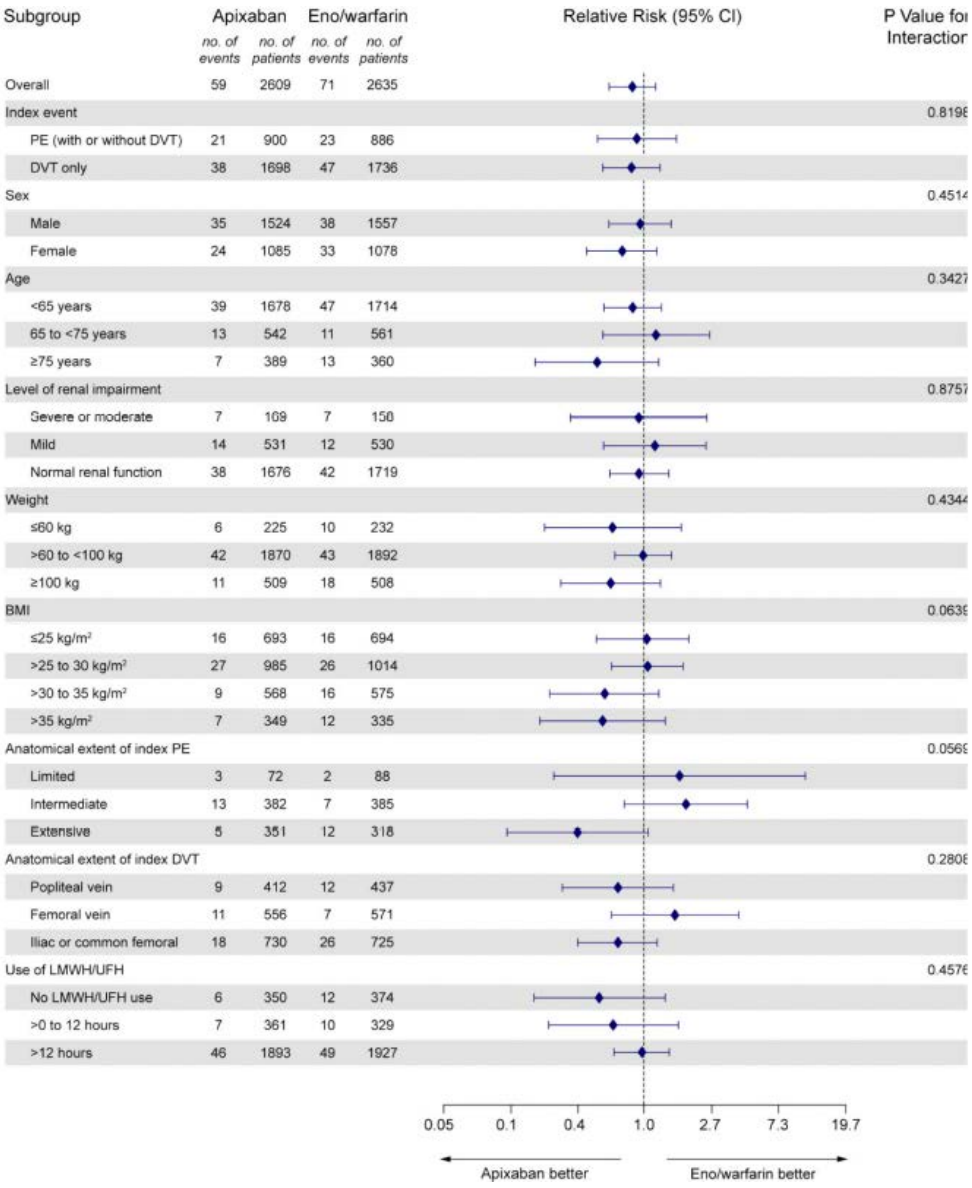
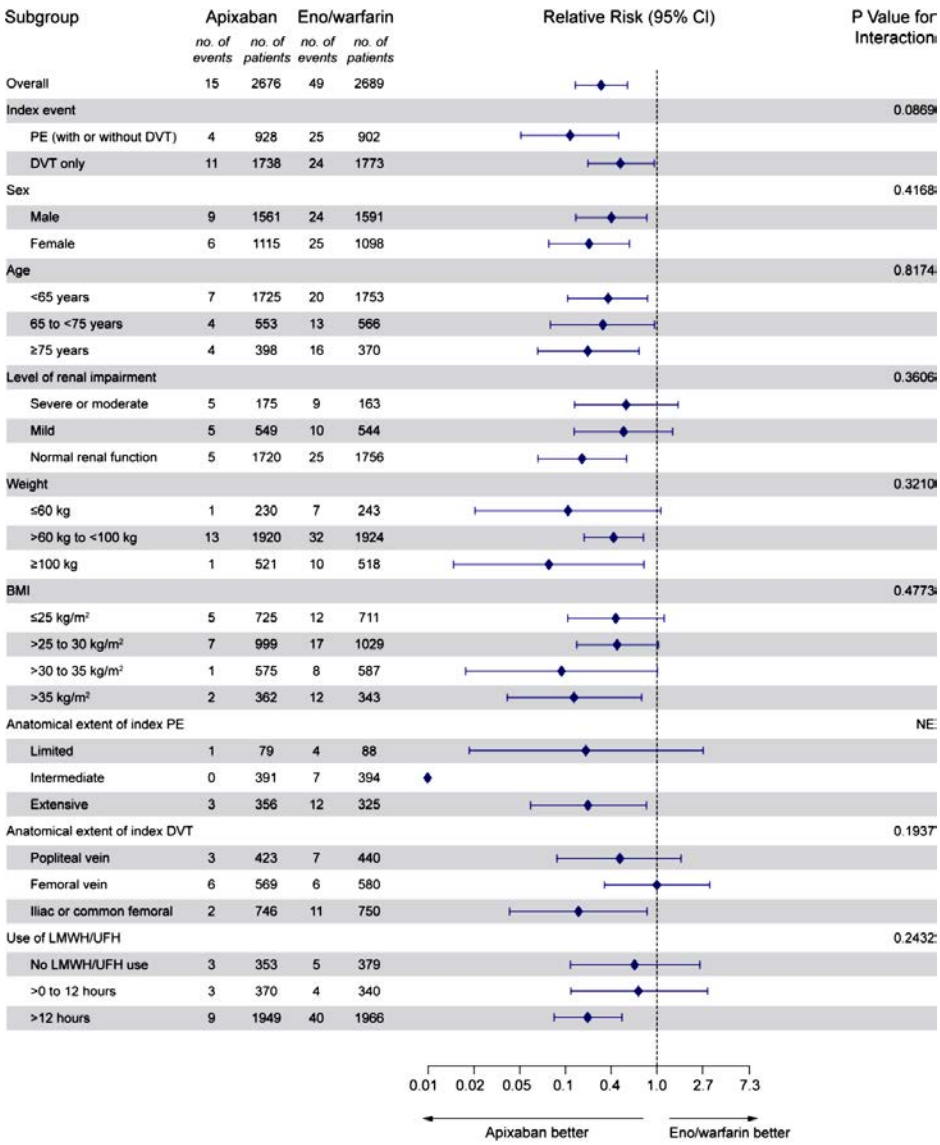


