Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Apixaban

Proprietary Product Name: Eliquis

Sponsor: Bristol Myers Squibb Australia Pty Ltd

June 2013

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 Ageing, 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 <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (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, in that it will provide 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

I. Introduction to product submission

Submission details

Type of Submission:	Extension of indications Registration of a new strength (5 mg)
Decision:	Approved
Date of Decision:	29 April 2013
Active ingredient:	Apixaban
Product Name:	Eliquis
Sponsor's Name and Address:	Bristol-Myers Squibb Australia Pty Ltd PO Box 1080 Mount Waverley VIC 3149 Australia
Dose form:	Tablet
Strengths:	2.5 mg and 5 mg
Container:	Blister pack
Pack sizes:	10, 20, 30, 60 and 100 tablets
Approved Therapeutic use:	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.
Route of administration:	Oral
Dosage (abbreviated):	*Prevention of stroke and systemic embolism: Non-valvular atrial fibrillation:* The recommended dose of Eliquis is 5 mg taken twice daily. The recommended dose of Eliquis is 2.5 mg taken twice daily in patients with at least two of the following characteristics: · ≥80 years; · body weight ≤60 kg; · serum creatinine ≥133 µmol/L.
ARTG Numbers:	172244 (2.5 mg) and 193474 (5 mg)

Product background

Apixaban is an orally active, reversible, selective inhibitor of coagulation Factor Xa (FXa) that prevents thrombin generation and thrombus formation by decreasing the conversion of prothrombin to thrombin. It does not require antithrombin III for its antithrombotic activity and has no direct effects on platelets but indirectly inhibits platelet aggregation

induced by thrombin. Factor Xa is a common mediator of both the extrinsic and intrinsic pathways of coagulation.

Eliquis tablets containing 2.5 mg of apixaban were first approved in Australia in July 2011 for the following 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.*

This AusPAR describes the application by Bristol-Myers Squibb Australia Pty Ltd (the sponsor) to extend the approved indications for Eliquis to include the following:

> *Eliquis is indicated to reduce the risk of stroke, systemic embolism, and death in patients with non-valvular atrial fibrillation with at least one additional risk factor for stroke.*
>
> *Eliquis also reduced the risk of major bleedings when compared to warfarin (see Clinical Trials).*

In addition, the sponsor proposed to register a new strength of Eliquis tablets, containing 5 mg of apixaban.

Regulatory status

The 2.5 mg product received registration on the Australian Register of Therapeutic Goods (ARTG) in July 2011. The 5 mg product was registered on 2 May 2013.

The overseas status concerning similar applications (for the indication in prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation) at the time this submission was considered by the TGA is shown in Table 1.

Table 1. Overseas registration status of apixaban

Country	Submission date	Approval date	Indications
European Union	29 Sep 2011	19 Nov 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).
United States	28 Sep 2011	28 Dec 2012	ELIQUIS® (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Country	Submission date	Approval date	Indications
Canada	22 Dec 2011	05 Dec 2012	ELIQUIS (apixaban) is indicated: · for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective knee or hip replacement surgery. · for the prevention of stroke and systemic embolism in patients with atrial fibrillation.
New Zealand	30 Aug 2012	Under evaluation	
Switzerland	28 Nov 2011	Under evaluation	

Product Information

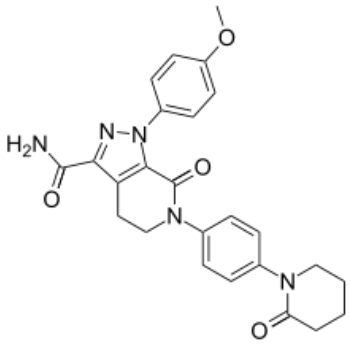
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Apixaban has the following structure:

Figure 1. Structure of apixaban



Apixaban is non-ionisable, thus its aqueous solubility is not affected by changes in pH. The drug substance is highly soluble for doses up to 10 mg. It is considered a low permeable drug given that the fraction of oral dose absorbed is <90%. All aspects relating to the drug substance for the proposed 5 mg tablet are identical to those approved for the registered 2.5 mg strength.

Drug product

The tablets are to be manufactured by using processes as for the registered strength. The 2.5 mg and 5 mg strengths are direct scales. The 5 mg strength is distinguished from the registered strength by colour, tablet shape and markings.

Real-time release testing for assay and content uniformity is to be used in the control of the 5 mg tablet (as for the registered strength).

The tablets are well controlled with satisfactory limits at release and expiry.

The stability data provided supports a shelf life of 3 years when stored below 30°C in the proposed packaging.

Biopharmaceutics

A study (Study CV 185029) comparing the oral bioavailability of the apixaban Phase III formulation tablets (10 mg: two 5 mg tablets) relative to an apixaban oral solution formulation (10 mg: 25 mL of a 0.4 mg/mL solution) was provided.

The 90% confidence intervals (CIs) for the area under the concentration time curve (AUC) from time zero to the last sampling time (AUC_{0-t}) and over time zero to infinity ($AUC_{0-\infty}$) were found to be within the usual criteria to conclude equivalence (80-125%). The 90% CIs for the maximum concentration (Cmax; 76-126%) were found to be outside the usual equivalence interval (80-125%). The company attributes the magnitude of the observed CIs to the limited statistical power inherent in the study's relatively small sample size (n=13). This has been brought to the attention of the clinical Delegate.

The relative bioavailability of apixaban in the solution and tablet formulations is 105%.

The proposed commercial tablet formulation has the same core formulation as the Phase III formulation but differs slightly in tablet shape and the colouring agent used in the film-coat. The company's justification for not conducting a bioequivalence study of the commercial formulation versus the Phase III formulation is acceptable to the Pharmaceutical Chemistry Section of TGA.

Advisory committee considerations

This application was not submitted for advice from the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

Quality summary and conclusions

There are no objections to the registration of the proposed new strength, Eliquis 5 mg apixaban tablets, with regard to chemistry, manufacturing and controls.

III. Nonclinical findings

Introduction

Three new nonclinical studies (two pharmacokinetic drug interaction and one juvenile repeat dose toxicity) as well as a minor amendment to a previously submitted embryofetal developmental study were submitted. While the overall quality of the nonclinical dossier was satisfactory and complied with principles of Good Laboratory Practice (GLP), the

submitted data were not directly relevant to the proposed extension of indication or higher dosage/strength *per se*.

Pharmacology

No new pharmacology studies were provided.

Pharmacokinetics

Pharmacokinetic drug interactions

The two new drug interaction studies consisted of *in vitro* cell assays (Caco-2 (human epithelial colorectal adenocarcinoma) cells and LLC-PK1 (pig kidney epithelial) cell monolayers) examining the effects of various non-steroidal anti inflammatory drugs (NSAIDS) and diltiazem on P-glycoprotein (P-gp)-dependent efflux of the model substrate digoxin.

Caco-2 cells

Digoxin had an efflux ratio in Caco-2 cells of 30, similar to the ratio of 24-29 previously shown for apixaban in the same cell type in a study included in the original apixaban registration submission. The same study showed that cyclosporin A and ketoconazole (strong P-gp inhibitors; both at 50 μM) incompletely inhibited apixaban efflux by 40-50% and 70-80%, respectively, compared to a complete inhibition of digoxin efflux, suggesting that transport of apixaban involves multiple transporters.

In the new study using Caco-2 cells (Study 930037853), digoxin (5 μM) efflux was inhibited 42%, 58% and 47% by naproxen (8 mM), diclofenac (2 mM) and diltiazem (0.03 mM), respectively. The result with naproxen compares favourably with the 42% inhibition of apixaban (3 μM) efflux previously observed with naproxen (6 mM) in the same cell type.

LLC-PK1 cells

In LLC-PK1 cells (Study 930037205), the permeability of digoxin (5 μM) was mildly impaired by ibuprofen (1 mM, 23%), sulindac (2.5 mM, 20%) and diltiazem (0.03 mM, 33%) but was almost completely inhibited by ketoconazole (30 μM, 97%). Apixaban (3 μM) efflux in LLC-PK1 cells was previously shown to be inhibited 51% by 30 μM ketoconazole, again suggesting that apixaban efflux (unlike digoxin) involves multiple transporters.

Overall, the nonclinical data on apixaban and P-gp transport are consistent with previously submitted clinical data where co-administration of apixaban with diltiazem or naproxen in healthy subjects enhanced the plasma AUC of apixaban by 40% and 54%, respectively (Study CV185032 and Study CV185054). These findings are suitably acknowledged in the *'Interaction with other medicines* section of the proposed PI.

Relative exposure

Animal-to-human exposure ratios are shown in Table 2, below, and are based on steady state values cited in the sponsor's *Nonclinical overview*, where in reference to the recommended human dose of apixaban (10 mg, or 5 mg twice daily (bid)) for atrial fibrillation (AF) the Cmax was 0.21 μg/mL and AUC over time zero to 24 h ($AUC_{0\text{-}24\ h}$) was 3.1 μg.h/mL. To account for differences in plasma protein binding in rat (96%), mouse (50%), rabbit (67%) and human (adults 87%), the following adjustment factors were applied 0.04, 0.5, 0.33 and 0.13, respectively (assuming similar plasma protein binding between adult and juvenile rats). Based on histopathological changes to the male

reproductive tract and report of one high dose (HD) group dam losing all her pups by post natal day (PND) 6, the no observed adverse effect level (NOAEL) was established at 50 mg/kg per day for both male and female rats. Data from previously evaluated studies in adult rats are also provided with revised exposure ratio measures based on the new dosage for AF.

No information was provided on exposure to apixaban in juvenile populations (that is, differences in plasma protein binding), thus the tabulated exposure measures do not reflect paediatric use.