Figure 7: Forest Plot for Adjudicated Major Bleeding During the Treatment Period in Study CV185056 - Treated Subjects



4. *Does the committee consider the precautionary statement about the Use in Lactation is adequate to convey the risks?*

Based on the finding that significant amounts of apixaban are excreted into milk of lactating rats there is clearly a potential risk for infant exposure to apixaban via breast milk. The sponsor's position is that the current language in the Pregnancy and Lactation section of the PI sufficiently addresses the concern regarding the use of apixaban during breast feeding and provides clear guidance to patients and physicians. Furthermore, this is also in alignment with the approved PI for the VTE prevention and stroke prevention in atrial fibrillation indications in Australia.

Issues raised in delegate's overview

The following issue was raised in the Delegate's Overview and a summary of the response is provided below.

1. *Revision of the Australia Specific Annex in accordance with the requirements of the RMP evaluator as outlined in the second round RMP Evaluation report.*

    a. It is recommended that the identified risk '*Transient elevation of liver tests*' is amended to incorporate all indications.

The sponsor proposes that '*transient elevation of liver tests*' is subsumed within the Important Potential Risk of '*Liver injury*' across all indications.

b. The ACSOM advised that the following safety concerns should be included for consideration in the RMP:

- patients with extremes of body weight, cancer-related venous thromboembolic events (VTE) and provoked VTE;
- patients requiring rapid reversal of effect (for example, semi-urgent surgery); and
- drug-drug interactions.

All of the above safety concerns, except for drug-drug interactions, will be included in the next version of the ASA.

2. Questions for the sponsor

The sponsor was requested to address the following issues and a summary of the responses to these questions are provided below.

i. Enteroenteric re-circulation of apixaban has been demonstrated in animal models for apixaban, and activated charcoal has been demonstrated to reduce exposure in animals and humans. Does the sponsor plan to investigate the use of repeat dose activated charcoal?

The sponsor has no plan to investigate the use of repeat dose activated charcoal.

ii. *The bioequivalence of the oral solution and crushed tablet has been demonstrated in studies included in this submission. Please indicate how the bioequivalence of the whole 5 mg tablet and the crushed 5 mg tablet has been identified.*

The sponsor has conducted a study in crushed tablets versus whole tablets and this will be the subject of a future update.

iii. *The population PK derived fractional clearance for subjects of Asian race was decreased by 16.8% Please indicate the reason the sponsor has not included this information in the relevant section of the PI*?

Considering the totality of available data, the impact of Asian race on apixaban PK is minimal and not clinically meaningful and therefore the sponsor does not believe this information should be added to PI.

iv. During Study CV185056 and CV185057 3 to 4% of subjects took non study anticoagulants. Please comment on the impact of these major protocol violations on the outcomes of the studies. In the response please include a comment on the impacts for safety as well as efficacy.