Table 2. Relative exposure to apixaban based on steady state mean $AUC_{0\text{-}24\,h}$ (3.1 µg.h/mL) and Cmax (0.21 µg/mL) in healthy human subjects given 10 mg (5 mg, oral bid) apixaban

Study, species	Duration of treatment [study number]	Dose mg/kg/day	C_{max} µg/mL	$AUC_{0\text{-}24\,h}$ µg·h/mL	Exposure ratio#	
					C_{max}	$AUC_{0\text{-}24\,h}$
Repeat dose toxicity* Rat (Adult SD)	3 month [DN04100] (diet)	600	1.5 (0.06)	29.5 (1.18)	2.2	3
		1800	1.6 (0.064)	29.9 (1.196)	2.4	3
		2400	**1.95 (0.078)**	**37 (1.48)**	**2.9**	**4**
	3 month [DN02043] (gavage)	50	3 (0.12)	21.5 (0.86)	4.4	2
		200	3 (0.12)	24.4 (0.98)	4.4	2.4
		600	4.2 (0.17)	35 (1.4)	6.3	3.5
Repeat dose toxicity (NEW STUDY) Rat (Juvenile SD) (Gavage)	3 month [DN09014] @ PND 21 – Male	10	1.91 (0.076)	14.5 (0.58)	2.8	1.4
		50	**4.86 (0.194)**	**34.4 (1.376)**	**7.1**	**3.4**
		600	9.27 (0.37)	69.5 (2.78)	14	7
	3 month [DN09014] @ PND 21 – Female	10	2.57 (0.103)	21.6 (0.864)	3.8	2.1
		50	**5.02 (0.201)**	**29.2 (1.168)**	**7.4**	**3**
		600	9.47 (0.38)	88.1 (3.52)	14	9
	3 month [DN09014] @ PND 87 – Male	10	1.01 (0.04)	7.89 (0.316)	1.5	1
		50	**3.05 (0.122)**	**16.8 (0.66)**	**4.5**	**1.6**
		600	3.38 (0.135)	24.1 (0.96)	4.9	2.4
	3 month [DN09014] @ PND 87 – Female	10	1.34 (0.054)	9.49 (0.38)	2.0	1
		50	**3.3 (0.132)**	**18.5 (0.74)**	**4.8**	**2**
		600	4.91 (0.196)	29.9 (1.196)	7.2	3
Carcinogenicity* Mouse	24 months [DN05068] Male	150	0.23 (0.12)	2.8 (1.4)	4.4	3.5
		500	0.31 (0.16)	5.1 (2.6)	5.9	6.5
		1500	**0.37 (0.19)**	**7.3 (3.7)**	**7.0**	**9.2**
Carcinogenicity* Mouse	24 months [DN05068] Female	150	0.4 (0.2)	5.2 (2.6)	7.3	6.5
		500	0.6(0.3)	10.4 (5.2)	11	13
		1500	**0.89(0.45)**	**16.8 (8.4)**	**17**	**21**
Carcinogenicity* Rat	24 months [DN05069]	50	0.82 (0.033)	16.9 (0.676)	1.2	1.7
		200	1.28 (0.05)	27.2 (1.088)	1.8	2.7
		600	**1.35 (0.054)**	**27.9 (1.116)**	**2.0**	**2.8**
Fertility* Rat (Male)	2 week [DN05056]	50	1.63 (0.065)	12.8 (0.512)	2.4	1.3
		200	2.78 (0.111)	24.4 (0.976)	4.1	2.4
		600	**3.9 (0.156)**	**27.6 (1.104)**	**5.7**	**2.7**
Embryofetal development* Mouse (Female) (gavage)	GD 6-15 [DN06023]	600	3.23 (1.62)	14.6 (7.3)	59	18
		900	2.54 (1.27)	17.5 (8.8)	47	22
		1500	**4.02 (2.01)**	**15.9 (8)**	**74**	**20**

Study, species	Duration of treatment [study number]	Dose mg/kg/day	C_{max} µg/mL	AUC_{0-24h} µg·h/mL	Exposure ratio#	
					C_{max}	AUC_{0-24h}
Embryofetal development* Rat (gavage)	GD 6-15 [DN03042]	**3000**	**7.2 (0.288)**	**42.7 (1.708)**	**11**	**4.2**
Embryofetal development* Rabbit (gavage)	GD 7-19 [DN03045]	**1500**	**0.025 (0.0093)**	**0.355 (0.1313)**	**0.3**	**0.3**
Pre/postnatal development* Rat (gavage)	GD 6–PND 20 [DN08001]	**25**	**1.51 (0.06)**	**11.7 (0.468)**	**2.2**	**1.2**
		200	4.9 (0.196)	43.4 (1.736)	7.2	4.3
		1000	4.94 (0.197)	47.5 (1.9)	7.2	4.7
Steady state Human (healthy subjects)	**Adults**	10 mg (5 mg, oral bid)	0.21 (0.0273)	3.1 (0.403)	–	

= animal:human plasma $AUC_{0-24\ h}$;* Previously assessed as part of the nonclinical evaluation report to register apixaban; @: sampling day; NOAELs are bolded; ( ) Adjusted Cmax and AUC values using conversion factors to account for differences in plasma protein binding – mouse: 0.5 (50% bound); rat: 0.04 (96% bound); rabbit: 0.37 (67% bound); human: 0.13 (87% bound); GD = gestation day.

The exposure margins in the table above are smaller than those previously ascertained (due to the doubling of tablet strength and hence daily dosage) and require that the sponsor provide revised exposure values in the product information.

Toxicology

Repeat dose toxicity

While no paediatric extension of indication is being sought in this submission, the sponsor submitted a completed report of a 3 month repeat dose toxicity in juvenile rats that was ongoing at the time of the previous submission to register apixaban. Sprague Dawley rats received apixaban by oral gavage on postnatal days (PND) 4 to 94 followed by a one month recovery period and a subsequent mating period to assess potential effects on fertility and early development. There were no apixaban-related mortalities, and clinical observations were of relatively minor significance (that is, chromorhinorrhea, salivation). The main treatment-related effect was prolongation of coagulation parameters (prothrombin time, activated partial thromboplastin time, as well as higher fibrinogen levels in males), which normalised once treatment had ceased.

Serum analyses indicated slight rises in glucose levels, which persisted in the male recovery group. In contrast to findings reported previously for the submission to register apixaban, where apixaban caused decreases in plasma potassium in rats and dogs, this was not seen in the current juvenile toxicity study. There were some instances of hepatocyte vacuolation (2 out of 9 males; 2/10 females), though these did not differ from the vehicle control groups (1/10 males; 3/10 females). The previous Risk Management Plan (RMP) for apixaban raised this as a potential issue, but it was noted that there was no evidence for hepatotoxicity in previous studies or the current study.

Histopathological observations indicated epididymidal hypospermia (in 2/9 rats) and degeneration of seminiferous tubule (in 3/9 rats) in HD treated male rats, whereas in females there were more HD treated rats found to have mineralisation in the kidneys than vehicle treated. Male observations in the kidney were not provided.

Reproductive toxicity

A subset of treated juvenile rats in the 3 month study was set aside to assess the effects of apixaban exposure on fertility and early embryonic development (at the end of the dosing period; PND 89 or 94). Pregnancies resulting from treated male and untreated female pairings were used to determine litter values, while treated female and untreated male pairings were used to assess gestational periods and natural deliveries.

No adverse effects on mating or fertility indices were reported irrespective of the pairings, noting also that the higher instances of hypospermia (2/9 rats) and degeneration of seminiferous tubules (3/9 rats) seen in the HD group did not impair successful mating. There were no alterations to gestational periods or delivery of pup litters. One dam from the HD group lost all her pups by postpartum days 5-6, which was attributed to an isolated instance of decreased maternal care, nesting and grooming behaviour. In the mid dose (MD) group 3 dams had a pup from their litters missing (that is, partially cannibalised with missing extremity). This may be compared with the vehicle group where only one dam had a missing pup. However, the remainder of the pups were delivered normally with no adverse effects resulting from maternal exposure to apixaban.

In the previous submission, fertility and early embryofetal development in rats were not affected by apixaban at any of the tested doses (maximum dose 600 mg/kg oral gavage, n=22-25 per group, compared with n=9-10 in the current study). In that study, treatment-related effects were confined to prolonged coagulation, with a no observed effect level (NOEL) established at 600 mg/kg/day.

While there were no effects on mating and resulting pregnancies in the current fertility study, the NOAEL was set at 50 mg/kg per day on the basis that hypospermia and degeneration of seminiferous tubules was observed in the HD group and one dam from the HD group lost all her pups.

Paediatric use

Although the current submission contained a completed developmental toxicity study in juvenile rats, the sponsor is not seeking to register Eliquis for paediatric use.

Comments on the safety specification of the risk management plan

Results and conclusions drawn from the nonclinical program for apixaban detailed in the sponsor's draft RMP are in general concordance with those of the nonclinical evaluator.

Nonclinical summary and conclusions

- The nonclinical studies complied with GLP and were scientifically sound. The submitted studies contributed to the understanding of apixaban drug interaction mechanisms and the toxicity of apixaban in juvenile animals but did not directly address the extension of indications or higher dosage/strength *per se*.
- Two *in vitro* cell assay drug interaction studies were submitted that investigated potential interactions between candidate P-gp inhibitors and digoxin (as a model substrate). The results suggested that several commonly used medicines in AF (for example, naproxen and diltiazem) have mild to modest inhibitory effects on P-gp *in vitro* and may account for the modest increase in plasma AUC for apixaban observed in drug-interaction clinical trials (54% for naproxen, 40% for diltiazem; according to the sponsor's *Clinical overview*).
- The sponsor also submitted a 3 month repeat-dose toxicity study in juvenile rats which was ongoing at the time the original submission to register apixaban was

submitted. This study did not uncover any toxicities of major concern nor were there treatment-related mortalities. The most common apixaban-related effect concerned prolongation of coagulation parameters, which is characteristic of this class. Following a recovery period, no remarkable effects on male or female fertility or early embryonic development were observed in rats that received apixaban.

Recommendation

There are no nonclinical objections to the approval of apixaban for the new indication and the related increase in dose strength and daily dose.

The decision to approve the extension of indication to non-valvular AF will depend on clinical data as no nonclinical efficacy data were presented. The increased dose strength and maximum daily dose for this indication produce corresponding decreases in the relative exposure margins for apixaban attained in the animal studies and such changes should be documented in the draft PI.[1]

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

Apixaban is a reversible, selective inhibitor of FXa used to prevent thrombin generation and thrombus formation. It has numerous potential indications for the prevention of venous and arterial thrombotic and embolic events.

The approved indication is the prevention of venous thromboembolic events (VTEs) in adult patients who have undergone elective total hip or total knee replacement surgery.

The proposed additional indication is to reduce the risk of stroke, systemic embolism (SE) and death in patients with non-valvular AF with at least one additional risk factor for stroke.

Clinical rationale

Apixaban is an orally active, potent, direct, selective inhibitor of coagulation FXa. It directly and reversibly binds to the active site of FXa and exerts anticoagulant and antithrombotic effects by reducing the conversion of prothrombin to thrombin. At an oral dose of 2.5 mg bid, it has been approved for venous thromboembolism prophylaxis in patients who have undergone elective knee and hip replacement. As an alternative to warfarin, it has also been developed as an anticoagulant for prevention of stroke and SE in patients with non-valvular AF.

Atrial fibrillation is a common cardiac arrhythmia associated with a five-fold increase in the risk of stroke.[2,3] In patients with AF, anticoagulant agents such as warfarin or other vitamin K antagonists (VKAs)[4] are recommended for prevention of stroke and SE.[5] These

[1] Details of recommended revisions to the PI are beyond the scope of this AusPAR.

[2] Go AS *et al.* Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370-2375.

[3] Wolf PA *et al.* Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983-988.

[4] For simplicity, 'warfarin' therapy is assumed to include other vitamin K antagonists when used in the clinical parts of this document to describe non-study drug anti-coagulation therapy.

compounds exert their anticoagulant effect by antagonising the vitamin K-dependent clotting cycle and they are monitored by means of the international normalised ratio (INR, a measure of blood coagulation time). Current therapies for stroke prevention include warfarin, acetyl salicylic acid (ASA, also known as aspirin) and more recently, dabigatran. Antiplatelet therapy with low dose aspirin is recommended in patients with AF who are at low risk for stroke. Acetyl salicylic acid is also recommended for some patients at moderate risk for stroke if they are at high risk of bleeding, or in patients who have no access to adequate anticoagulation monitoring.[6] Warfarin provides effective protection against stroke but it is not prescribed in up to 50% of AF patients, due mainly to bleeding concerns, low risk of embolus, difficulty of use, or patient refusal. Moreover, INRs are in the therapeutic range only about 60% of the time during chronic warfarin therapy.[7] An oral FXa inhibitor which prevents stroke and reduces bleeding and death with a similar efficacy and safety profile compared with warfarin would significantly improve the long-term care and outcome of patients with AF.

Guidance

The proposed Phase III program, including apixaban dose selection, comparator selection, efficacy and safety endpoints, and statistical analyses, were discussed in depth with the FDA and the European Medicines Agency (EMA) progressively over 2005-2011. Pre-submission meetings were held with the FDA and EMA, and with the TGA in September 2011.

Contents of the clinical dossier

The submission contained the following clinical information:

- Three clinical pharmacology studies, including 3 that provided pharmacokinetic (PK) data and one that provided pharmacodynamic (PD) data.
- One population pharmacokinetic (PPK) analyses.
- Two pivotal Phase III efficacy/safety studies (Study CV185030 (known as ARISTOTLE) and CV185048 (known as AVERROES)) and one supportive Phase IIb study (Study CV185068).
- Clinical overview, summaries of clinical efficacy and clinical safety, and literature references.

Additional materials provided by sponsor:

- Supplementary data for apixaban Study CV185036 (known as ADOPT).
- Erratum to the sponsor's summary of the clinical pharmacology.
- Report into suspected misconduct at investigator site 1200 in China during the apixaban ARISTOTLE Study CV185030.

Paediatric data

The submission did not include paediatric data.

[5] ACC/AHA/ESC 2010 Guidelines for the management of patients with atrial fibrillation – executive summary. *Eur Heart J* 2010;31:2369-2429.

[6] Guidelines for the primary prevention of stroke: A guideline for healthcare professionals from the American Heart Association/Stroke Association. *Stroke* 2011; 42:517-584.

[7] Jones M *et al*. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of treatment with warfarin in patients with non-valvular atrial fibrillation: a record linkage study in a large British population. *Heart* 2005;91:472-477.

Good clinical practice

All studies were conducted according to International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and complied with the principles of the Declaration of Helsinki. The studies were monitored by the sponsor and Pharmaceutical Product Development (PPD) Inc.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 3 shows the studies relating to each PK topic.

Table 3. Submitted pharmacokinetic studies.

PK Topic	Subtopic	Study ID	Primary aim of the study
PK in health adults	General PK single dose multi-dose	 N/A Study CV185074	 Assess the multi-dose PK of apixaban and rivaroxaban
	Bioequivalence† single dose multi-dose	 Study CV185029 N/A	 Assess the oral bioavailability of apixaban solution formulation relative to tablets.
	Food Effect	N/A	
PK in special populations	Target population § single dose multi dose	 N/A N/A	
	Hepatic impairment	Study CV185025	Assess stable hepatic impairment on the PK of apixaban
	Renal impairment	N/A	
	Neonates/infants/ children/adolescents	N/A	
	Elderly	N/A	
	Other special populations	PPK Study	To describe the PK of apixaban in healthy subjects and individuals with non-valvular AF
Genetic/ gender-related PK	Males versus females.	PPK study	See above.
PK Interactions	None	None	
Population PK Analyses	Healthy subjects	PPK Study	See above.
	Target Population	PPK Study	See above
	Other	N/A	

† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's overall conclusions on pharmacokinetics

- Following 4 days of oral dosing of apixaban 2.5 mg every 12 h in healthy subjects the Cmax, time to reach Cmax (Tmax), AUC over the dosing interval (AUCtau) and half life (t½) of apixaban were 80.5 ng/mL, 2 h, 527 ng.h/mL and 8.65 h, respectively.
- The bioavailability (F) of 10 mg of the solution and tablet formulations were similar (F=105%), suggesting that the solution and tablet formulations may be used interchangeably.
- The AUC of 10 mg of the solution and tablet formulations were equivalent, whereas the Cmax was similar.

- No studies directly compared apixaban PK in patients with non-valvular AF and healthy subjects.
- Mild and moderate hepatic impairment did not significantly affect the PK of a single 5 mg oral dose of apixaban.
- No studies examined the PK of apixaban in subjects with severe hepatic impairment.
- PPK analysis indicated that the subject's age and gender were predictive covariates on apparent non renal clearance (CLNR/F). Body weight and patient population were found to influence the volume of distribution central compartment (Vc/F); and Asian race, AF, recent acute coronary syndrome and strong or moderate cytochrome P450 3A4 (CYP3A4)/P-gp inhibitors resulted in decreased clearance compared to clearance in non-Asian subjects, healthy subjects or patients who did not receive strong or moderate CYP3A4/P-gp inhibitors, respectively.

Pharmacodynamics

Apixaban is a reversible, direct and highly selective inhibitor of FXa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound FXa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, apixaban prevents thrombin generation and thrombus development.

Studies providing pharmacodynamic data

Table 4 shows the studies relating to each PD topic.

Table 4. Studies relating to pharmacodynamics.

PD Topic	Subtopic	Study ID	Primary aim of the study
Primary Pharmacology	Anti-FXa effect	Study CV185074	To assess the multi-dose anti-FXa activity of apixaban in healthy subjects.
Secondary Pharmacology	NA	NA	
Gender other genetic and Age-Related Differences in PD Response	Effect of gender	N/A	
PD Interactions	None provided.	None	
Population PD and PK/PD analyses	Healthy subjects	N/A	Characterisation of the relationships between apixaban plasma concentration and anti-FXa activity.
	Target population	N/A	See above.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.
‡ And adolescents if applicable.

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

Evaluator's overall conclusions on pharmacodynamics

In healthy subjects:

- there was a close temporal relationship between changes in apixaban and rivaroxaban (also a FXa inhibitor) plasma concentrations and changes in anti-FXa activity, with no delay of onset observed.

- for both apixaban and rivaroxaban, a linear relationship between plasma concentration and anti-FXa activity was observed. However, further PPK modelling indicated that a linear relationship between concentration and anti-FXa activity was not sufficient to accurately predict the effects of apixaban at both low and high concentrations in patients with non-valvular AF.
- rivaroxaban and apixaban induced anti-FXa activity with a median Tmax of 2 h; however, the geometric mean peak anti-FXa activity was approximately 2.5 fold higher following rivaroxaban than following apixaban treatment.

No studies directly compared apixaban PD in patients with non-valvular AF and healthy subjects.

Following a single 5 mg oral dose of apixaban, mild and moderate hepatic impairment had no effect on the ability of the drug to modify INR and activated partial thromboplastin time (aPTT), or on its anti-FXa activity activity.

Dosage selection for the pivotal studies

For comparator studies, the dose of warfarin was adjusted to an INR of 2.0-3.0, a range universally accepted for deep venous thrombosis (DVT) treatment and stroke prevention in patients with AF. The ASA dose was selected at the discretion of the investigator within the range 81–324 mg once daily to accommodate differences in local and international usage guidelines for low dose aspirin prophylaxis.

The dose of apixaban was selected from the Phase II study (Study CV185010) which compared daily apixaban doses of 5, 10 and 20 mg, given both once daily and bid, against blinded enoxaparin 30 mg by subcutaneous (SC) injection every 12 h and open-label warfarin.

Study CV185010 was fully evaluated by the TGA for the initial apixaban registration submission of 2011 for the indication of elective knee and hip replacement surgery. For all apixaban groups, VTE/all-cause death rates were at least 21% lower compared with the rate on enoxaparin, and at least 53% lower than the rate in subjects on warfarin. All doses of apixaban had favourable efficacy but the higher doses, 10 and 20 mg/day, had similar or higher rates of bleeding than enoxaparin. Apixaban had lower rates of bleeding compared with enoxaparin at the lower doses of 2.5 mg bid and 5 mg once daily. There was also a significant efficacy advantage in favour of bid dosage compared with once daily dosage. The event rate was 8.4% for the apixaban 2.5 mg bid regimen, and 13.1% for the apixaban 5 mg once daily regimen for the primary endpoint.

A Phase II study (Study CV185017) of DVT prevention compared three apixaban groups (5 mg bid, 10 mg bid and 20 mg bid) with an open-label warfarin group in subjects who had undergone elective hip or knee replacement surgery. Study CV185017 has not been reviewed as the Clinical Study Report (CSR) was not included in the data package. A brief study design and outcome were recorded in a commentary provided by the sponsor in the current submission. Venous thromboembolic event rates were low in all groups and there was no excess bleeding in any apixaban group.

For the proposed indication of AF, stroke prevention was considered to outweigh the risk of bleeding and an apixaban dose of 5 mg bid was selected to provide the optimum balance of efficacy and safety. However, patients considered at high risk of bleeding[8] by the investigators were given the lower apixaban dose of 2.5 mg bid. No dose ranging studies were performed in subjects with AF.

[8] Those meeting at least 2 of the following criteria: age ≥80 years, body weight ≤60 kg or serum creatinine ≥133 µmol/L.

Efficacy

Studies providing efficacy data

Pivotal efficacy studies

Study CV185030. The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)[9]

This was an active-controlled (warfarin), randomised, double-blind, double-dummy, parallel group study comparing apixaban to warfarin, with titration of warfarin based on central monitoring of the INR.

Subjects with AF and at least one additional risk factor for stroke were randomised 1:1 to receive either apixaban 5 mg bid or warfarin titrated to INR 2.0-3.0 with matched placebo tablets. There was a screening period of up to 14 days or until the patient's INR was stabilised within the acceptable range. This was followed by a treatment phase lasting until the earlier of subject discontinuation or the recording in the study population of approximately 448 primary efficacy events, with a post-treatment follow-up period of 30 days.

Apixaban (or matching placebo) was given 5 mg bid. It was given 2.5 mg bid if any two[10] of the following criteria applied at baseline: age ≥80 years, body weight ≤60 kg or serum creatinine ≥133 µmol/L. Dosing of warfarin or matching placebo employed a standard algorithm with central monitoring of INR measurements using encrypted point-of-care devices. All subjects were followed for the development of stroke (haemorrhagic, ischaemic or unspecified), SE, myocardial infarction (MI), death, bleeding, hospitalisation or treatment discontinuation, until the end of the study. All efficacy and safety endpoints were evaluated by an independent, external, blinded Events Adjudication Committee.

The primary efficacy outcome was to determine if apixaban was non-inferior to warfarin (INR target range 2.0-3.0) for the combined endpoint of stroke (haemorrhagic, ischaemic or unspecified) or SE in subjects with AF and at least one additional risk factor for stroke.

Other efficacy outcomes were to determine if apixaban was superior to warfarin for:

- the combined endpoint of stroke or SE
- major bleeding
- all cause death

Study CV185048. The Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment study (AVERROES)

This was a randomised, double-blind, double-dummy, parallel-group study comparing apixaban and ASA for the prevention of stroke in AF subjects who have failed or are unsuitable for warfarin treatment. A total of 6,421 subjects were enrolled in the study and 5,598 (2,798 on apixaban and 2,780 on ASA) were randomised to receive study treatment.