The subjects with protocol violations for non-study anticoagulant medications were included in the primary efficacy and safety analyses. No formal analysis was conducted for these subjects with protocol violations due to taking non-study anticoagulants. Since these included less than 5% of subjects overall and the numbers were relatively balanced between treatment groups they would not be expected to have a significant impact on the study safety or efficacy assessments.

v. Please provide a justification for not including a precautionary statement against the use of apixaban in subjects with active cancer, similar to the one that appears in the SmPC.

The sponsor has updated the PI to include the precautionary statement.

vi. *The clinical evaluator was not satisfied with the response to the question about symptomatic DVT. Please indicate if the sponsor considered a DVT 'symptomatic' if it was proximal, regardless of the symptoms the subject complained of. If not, please identify what the sponsor considered 'symptomatic' in these subjects.*

All events of index and recurrent VTE had to be both symptomatic and image confirmed in order to be adjudicated as a symptomatic DVT or PE. No specific list of symptoms was provided by the sponsor to the investigators or the adjudication committee. If the adjudication committee considered the symptoms and images provided by the investigator met criteria for a symptomatic event, they were adjudicated as a symptomatic DVT or PE.

vii. *A larger proportion of patients reported thromboembolic events during days 3 to 30 after the completion of Study CV185057 in the apixaban groups compared to placebo. Please provide comment on whether there is a 'rebound' or withdrawal phenomenon in VTE patients.*

Although there were more VTE events in the Days 3 to 30 follow-up period in patients who stopped apixaban versus those who stopped placebo, the great majority of these events occurred after Day 9. This is consistent with an ongoing risk of recurrent VTE in these patients after discontinuing an effective anticoagulant rather than suggesting a rebound phenomenon, which would be expected to produce a clustering of VTE events sooner after discontinuing apixaban once circulating drug has cleared. Data from Study CV185057 do not demonstrate a rebound increase in recurrent VTE, myocardial infarction (MI) or ischaemic stroke events in Days 3 to 9 following discontinuation of apixaban, which is the most relevant time period for evaluating rebound effects.

The sponsor has found no evidence of a rebound effect upon discontinuation of apixaban in Study CV185057 or in any other study conducted during the apixaban development program for other indications.

In conclusion

The sponsor welcomes the Delegate's recommendation to approve the application to register a new indication for Eliquis (apixaban):

For the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adult patients and for the prevention of recurrent DVT and PE in adult patients.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM resolved to recommend to the TGA delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy advised that Eliquis, film-coated tablet blister pack, containing 2.5 mg and 5 mg of apixaban has an overall positive benefit–risk profile for the indication:

Eliquis is indicated for

- *the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).*
- *the prevention of recurrent DVT and PE.*

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM proposed the following amendments to the PI:

- Under *Precautions*, add information on the use of apixaban in lactation to highlight risk of exposure to prevent possible bleeding in new-borns. A statement about lactation should also be added to the CMI.
- Under *Use in Pregnancy*, add advice on what to do if there is advertent exposure to apixaban, such as becoming pregnant whilst taking apixaban.

Specific advice

The ACPM advised the following in response to the specific Delegate's questions on this submission:

1. *Does the committee consider the findings for the study populations are generalizable to the likely population?*

The ACPM advised that the variability in the study populations are generalizable to the probable population.

2. *Is the choice of comparator (placebo) reasonable for the prevention study?*

The ACPM advised that the comparator, placebo, for the prevention study was reasonable as current guidelines do not recommend long-term preventative treatment.

3. *The sponsor has proposed that there should not be any dose adjustment for age or renal function. Does the committee support this proposal?*

The ACPM advised the evidence suggests that dosage adjustment for age or renal function is not needed. The ACPM noted that patients with moderate renal impairment did not have a worse outcome in the studies. There is no clinical experience in severe renal failure, and the ACPM considered that this is covered adequately in the PI.

4. *Does the committee consider the precautionary statement about the Use in Lactation is adequate to convey the risks?*

The ACPM advised that there should be a stronger warning in the PI/CMI regarding use of apixaban in lactation and that the information about lactation should also be included under *Precautions*. This would further highlight the risk of exposure to apixaban and possible increased risk of bleeding in exposed new-borns.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Eliquis tablets containing apixaban for oral administration, indicated for:

> *Eliquis is indicated for the treatment of deep vein thrombosis (DVD) and pulmonary embolism (PE) in adult patients.*
>
> *Eliquis is indicated for the prevention of recurrent DVT and PE in adult patients.*

Specific conditions of registration applying to these goods

The apixaban EU-Risk Management Plan (EU-RMP), version 13, document date 7 July 2014, data lock point 17 May 2013) and Australian Specific Annex (version 7, dated 17

April 2015), included with submission PM-2014-00349-I-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Eliquis at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>

Attachment 2. Extract from the Clinical Evaluation Report

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