The trial required subjects who had at least one additional risk factor for stroke and who had previously used or were unsuitable for warfarin. They were screened during a 28 day period and then randomised 1:1 to receive apixaban or ASA. Following randomisation, visits were scheduled at Months 1 and 3, and then every 3 months until completion of the

[9] Issues relating to a breach of GCP at a clinical trial site in China and to an unusually high incidence of potential dosing errors in this study were considered during the evaluation of these data (see *List of Questions*, *Second Round Clinical Summary and Conclusion*, and *Overall Conclusion and Risk/Benefit Assessment*, below).

[10] Sponsor clarification: subjects were required to meet at least two of the stated criteria.

double-blind phase of the study. Subjects who discontinued study treatment were followed for outcome events until the end of the double-blind period. The double-blind treatment period was to end after at least 226 primary efficacy endpoints were recorded.

Subject numbers and study duration were based on event rates from similar studies. However, following a planned interim analysis the Data Monitoring Committee (DMC) stopped the study early because of superior efficacy in the apixaban group.

All subjects were followed for the development of stroke (haemorrhagic, ischaemic or unspecified), SE, MI, death, bleeding, hospitalisation or treatment discontinuation until the end of the study.

Subjects were randomised 1:1 to receive either:

- Apixaban 5 mg bid (or 2.5 mg for at risk subjects) or matching placebo.
- ASA 81 to 324 mg once daily or matching placebo.

Apixaban (or matching placebo) was given as a 5 mg tablet bid, or as a 2.5 mg tablet bid for subjects at increased risk of bleeding; namely those who met at least two of the following criteria: age >80 years, body weight ≤60 kg or serum creatinine ≥133 μmol/L.

The ASA dose was selected at the discretion of the investigator. More than 90% of subjects were receiving a dose of either 81mg or 162 mg on the day of randomisation.

The main efficacy outcome was to determine if apixaban 5 mg bid (2.5 mg bid in selected at risk subjects) is superior to ASA (81 to 324 mg once daily) for preventing the composite outcome of stroke or SE in subjects with AF and at least one additional risk factor for stroke who failed or are unsuitable for warfarin therapy.

Other efficacy outcomes included:

- To determine if apixaban is superior to ASA for prevention of the composite endpoint of stroke, SE, MI or vascular death (major vascular events).
- To determine if apixaban is superior to ASA for all-cause death.
- To compare apixaban and ASA with respect to: the composite outcome of stroke, SE, MI, vascular death, or major bleeding (net clinical benefit); the composite endpoint of all-cause death, stroke, or SE; vascular death; or major bleeding.

Other efficacy studies

Study CV185067

This was a Phase IIb, randomised, partially blind (double-blind apixaban, open-label warfarin), active controlled (warfarin), multicentre study to evaluate the safety and dose-response relationship of two doses (2.5 mg bid and 5 mg bid) of apixaban compared to warfarin (controlled INR 2.0-3.0) administered for 12 weeks in Japanese subjects with non-valvular AF.

The primary objective was to assess the effects of two doses of apixaban (2.5 mg bid and 5 mg bid) compared with warfarin on the composite endpoint of major and clinically relevant non-major (CRNM) bleeding events during the treatment period.

Secondary objectives included:

- To compare the effects of two doses of apixaban and warfarin on all bleeding events (major bleeding, CRNM bleeding and minor bleeding).
- To compare the effects of two doses of apixaban on major bleeding events.
- To assess the overall safety and tolerability of apixaban and warfarin.

- To compare the effects of two doses of apixaban and warfarin on efficacy endpoints (stroke, SE, all-cause death and MI).
- PK, PD and biomarker data to characterise the profile of apixaban in Japanese subjects.

Study CV185036. Study of Apixaban for the Prevention of Thrombosis-related Events in Patients With Acute Medical Illness (ADOPT).

Study CV185036 (ADOPT) was a Phase III randomised, double-blind, parallel-group, multi-centre study of the safety and efficacy of apixaban for prophylaxis of VTE in acutely ill medical subjects during and following hospitalisation. A total of 6,528 subjects were randomised 1:1 to receive either enoxaparin 40 mg SC once daily while in hospital or oral apixaban 2.5 mg bid for 30 days.

The primary efficacy endpoint was the composite of adjudicated total VTE (fatal and non-fatal pulmonary embolism (PE), and symptomatic or asymptomatic proximal and distal DVT) and VTE-related death during the intended treatment period.

Superiority of apixaban for the primary efficacy endpoint was not demonstrated. Event rates were 2.71% in the apixaban group compared with 3.06% in the enoxaparin group and the trend in favour of apixaban was not statistically significant (hazard ratio (HR) 0.87 [95% CI 0.62-1.23, p<0.44]).

This was a study of a lower dose of apixaban with a different comparator given for a shorter duration for a different indication. The study failed its primary endpoint but it is included in the clinical evaluation for its additional safety data in relation to apixaban.

Evaluator's conclusions on clinical efficacy for the indication: to reduce the risk of stroke, systemic embolism and death in patients with non-valvular AF with at least one additional risk factor for stroke

Two large Phase III studies demonstrated a statistically significant superiority for apixaban compared to warfarin and ASA for the composite endpoint of stroke (haemorrhagic and ischaemic) and SE. The great majority of events were stroke with fewer SE, consistent with other studies of anticoagulation in subjects with AF. No formal analyses of pooled data were performed but the results in both studies were internally consistent.

In Study CV185030 (ARISTOTLE), stroke or SE occurred in subjects on apixaban at a rate of 1.27%/year compared with 1.6%/year in subjects on warfarin (p=0.0114, HR 0.79 [95% CI 0.66-0.95]). In Study CV185048 the rates were 1.62% in subjects who were given apixaban, and 3.63%, in subjects given ASA (p<0.0001, HR 0.45 [95% CI 0.32-0.62]). All-cause death rates were also lower in subjects who received apixaban in both studies, although the difference was statistically significant only in Study CV185030 (p<0.0465, HR 0.89 [95% CI 0.80-1.00]). In both studies, individual event rates for ischaemic and undetermined stroke, haemorrhagic stroke, SE and MI were numerically less frequent in the apixaban groups compared with the warfarin and ASA groups.

Study CV185048 (AVERROES) was stopped early by the DMC because of clear superiority for the primary endpoint in favour of apixaban compared with aspirin. It is possible that superiority for secondary endpoints such as all-cause death might have achieved statistical significance if the trial had run its full course. Apixaban was statistically superior to ASA for prevention of stroke (haemorrhagic or ischaemic) and SE (HR 0.45 [unadjusted 95% CI 0.32-0.62]). It was also associated with a reduction in major vascular events (composite of stroke, SE, MI and vascular death). The incidence of individual endpoints including haemorrhagic stroke, ischaemic stroke, unspecified stroke, vascular death and MI was lower in the apixaban group compared with the warfarin group.

The studies were designed in compliance with EMA and FDA guidelines for thrombotic therapy. The studies were adequately powered and conducted, randomised, double-dummy, double-blind, active controlled and parallel group. The studies were well balanced for baseline characteristics including medical history, age, gender and race, and the study population represented the target population for apixaban in this submission. Study withdrawals and significant deviations from the protocol were not excessive. The efficacy and safety endpoints were appropriately monitored and confirmed by an independent, external adjudicating committee.

The key objective in the pivotal Study CV185030 was non-inferiority of apixaban compared with warfarin. This objective was not only achieved but statistically significant superiority of apixaban over warfarin was also demonstrated. The percentage benefit was small but clinically meaningful given the major consequences of the efficacy outcomes in question.

Apixaban was superior to warfarin in subjects considered suitable for warfarin therapy. Apixaban was also superior to ASA for subjects considered unsuitable for warfarin therapy. The benefit was apparent in subgroups including age, gender, race and renal function. A similar benefit was observed in at-risk subjects (those with at least two of following criteria: age ≥80 years, body weight ≤60 kg or serum creatinine ≥133 μmol/L) who received a lower dose of apixaban 2.5 mg bid.

Apixaban was superior to warfarin and ASA for all efficacy endpoints but most of the benefit was driven by a reduction in stroke. There were numerical benefits in favour of apixaban for individual endpoints such as SE but the numbers were small and the differences were not statistically significant. The practice is widespread but it is a moot point whether claims for such infrequent events should be captured in composite endpoints.

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies:

The pivotal Phase III Studies CV185030 (ARISTOTLE) and CV185048 (AVERROES) provided the main safety data in the target population treated for up to 2.1 years. Adverse events (AEs) could be reported spontaneously or during open-ended questioning, examination, or evaluation of subjects at each study visit. To prevent bias, subjects were not questioned about the specific occurrence of AEs.

Other studies evaluable for safety only:

The non-pivotal Phase II efficacy Study CV185067 provided limited safety data.

Additional safety data:

These were evaluated in the unrelated Study CV185036 (ADOPT). Major bleeding occurred in 0.47% in the apixaban group and 0.19% in the enoxaparin group. The adjusted difference between groups was 0.29% (95% CI 0.01-0.57, p<0.44). The frequency of AEs, serious AEs (SAEs), deaths, and discontinuations due to AEs was similar in both treatment groups. The frequency of hepatic events and marked laboratory abnormalities was also similar in both treatment groups.

Major bleeding events were infrequent in both treatment groups but numerically more frequent in the apixaban group. Some of the excess bleeding events in the apixaban group can be attributed to the longer treatment duration (approximately 30 days for apixaban

and 7 days for enoxaparin). Overall, the safety profile of apixaban in this study is compatible with the profile observed in the AF pivotal studies discussed below.

Patient exposure

Total exposure was high in the 23,718 subjects included in two pivotal Phase III studies. Exposure in Study CV185030 was 15,534 and 15,184 patient-years for apixaban and warfarin respectively, with an average duration of treatment of approximately 1.7 years. Exposure in Study CV185048 was 3,193 and 3,150 patient-years for apixaban and ASA respectively in-study, with an average duration of treatment of approximately 1.1 years.

In eight completed Phase II and III studies in other indications, safety data are available for an additional 11,929 subjects who received apixaban. Of these, 4,452 subjects received apixaban 10 mg/day, either as 5 mg bid or 10 mg once daily.

Evaluator's overall summary and conclusions on clinical safety

Monitoring of standard safety endpoints (including AEs, SAEs, laboratory investigations, vital signs, electrocardiograms (ECGs), liver function tests (LFTs) and neurologic AEs) demonstrated no clinically significant differences between subjects treated with apixaban and the active comparators warfarin and ASA. There were no placebo control subjects. However, exposure was high in all treatment groups (15,534 and 15,184 patient-years for apixaban and warfarin respectively in Study CV185030; 3,193 and 3,150 patient-years for apixaban and ASA respectively in Study CV185048). Duration of treatment averaged approximately 1.7 years for study CV185030 and 1.1 years for study CV158048 so it is unlikely that a significant, common safety signal for apixaban was overlooked.

The primary safety endpoint in both pivotal studies was bleeding. Bleeding events were categorised *a priori*, investigated and recorded carefully, and major events were confirmed by an independent, external adjudicating committee.

In Study CV185030, the safety profile of apixaban in relation to major and minor bleeding was superior to warfarin. The difference was highly significant and clinically relevant. In contrast, in Study CV185048 there was a higher incidence of major bleeding in the apixaban group compared with the ASA group. The difference was not statistically significant and the number of fatal bleeds and intracranial haemorrhages was the same in both groups. However, there was a statistically significant increase in the composite of both major + CRNM bleeding and all-bleeding in the apixaban group compared with the ASA group. On balance, the evidence suggests that apixaban is more likely to cause bleeding than ASA (as might be predicted from the pharmacology of the two compounds).

The safety profile of apixaban was similar in subgroups which included the elderly, subjects with renal failure, and both warfarin-experienced and warfarin-naïve subjects. Of special note, apixaban was not associated with an increased risk of MI in either pivotal study although approximately one third of subjects had pre-existing coronary artery disease.

Overall, the safety summary provided by the sponsor is acceptable.

List of questions

Pharmacokinetics

Other than information contained in the PPK report, have the PK of apixaban in patients with AF and healthy subjects been directly compared in a single study? If so, the sponsor is requested to provide the relevant details.

The sponsor is requested to provide the report of Study CV185025 for review within the Round 2 evaluation phase of this submission.

Pharmacodynamics

Other than information contained in the PPK report, have the PD of apixaban in patients with AF and in healthy subjects been directly compared in a single study? If so, the sponsor is requested to provide the relevant details.

Regulatory concerns

The sponsor is requested to provide a copy of its responses to all of the questions asked in the US FDA Complete Response Letter (CRL) addressed to Bristol-Myers Squibb in the USA and signed on 22/06/2012[11], a copy of which has been provided to the TGA. If there are questions and/or issues from this CRL which are still unresolved by the due date for responding to the TGA questions, the sponsor is requested, in that response, to identify these questions and/or issues so that the Delegate can seek to resolve them *via* the Delegate's overview (see *Overall conclusion and Risk/Benefit assessment* in this AusPAR).

First round clinical summary and conclusions

First round benefit-risk assessment

First round assessment of benefits

The lifetime risk of AF in those over 55 years of age is 20-25% in both genders in the US and Europe and the incidence will rise as these populations age. Atrial fibrillation reduces exercise tolerance and may exacerbate cardiac failure. However, the most significant association is stroke which is increased five fold in those with AF. More than 15% of strokes are associated with AF and 70% of these are fatal. The risk of stroke is 2.8% in those aged 60-69 years: 9.9% in those aged 70-79; and 23.5% in those aged 80-89.[12] The mortality in subjects with AF is twice that of age-matched subjects with sinus rhythm, due at least in part to the increased risk of stroke. The risk of stroke is enhanced by the association with other risk factors encapsulated in the cardiac failure, hypertension, age, diabetes and stroke (including transient ischemic attack; TIA) (the $CHADS_2$[13]) score.[14]

Warfarin is the gold standard for the prevention of stroke in subjects with AF and stroke rates may be reduced by up to 64% compared with subjects treated with placebo.[15] However, up to 50% of subjects with AF receive treatment other than warfarin (approximately 30% are treated with ASA and 20% receive no antithrombotic therapy).[16] Antiplatelet agents such as ASA reduce stroke in AF subjects by 20%, but warfarin reduces stroke by 40% compared with anti-platelet agents.[17]

[11] This document is available on the FDA website at <http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202155Orig1s000TOC.cfm>
[12] Marini C *et al*. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke* 2005;36:1115-1119.
[13] The CHADS2 score assigns one point each for congestive heart failure [C], hypertension [H], age 75 years or older [A], and diabetes [D], and two points for a previous stroke [S2] or transient ischaemic attack.
[14] Gage BF *et al*. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;13:2864-2870.
[15] Hart RG *et al*. Adjusted-dose warfarin versus aspirin for preventing stroke in patients with atrial fibrillation. *Ann Intern med* 2007;147:590-592.
[16] Birman-Deych E *et al*. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. *Stroke* 2006;37:1070-1074.
[17] Hart RG *et al*. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; 146:857-867.

Several European and US guidelines together advocate the use of warfarin for subjects with two or more risk factors for stroke, and ASA as a less preferable alternative for those with only a single risk factor. Up to 50% of subjects are considered unsuitable for warfarin therapy, mainly due to the risk of bleeding. Moreover, the benefit of warfarin therapy depends on the maintenance of INR within 2.0-3.0 but this is notoriously difficult to achieve, especially in elderly subjects. Treatment is complicated by concomitant illnesses such as hepatic and renal impairment, concomitant medications with the risk of drug-drug interactions, poor treatment compliance and logistic difficulties associated with long-term INR monitoring.

Acetyl salicylic acid reduces the risk of stroke, but not fatal stroke, in AF patients by up to 22% compared with placebo. However, ASA has been shown to be less effective than warfarin in preventing stroke, with event rates of 4.5% and 2.4% respectively (HR 0.55 [95% CI 0.43-0.71]).[18]

The primary efficacy endpoint in both pivotal studies provided for this submission was stroke (ischaemic, haemorrhagic or unspecified) or SE. Secondary endpoints were all-cause death in both studies, and major vascular events (stroke, SE, MI, vascular death) in Study CV185048. The primary endpoint for Study CV185030 was non-inferiority or superiority if non-inferiority was demonstrated. Non-inferiority was demonstrated and apixaban was significantly superior to warfarin and to ASA for the composite endpoint of stroke and SE. The incidence of SE was low compared with stroke, as demonstrated in previous AF studies. Apixaban had the largest benefit on haemorrhagic stroke as shown in Table 5 and Table 6:

Table 5. Key efficacy outcomes in subjects with AF in Study CV185030

	Apixaban N=9120 n (%/yr)	Warfarin N=9081 n (%/yr)	Hazard Ratio (95% CI)	P-Value
Stroke or systemic embolism*	**212 (1. 27)**	**265 (1. 60)**	**0. 79 (0. 66, 0. 95)**	**0. 0114**
Stroke				
Ischemic or undetermined	162 (0. 97)	175 (1. 05)	0. 92 (0. 74, 1. 13)	
Hemorrhagic	40 (0. 24)	78 (0. 47)	0. 51 (0. 35, 0. 75)	
Systemic embolism	15 (0. 09)	17 (0. 10)	0. 87 (0. 44, 1. 75)	
All-cause death*†	**603 (3. 52)**	**669 (3. 94)**	**0. 89 (0. 80, 1. 00)**	**0. 0465**

Table 6. Key efficacy outcomes in subjects with AF in Study CV185048

	Apixaban N=2807 n (%/year)	Aspirin N=2791 n (%/year)	Hazard Ratio (95% CI)	P-Value
Stroke or Systemic embolism*	**51 (1. 62)**	**113 (3. 63)**	**0. 45 (0. 32, 0. 62)**	**<0. 0001**
Stroke				
Ischemic or undetermined	43 (1. 37)	97 (3. 11)	0. 44 (0. 31, 0. 63)	
Hemorrhagic	6 (0. 19)	9 (0. 28)	0. 67 (0. 24, 1. 88)	
Systemic embolism	2 (0. 06)	13 (0. 41)	0. 15 (0. 03, 0. 68)	
Stroke, SE, MI, or vascular death*	**132 (4. 21)**	**197 (6. 35)**	**0. 66 (0. 53, 0. 83)**	**0. 003**
Myocardial infarction	24 (0. 76)	28 (0. 89)	0. 86 (0. 50, 1. 48)	
Vascular Death	84 (2. 65)	96 (3. 03)	0. 87 (0. 65, 1. 17)	
All-cause death*†	**111 (3. 51)**	**140 (4. 42)**	**0. 79 (0. 62, 1. 02)**	

[18] Camm AJ *et al*. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31:2369-2429.

Apixaban significantly reduced all-cause death compared with warfarin, with a trend in favour of apixaban compared with ASA. In Study CV185048, there was a significant benefit in favour of apixaban on major vascular events. The efficacy benefit was apparent in all subgroups and appeared to be independent of previous warfarin use, age, gender, number of risk factors for stroke, renal function, and apixaban dose reduction in at risk subjects. Apixaban was also superior to warfarin even in subjects whose INR control was in the optimal range.

The statistical benefit in favour of apixaban was highly significant when compared with both warfarin and ASA. The benefit in favour of apixaban was clinically worthwhile but modest compared with warfarin (HR 0.79 [95% CI: 0.66-0.95] for stroke; HR 0.89 [95% CI: 0.80-1.00] for all-cause death). However, the clinical benefit in favour of apixaban compared with ASA was more marked than that with warfarin (HR 0.45 [95% CI: 0.32-0.62] for stroke; HR 0.66 [95% CI: 0.53-0.83] for major vascular events). Overall, there is strong evidence that apixaban is equally effective or superior to the current gold standard therapies for stroke prevention in AF.

First round assessment of risk

Standard safety endpoints included AEs, SAEs, death, discontinuations due to AEs, neurologic and laboratory assessments including LFTs were recorded. Overall, the frequency of all the safety indices was acceptable with no evidence to suggest excess risk in the apixaban group compared with the warfarin and ASA groups.

The single greatest risk of apixaban for the proposed indication is bleeding. The frequency of bleeding with apixaban has been compared with warfarin, the most widely used anticoagulant therapy, and ASA, the most widely used antiplatelet agent for prophylaxis in AF. The frequency of bleeding was carefully evaluated and classified according to accepted guidelines such as *International Society on Thrombosis and Hemostasis* (ISTH), *Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries Trial* (GUSTO) and *Thrombolysis in Myocardial Infarction* (TIMI). Bleeding endpoint criteria were closely defined and adjudicated by a blinded expert panel for consistent reporting and to avoid bias.

The frequency of major bleeding, fatal haemorrhages, intracranial haemorrhages and all-bleeding was less in the apixaban group compared with the subjects on warfarin, as shown below in Table 7. The benefit in favour of apixaban was statistically significant, clinically relevant, and was independent of INR control in the warfarin group. Major bleeding at critical sites was similar or lower in the apixaban group compared with the warfarin group, with the possible exception of intraocular bleeding.

Table 7. Bleeding events in Subjects with AF in the Study CV185030

	Apixaban N=9088 n (%/year)	Warfarin N=9052 n (%/year)	Hazard Ratio (95% CI)	P-value
Major*†	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Fatal	10 (0.06)	37 (0.24)		
Intracranial	52 (0.33)	122 (0.80)		
Major + CRNM	613 (4.07)	877 (6.01)	0.68 (0.61, 0.75)	<0.0001
All	2356 (18.1)	3060 (25.8)	0.71 (0.68, 0.75)	<0.0001

* Assessed by sequential testing strategy for superiority designed to control the overall type I error in the study.

Major bleeding occurred more often in the apixaban group compared with the ASA group as shown below in Table 8. The difference was not statistically significant and there was no increase in the number of subjects with fatal or intracranial bleeds. However, there was

a statistically significant benefit in favour of ASA for the composite of major + CRNM bleeding and all-bleeding.

Table 8. Bleeding events in Subjects with AF in the Study CV185048

	Apixaban N=2798 n(%/year)	ASA N=2780 n (%/year)	Hazard Ratio (95%CI)	P-value
Major†	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.0716
Fatal, n	5 (0.18)	5 (0.18)		
Intracranial, n	11 (0.39)	11 (0.40)		
Major + CRNM	140 (4.46)	101 (3.24)	1.38 (1.07, 1.78)	0.0144
All	325 (10.85)	250 (8.32)	1.30 (1.10, 1.53)	0.0017

The frequency of bleeding is clearly less in subjects treated with apixaban than with warfarin and the benefit is clinically meaningful. As would be expected, the frequency of bleeding is greater in subjects treated with apixaban compared with ASA. The excess risk is small but clinically meaningful despite the similar frequency of fatal and intracranial bleeds in both treatment groups.

First round assessment of benefit-risk balance

The benefit-risk balance of apixaban 5 mg bid, given for the proposed usage, is favourable.

First round recommendation regarding authorisation

Authorisation is recommended for apixaban 2.5 mg bid or 5 mg bid for the proposed additional indication *to reduce the risk of stroke, systemic embolism and death in patients with non-valvular AF with at least one additional risk factor for stroke*.

Second round clinical summary and conclusions

Evaluation of clinical data submitted in response to questions

This section provides the TGA clinical evaluator's summary and assessment of the sponsor's responses to the List of Questions (above).

Question. The sponsor is requested to provide the report of PK Study CV185025 for review within the Round 2 evaluation phase of this submission.

Sponsor's response. Study CV185025 was previously submitted in the application to register Eliquis for prevention of VTE. At the request of the TGA an additional copy of this study was provided prior to the due date of this response.

Evaluator's response. Study CV185025, which examined the apixaban PK in subjects with mild to moderate hepatic impairment and in healthy subjects, was received prior to the clinical evaluator finalising the First Round Evaluation (above); therefore, the results and findings of this study were reviewed before the Second Round Evaluation commenced.

Questions. Other than information contained in the PPK report, have the PK [and/or PD] of apixaban in patients with AF and in healthy subjects been directly compared in a single study? If so, the sponsor is requested to provide the relevant details.

Sponsor's response. There is no single study comparing the PK/PD of apixaban between healthy subjects and patients with AF. All comparisons between healthy subjects and patients with AF have been made on the basis of population pharmacokinetic modelling.

Evaluator's response. The sponsor has confirmed that no studies directly compared the PK/PD in patients with AF and healthy subjects. The PPK modelling study indicated that

AF patients had decreased apixaban CL/F (13.9%) compared to non-Asian healthy subjects, suggesting that apixaban exposure is increased in subjects with AF compared with healthy non-Asian subjects. In addition, Asian race reduced apixaban clearance by 14%; and a 15% to 30% increase in AUC (compared to control) was observed for intrinsic factors such as age (≥65 years), gender, and low body weight (≤50 kg), whereas, body weight ≥120 kg was associated with an approximately 30% lower $AUC_{0-\infty}$. Therefore in the absence of clinical trial data that directly examine the effects of these characteristics on apixaban PKs and PDs, the evaluator recommends that the *Precautions* section of the PI is modified to identify that these characteristics may alter apixaban PK and PD.[19]

Question. The sponsor is requested to provide a copy of its responses to all of the questions asked in the US FDA CRL.

Evaluator's assessment: A copy of the sponsor's responses to the FDA CRL was provided to the TGA. The clinical evaluator's summary and assessment of the issues in relation to matters raised by the FDA are summarised below.

The questions raised by the FDA relate mainly to dispensing errors in the ARISTOTLE study and potential root cause analyses.

FDA Question 1: The most significant concern was related to dosing errors in the ARISTOTLE study (CV185030) where (according to the CSR) it appeared that at some point in the study 7.3% of subjects in the apixaban group and 1.2% of subjects in the warfarin group received a study medication container of the incorrect type. In a report to the EMA, the sponsors stated that the frequency of drug dispensation errors to patients was <0.1%. However, the FDA requested a more detailed analysis to ensure there was no impact on any primary efficacy or safety endpoints due to patients who may have received two active study drugs (apixaban and warfarin), or no active study at all.

Three independent, mutually exclusive audits were conducted on random samples of tear-off dispensing labels attached to the study drug containers. The first audit of an 8% patient sample was initiated by the sponsor and a further 12% sample was analysed at EMA request. The FDA requested a further sample of 20%, taking the complete sample to 40% of all study subjects. Legible labels were obtained in 99.2% of the total sample.

In the FDA initiated audit, dispensing the wrong study medication occurred in 0.1% of apixaban patients and 0.116% of patients assigned to warfarin. In the initial 20% sample audit the frequencies were 0.048% for apixaban and 0.041% for warfarin. Although the numbers were small, the frequency of detected errors was double in the 40% audit compared with the 20% audit. However, sampling errors become less frequent as sample size increases and the true error rate is unlikely to be significantly different from the rate detected in the 40% sample.

The average number of dispensations in each patient was twenty: most errors were isolated and multiple errors did not occur in individual patients. Observed errors were combined with missing data to give an estimate of total error, assuming that the observed and missing error rates were the same. Using this worst case analysis, the overall frequency of incorrect dispensations was up to 0.47% and 0.54% in the apixaban and warfarin groups respectively.

The clinical evaluator considered that using these worst case assumptions, the frequency of dosing errors was small, and the superiority of apixaban over warfarin for stroke, SE, bleeding and all-cause death was maintained. Only if errors in missing data were 100 fold higher than the observed rate would the statistical significance of the superiority exceed p=0.05 (p=0.053). As an example, the results of the sensitivity analysis relating to stroke

[19] Note that details of recommended revisions to the PI are beyond the scope of the AusPAR.

and SE (SSE) are shown below in Table 9. Hazard ratios and 95% CI were comparable in the different censoring scenarios.

Table 9. Sensitivity analysis for Time to SSE with different censoring scheme – randomised subjects in combined random sample

	Hazard Ratio (Apixaban/Warfarin)	95% CI
No Censoring	0.84	(0.62, 1.15)
Censoring Subjects Only Legible Label Errors	0.82	(0.60, 1.13)
Legible Label Errors + 50% Missing Labels	0.84	(0.61, 1.16)
Legible Label Errors + All Missing Labels	0.88	(0.63, 1.23)

Source: Appendix 1.7D

The evaluator concluded that these further analyses largely confirm the analysis and conclusions discussed in the first round evaluation. The superiority for apixaban compared with warfarin has been confirmed.

FDA Question2: The FDA requested an estimate of the number of patients unblinded by investigators without reporting them to the sponsor. Based on the random sample audits, the frequency of unreported unblinding was 3/8000 patients. This can be considered trivial.

FDA Question 3: The FDA requested details of the Site Monitoring Plan to understand how dispensing errors were allowed to occur. The sponsor responded that site monitoring was conducted to a high standard in accordance with their SOPs. The processes are described in detail and the sponsor points out that they were good enough to detect the errors in this case.

The evaluator concluded that in general, most errors were transcriptional in the electronic case report form (eCRF) and relatively few actual dispensing errors occurred.

FDA Question 4: The FDA questioned manual changes to the automated interactive voice response system (IVRS). They were concerned that human error may have contributed to dispensing errors. The sponsors justify this practice which is occasionally necessary and described the pre-defined procedures and methods used for manual changes. In the event, there were only 107 manual changes out of over 400,000 study treatment containers so they were unlikely to have contributed to the dispensing error rate.

FDA Question 5: A 'cursory examination' of the study datasets by the FDA revealed that they did not always match the information in the eCRFs. The sponsor replies that the perceived error rate was overstated and that accuracy is ensured by data management and statistical standard operating procedures (SOPs), the use of validated systems, and the use of additional quality checks and validation procedures.

FDA Question 6: Some patients had a unique AE listed multiple times as both non-serious and serious and the sponsor was requested to prepare a new AE analysis dataset. The sponsor offered a variety of legitimate reasons why such apparent dual listings may occur. However, they prepared a new dataset. The evaluator considered that minor changes did not impact on the safety profile of apixaban previously noted in the ARISTOTLE study.

Following review of the sponsor's responses to the FDA questions, the TGA requested the sponsor address the following additional matters:

- Clarification of all analysis conducted (that is, 12%, 20%, 40).
- Confirmation that all of the above audits were mutually exclusive.
- Time of request received and from which regulatory authority.
- Strategy of sample size selection for each analysis conducted.

· Timelines for all analyses conducted and responses/results being made available.

The sponsor confirmed that all the audits were mutually exclusive. Satisfactory responses were also provided to the other questions. It was noted that the FDA had not raised further concerns.

Second round benefit-risk assessment

The second round risk-benefit assessment has not changed from the first round assessment.

Second round recommendation regarding authorisation

Authorisation is recommended for apixaban 2.5 mg bid or 5 mg bid for the proposed additional indication

> *to reduce the risk of stroke, systemic embolism and death in patients with non-valvular AF with at least one additional risk factor for stroke.*

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted the Apixaban Risk Management Plan (Version 1.0, Data Lock Point April 1, 2011. Document date 9 September 2011) with Australian-specific Annex (version 1.0 data lock point 1 April 2011) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing safety Concerns which are shown at Table 10.

Table 10. Summary of Ongoing Safety Concerns

Important Identified Risk	· Bleeding
Important Potential Risks	· VTEp: Transient Elevation of Liver Tests · AF: Liver Injury
Important 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 valves · Off –label use

VTEp: specific to the VTE prophylaxis indication. AF: specific to proposed AF indication

In the Australian Specific Annex, the Summary of Ongoing Safety Concerns specific to Australia appears to provide a list of important missing information only. This includes two additional ongoing safety concerns (Table 11) that are not listed in the Core Company RMP:

Table 11. Summary of Ongoing Safety Concerns specific to Australia

Important Missing Information	· Use in the very elderly (VTEp indication) · Overdose/coagulation monitoring

In the revised Australian Specific Annex Guillain-Barré Syndrome (GBS) was removed as an important potential risk for Australia and now is considered an "event of special interest". The TGA and sponsor discussed this at a pre-submission meeting for this application, and the sponsor has provided further justification for this change in the RMP.

OPR reviewer comment:

The removal of GBS as an important potential risk was discussed with the TGA at a pre-submission meeting for this application. It was agreed that given enhanced surveillance continues there was no objection in principle. The rationale provided by the sponsor in the RMP is acceptable and the evaluator has no objection to how this is currently handled given that enhanced surveillance continues.

Pharmacovigilance plan

Table 12 provides a summary of the proposed pharmacovigilance (PV) activities in the Core Company RMP:

Table 12. Proposed pharmacovigilance activities

Important Identified Risk:	
Bleeding	· Routine PV
Important Potential Risks:	
VTEp: Transient liver test abnormalities AF: Liver injury	· Routine PV · Blinded external liver expert review of prespecified liver cases · Comprehensive pivotal study clinical safety program for liver-related events (including supplemental case report forms) · Targeted questionnaires for spontaneous reports of liver events. · Ad hoc follow up contact with reporter for specific liver events as needed. · Applicant commits to keep "hepatotoxicity" under close monitoring in the PSUR.
Important missing/limited information:	
Pediatric population	· Routine PV · Paediatric program with oral formulation is planned and PK studies in children are ongoing.
Pregnancy and Lactation	· Routine PV
Severe hepatic impairment	· Routine PV
Severe renal impairment	· Routine PV
Hip fracture surgery	· Routine PV
Black/African Americans	· Routine PV
Patients with valvular disease or prosthetic heart valves	· Routine PV
Off-label use	· Routine PV · Drug utilisation study

VTEp: specific to the VTE prophylaxis indication. AF: specific to proposed AF indication

Table 13 provides a summary of the proposed PV activities for the additional items of important missing information in the Australian Specific Annex as well as an additional Australian-specific activity for the important identified risk 'bleeding'.

Table 13. Proposed pharmacovigilance activities: Australian specific

Important Identified Risk	
Bleeding	· Targeted questions for spontaneous bleeding reports
Important missing information	
Use in the very elderly (>75 years) for VTEp	· Routine PV
Overdose/Coagulation Monitoring	· Routine PV

Apart from that detailed above no other additional PV activities are proposed by the sponsor in the RMP or the Australian Specific Annex for the AF indication.

Risk minimisation activities

The sponsor proposes routine risk minimisation for all safety concerns. No additional risk minimisation activities are proposed.

The evaluator considers that routine risk minimisation (that is, product labelling) is insufficient to mitigate the risks associated with apixaban for the proposed indication. Approval of apixaban for the proposed indication is likely to result in widespread, long-

term use and the evaluator considers that this requires the implementation of a dedicated risk minimisation strategy for Australia.

Potential for medication errors

The RMP states the following:

> *Medication errors will be closely monitored through routine surveillance.*
>
> *Apixaban tablets will be presented in blister packs that are clearly identified. In addition, one single dosage will be available for the prevention of VTE in patients who have undergone elective hip or knee replacement surgery, lowering the potential for medication error.*

OPR reviewer comment:

This section of the RMP should include the measures in place to mitigate the risk of medication error given there will be two different strengths of apixaban if the proposed indication (5 mg) is registered.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted Core Company RMP (Version 1.0, Data Lock Point April 1, 2011, document date 9 September 2011) and Australian-specific Annex (version 1.0 data lock point 1 April 2011) are applicable without modification in Australia except in relation to the recommendations below:

- It is drawn to the Delegate's attention that the statement *"Eliquis also reduced the risk of major bleedings when compared to warfarin"* appears to be more of a marketing claim then a therapeutic one and consideration should be given to its removal from the proposed indication.
- It is recommended that 'management of severe bleeding' and 'potential drug interactions' are added as important missing information. The addition of these safety concerns should include consideration of the PV and risk minimisation activities that may apply and should be detailed in an update to the RMP and/or Australian Specific Annex.
- It is recommended that the sponsor clarify the mechanism for how the targeted questionnaires will be used in Australia and how the information obtained will be handled. This should be made clear in an update to the RMP or in the Australian Specific Annex.
- It is recommended that the overall safety profile related to bleeding events is also detailed separately in Periodic Safety Update Reports (PSURs).
- It is recommended that the sponsor should implement additional PV that will appropriately monitor the ongoing risks associated with apixaban in Australia. The nature and extent of the associated activities should be agreed with OPR prior to supply for this indication and detailed in an update to the Core Company RMP/ Australian Specific Annex once agreed.
- It is recommended that the sponsor be directed to add 'potential drug interactions' as important missing information and commit to further study of potential interactions. Further study of interactions should include (but not be limited to) antihypertensives, statins, oral antidiabetic agents, heart failure drugs and anti-anginals, and their effects on apixaban levels.

- It is recommended that the sponsor consider further study in the area of coagulation monitoring and overdose treatment to improve the safety of apixaban use.
- The medication error section of the RMP should include the measures in place to mitigate the risk of medication error given there will be two different strengths of apixaban if the proposed indication (5 mg) is registered. The sponsor should also include in this section a summary of the post-market experience of medication errors for the VTE prophylaxis indication thus far.
- It is recommended that the sponsor formulate and implement an Australian-specific patient and health professional education program as part of the risk minimisation plan that aims to ensure the safe use of apixaban in Australia. Specific details of the education program and associated materials should be agreed with the OPR prior to supply for this indication and included in an update to the RMP once agreed. It is further recommended to the Delegate that the requirement for a dedicated education program is imposed as a condition of registration.

Revisions to the proposed PI and consumer medicine information (CMI) were also recommended. Details of these are beyond the scope of this AusPAR.

VI. Overall conclusion and risk/benefit assessment

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

Apixaban was first approved in Australia in July 2011 for the following 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.*

Two other drugs, rivaroxaban and dabigatran, that are new oral anticoagulants, have also been approved for VTE prevention and also for the proposed indication here of stroke prevention in patients with AF. The full indications approved currently for rivaroxaban (a FXa inhibitor) are as follows:

> *Prevention of venous thromboembolism (VTE) in adult patients who have undergone major orthopaedic surgery of the lower limbs (elective total hip replacement, treatment for up to 5 weeks; elective total knee replacement, treatment for up to 2 weeks).*
>
> *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke*
>
> *Treatment of deep vein thrombosis (DVT) and for the prevention of recurrent DVT and pulmonary embolism (PE).*

The approved indications for dabigatran (a Factor IIa (thrombin) inhibitor) are as follows:

> *Prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement). (see Dosage and Administration section for details of treatment duration).*
>
> *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.*

Apixaban has been approved in the EU (November 2012) and Canada (December 2012) for the prevention of stroke and systemic embolism in NVAF patients. At the time the

Delegate's overview was prepared, apixaban has not been approved in the USA for this indication and the FDA had issued a CRL regarding this submission.[20]

FDA questions

The CRL discussed outstanding matters in relation to the proposed extension of indications for stroke prevention in patients with AF that led the FDA to being unable to approve the submission in its present form at the time. These issues covered dosing errors, unblinding and data management from the pivotal trial, ARISTOTLE, but did not include a request for new studies or relate directly to identified efficacy or safety concerns.

The ARISTOTLE CSR initially reported that 7.3% of apixaban subjects and 1.2% of warfarin subjects had received, at some point in the study, a study medication container of the incorrect type. This led the sponsor to conduct a detailed analysis of the study medication dosing records of the original labels for about 20% of the dispensations in the study. This analysis showed that the estimated rate of study medication errors was actually much lower at <0.1% of study medication dispensations in <1% of subjects and was balanced between the apixaban and warfarin groups. A sensitivity analysis on the primary endpoint, major bleeding and all-cause death showed the study endpoints were not impacted by this dosing error in this small group of patients.

The cause of the original and incorrect estimated rate of study medication errors was a higher than expected rate of data entry errors in one field of the eCRF, namely incorrect apixaban and warfarin container numbers entered into the form which led to a mismatch in the number of the container dispensed to the patient and the number that was entered onto the eCRF. This apparent imbalance in the original report was caused by a definition of study medication errors which preferentially counted these data entry errors as treatment errors in the apixaban group. The sponsor reports that although this process led to an assessment that did not adequately reflect the true rate of study medication errors (but rather, amplified it), examination of the root cause and retrospective verification of the data confirmed that the integrity of the trial and the interpretation of the results were not affected by this GCP finding.

The FDA requested a more detailed analysis of the data, which led the sponsor to conduct three independent, mutually exclusive audits of random samples of tear-off dispensing labels attached to the study drug containers. The first sample was of 8% of patients which was then expanded by a further 12% at the request of the EMA. This 20% of the study patients showed a dispensing error rate of 0.048% for apixaban and 0.041% for warfarin. The FDA then requested a further sample of 20% taking the complete sample to 40% of all study subjects. This 40% sample rate showed a doubling of the error rate to 0.1% for apixaban and 0.116% for warfarin. Most errors were isolated and multiple errors did not occur in individual patients. If observed errors were then combined with missing data, then this analysis showed a total error rate of potentially 0.47% for apixaban and 0.54% for warfarin. The Delegate considered these rates remain small and similar in both arms and are therefore unlikely to impact the overall results.

Regarding other issues raised by the FDA, the Delegate noted that the frequency of unreported blinding was very low; most errors were transcriptional and not dispensing; the small number of manual changes to the automated IVRS was unlikely to contribute to the error rate; and the updated AE listing was acceptable.

The sponsor also notified regulatory authorities of a breach in GCP requirements at a site in China. This breach involved potential alteration of source documents in preparation for an upcoming inspection by the FDA. A second site in China was also investigated but there was no evidence of alteration in source documentation at that site. Although these are

[20] On 28 December 2012, the FDA issued an approval letter as follows: *'ELIQUIS (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.'*

serious matters, the site only recruited 37 patients out of approximately 20,000 enrolled and the changes to the source data took place after the conclusion of the trial and after database lock. The alteration of the source documents appeared to be for the purpose of improving the outcome of the FDA inspection. The sponsor has undertaken action regarding training and their inspection program.

Guidance

There are no TGA adopted European guidelines specific to the proposed indication, however there are a number of general guidelines from the EMA's Committee of Human Medicinal Products (CHMP) and the ICH to consider:

- *Clinical Investigation of Medicinal Products for Long-Term Use*. (Adopted by TGA on 12 February 2002 with conditions)
- *Clinical Investigation of Medicinal Products in Geriatrics*. (previous reference CPMP/ICH/379/95, adopted by TGA 12 February 2002)
- *Note for guidance on the evaluation of the Pharmacokinetics of medicinal products in patients with impaired renal function*. CHMP/EWP/225/02 Effective: December 2004
- *Guideline on Reporting the results of Population Pharmacokinetic Analysis.* CHMP/EWP/185990/06. Effective: 27 January 2009
- *Guideline on the Choice of the Non-Inferiority Margin.* EMEA/CPMP/EWP/2158/99. Effective: January 2006.

Quality

The pharmaceutical chemistry evaluator has no objections to the registration of the new 5 mg strength tablet with regards to chemistry, manufacturing and quality control. The 2.5 mg and 5 mg strengths are direct scales and the 5 mg strength is distinguished from the 2.5 mg strength by colour, shape and markings. An oral bioavailability study of apixaban solution and apixaban Phase III formulation tablets showed bioequivalence based on AUC but slightly outside the usual interval for Cmax (76-126%). This is unlikely to be clinically significant and is not directly relevant to this submission. An acceptable justification was provided for not conducting a bioequivalence study of the commercial formulation and the Phase III formulation.

Nonclinical

The nonclinical evaluator has no objections to the registration of apixaban for the proposed indication and higher daily dose. The evaluator notes that no nonclinical data were submitted to support this specific submission. Studies were submitted that investigated potential interactions between P-gp inhibitors and digoxin which noted that some medicines have mild to moderate inhibitory effects on P-gp *in vitro* which may account for a modest increase in plasma AUC for apixaban observed in drug interaction trials. A 3 month repeat dose toxicity study in rats did not show any toxicities of major concern. No remarkable effects on male or female fertility or early embryonic development were observed. Changes for the exposure margins are proposed for the PI.

Clinical

The clinical evaluator has reviewed the submitted data, which included:

- Three new pharmacology studies.

- One PPK study
- Two Phase III pivotal studies (Study CV185030: ARISTOTLE, and Study CV185048: AVERROES)
- One Phase III supportive study (CV185036: ADOPT)
- One Phase IIb supportive study (CV185067)
- Erratum to the sponsor's summary of the clinical pharmacology
- Report into suspected misconduct at a site in China for the ARISTOTLE study
- CRL from the FDA and the sponsor's response

An additional PD study (CV185066) was reviewed by the evaluator after the clinical evaluation report (CER) was finalised and is summarised below.

Pharmacology

Three pharmacology studies were evaluated by the clinical evaluator (Studies CV185074, CV185029 and CV185025), one of which was a hepatic impairment study (CV185025) that had been previously evaluated in the VTE prevention submission. Some of the findings noted by the evaluator include:

- Apixaban's t½ of 8.65 h was similar to rivaroxaban's (7.89 h) but its twice daily dosing regimen compared to rivaroxaban led to a smaller peak to trough concentration ratio (Cmax/Cmin) of 4.7 compared to 16.9 for rivaroxaban in healthy volunteers, potentially implying a more consistent exposure for apixaban over 24 h. In patients with AF, the ratio was 1.33 for the 2.5 mg dose and 1.54 for the 5 mg dose.
- Bioavailability of an apixaban solution and tablets was similar.
- The justification for not providing bioequivalence data between the Phase III tablet formulation and the commercial formulation was acceptable on clinical grounds.
- No bioequivalence study was provided that compares the 2.5 mg and 5 mg strengths.
- Administration of apixaban in the evening resulted in a 43% reduction in absorption rate constant compared to morning dosing.
- Patients with mild and moderate hepatic impairment had similar PKs to healthy subjects for apixaban (AUC and Cmax). There were no data in severe hepatic impairment.
- No studies directly compared the PKs in AF patients and healthy subjects.
- Population PK analysis indicated that age and gender were predictive covariates on apparent CLNR. Body weight influenced apparent VDc. Atrial fibrillation, recent acute coronary syndrome and strong or moderate CYP3A4/P-gp inhibitors resulted in decreased clearance.
- There was a linear relationship between plasma concentration and anti-FXa activity but this wasn't accurate at low or high concentrations to predict the effects of apixaban.

Study CV185066 (submitted after the CER was finalised) compared the *in vitro* activity of apixaban (30 and 110 ng/mL) in plasma taken from 75 healthy adult and paediatric subjects of various ages. The results indicate that, on the whole, the PD activity of apixaban is similar, based on anti-FXa activity, endogenous factor X levels, mean prothrombin time (mPT)and prothrombin time (PT), in plasma taken from adult and paediatric subjects. However, the clinical evaluator considered this study should not be used to justify the administration of apixaban in paediatric subjects unless a full PK and safety profile for

apixaban is developed and compared in both paediatric and adult populations. As it stands it should be noted that this study was primarily conducted to compare PD activity between children and adults and that children do not form part of target population of the current submission.

Efficacy

The efficacy data submitted primarily focus on the large pivotal studies ARISTOTLE (CV185030) and AVERROES (CV185048). Supportive information was provided by a Phase IIb study (CV185067) and ADOPT (CV185036).

A dose of 5 mg bid was selected as the optimal dose for balancing safety and efficacy of apixaban, which was based on two studies, one of which was previously evaluated in the original registration submission for apixaban.

Summary of ARISTOTLE (Study CV185030)

This was a pivotal, Phase III, multinational, multicentre, randomised, double blind, double dummy, parallel design, non-inferiority and superiority trial comparing apixaban 5 mg bid (2.5 mg bid if at least two of the following criteria applied at baseline: age ≥80 years, body weight ≤60 kg or serum creatinine ≥133 μmol/L) and warfarin (INR 2-3, central monitoring, 43% warfarin naïve and 57% warfarin experienced, 60.5% median time in therapeutic range (TTR; 66% if exclude first 7 days of titration and warfarin interruptions)) in 18,201 patients with AF (ECG documented AF or atrial flutter not due to a reversible cause, 15% paroxysmal, 85% persistent or permanent) and one additional risk factor for stroke (67% had ≥2 risk factors: hypertension 87%, symptomatic CHF 35%, age ≥75 years 31%, diabetes mellitus 25%, prior stroke/TIA/SE 19%, mean $CHADS_2$ score of 2.1) for a mean 1.7 years of treatment.

There was a screening period of up to 14 days or until INR was stabilised. International normalised ratio measurements were conducted by a central laboratory using encrypted point of care devices and INR was measured monthly once it was stabilised. The primary analysis included all INRs irrespective of the titration period or warfarin interruption. Key exclusion criteria were: AF due to reversible causes; clinically significant mitral stenosis; contraindication to anticoagulation; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times the upper limit of normal (ULN) or total bilirubin >1.5 times ULN; creatinine clearance <25 mL/min; platelet count <100,000; persistent, uncontrolled hypertension; infective endocarditis; planned major surgery; or planned AF or flutter ablation surgery.

Baseline characteristics were similar between the groups (mean age 69 years, 65% male, 83% White, 41% normal renal function, 42% mild renal impairment, 15% moderate renal impairment and 1.5% severe renal impairment). Concomitant medications included angiotensin converting enzyme (ACE) inhibitor 71%, beta blocker 64%, aspirin 31%, clopidogrel 1.9%, digoxin 32%, calcium channel blocker 30%, and statin 45%.

Study discontinuation was 25% on apixaban and 28% on warfarin with similar reasons for both groups (7-8% due to AEs). Protocol deviations were slightly higher on apixaban (25% versus 19%) with these mainly being due to use of antithrombotics (7.0% apixaban versus 7.6% warfarin). Protocol deviations likely to effect the primary endpoint were pre-specified and occurred slightly higher on apixaban than on warfarin (13.6% versus 7.8%) but a sensitivity analysis showed that they did not impact on the primary study results. Completion for the intended treatment period was 86-87%.

Apixaban was considered non-inferior to warfarin if the upper bound of the 95% CI for the HR was less than the non-inferiority margin of 1.44 (based on 50% preservation of warfarin effect). The study had 90% power to establish non-inferiority of apixaban to warfarin using either the upper boundary of the 99% CI for the relative risk (RR) being

less than 1.44 or the upper boundary of the 95% CI for the RR being less than 1.38. The protocol allowed for testing of superiority of apixaban versus warfarin if non-inferiority was first attained and then if that was obtained it allowed for superiority testing for the primary safety endpoint of major bleeding, and then if that was obtained it allowed for superiority testing for all cause mortality.

The primary efficacy endpoint, which was to determine if apixaban was non-inferior to warfarin for the composite of time to first occurrence of stroke or SE in AF patients with at least one additional risk factor, showed apixaban was statistically significantly non-inferior to warfarin, with HR=0.79 (95% CI 0.66-0.95, p<0.0001 for non-inferiority, intention to treat (ITT) population), numbers needed to treat (NNT)=167.

The yearly event rate for stroke/SE was 1.27% for apixaban versus 1.60% for warfarin, which was primarily driven by the number of ischaemic strokes. Haemorrhagic stroke was lower on apixaban than on warfarin (0.44 versus 0.86%, HR 0.51, 95%CI 0.35-0.75). The number of SE events alone was low at 0.16% on apixaban versus 0.18% on warfarin. Fatal or disabling strokes were less on apixaban (0.50%/year versus 0.71%/year, HR=0.71, 95%CI 0.54-0.94). These data are summarised in Table 14.

Table 14. ARISTOTLE: Summary of adjudicated stroke or systemic embolism during the intended treatment period – randomised subjects

	Apixaban N = 9120	Warfarin N = 9081
STROKE/SYSTEMIC EMBOLISM, n (%)	212 (2.32)	265 (2.92)
EVENT RATE (%/YR)	1.27	1.60
HAZARD RATIO (APIXABAN/WARFARIN)	0.79	
95% CI FOR HAZARD RATIO	(0.66, 0.95)	
99% CI FOR HAZARD RATIO	(0.62, 1.00)	
1-SIDED P-VALUE FOR NI TEST (NI MARGIN = 1.38)	<.0001	
1-SIDED P-VALUE FOR NI TEST (NI MARGIN = 1.44)	<.0001	
2-SIDED P-VALUE FOR SUPERIORITY TEST	0.0114	
FIRST EVENT, n (%)		
ISCHEMIC OR UNSPECIFIED STROKE	159 (1.74)	173 (1.91)
HEMORRHAGIC STROKE	38 (0.42)	76 (0.84)
SYSTEMIC EMBOLISM	15 (0.16)	16 (0.18)
CENSORED, n (%)	8908 (97.68)	8816 (97.08)
DEATH DURING INTENDED TREATMENT PERIOD	514 (5.64)	547 (6.02)
WITHDREW CONSENT TO BE FOLLOWED-UP	292 (3.20)	304 (3.35)
LOST TO FOLLOW-UP	130 (1.43)	124 (1.37)
COMPLETED INTENDED TREATMENT PERIOD	7972 (87.41)	7841 (86.35)
FIRST EVENT AFTER COMPLETING ITP	27 (0.30)	10 (0.11)
STROKE, n (%)	199 (2.18)	250 (2.75)
ISCHEMIC STROKE	140 (1.54)	136 (1.50)
ISCHEMIC STROKE WITH HEMORRHAGIC CONVERSION	12 (0.13)	20 (0.22)
HEMORRHAGIC STROKE	40 (0.44)	78 (0.86)
SUBARACHNOID HEMORRHAGE	2 (0.02)	4 (0.04)
SUBDURAL HEMATOMA	5 (0.05)	6 (0.07)
INTRAPARENCHYMAL HEMORRHAGE	31 (0.34)	66 (0.73)
STROKE OF UNCERTAIN TYPE	14 (0.15)	21 (0.23)

For the secondary endpoints, the superiority of apixaban was assessed compared with warfarin, which demonstrated a significant benefit for the reduction in stroke (ischaemic, haemorrhagic and unspecified) and SE combined (p=0.0114 for superiority). In the response to the Delegate's overview, the sponsor is asked to comment on the "statistical significance" of this result given the alpha for this comparison was set at 0.005.

For first events, the frequencies for apixaban were slightly less than warfarin for ischaemic or unspecified stroke, clearly less for haemorrhagic stroke, and about the same for SE. Overall numbers of strokes were less on apixaban (2.18% versus 2.75%), however of these, ischaemic strokes, which were the majority of the strokes, were about the same

on both treatments (1.54% versus 1.50%), compared to a reduction in haemorrhagic stroke on apixaban (0.44% versus 0.86%).

Subgroup analysis showed that the HR results were <1 in all apixaban subgroups (including warfarin naïve and experienced, 2.5 and 5 mg bid groups, age >75 years, ≤1 or ≥2 risk factors, $CHADS_2$ scores and stroke risk factors) except for those whose age was <65 years.

Analysis of the primary endpoint by $CHADS_2$ score showed HRs all <1, but the 95% CI crossing 1 for the two lowest groups (score ≤1: HR=0.85, 95% CI 0.57-1.27, score=2: HR=0.90, 95% CI 0.66-1.23, score ≥3: HR=0.70, 95% CI 0.54-0.91). Some groups also had the 95% CI for the HR to be <1, but this should not be interpreted as being superior due to the multiple comparisons.

The secondary endpoint of all-cause death was less on apixaban than warfarin (6.61% versus 7.37%, HR 0.89, 95% CI 0.80-1.0, p=0.0465) and the clinical evaluator has commented on this as being of borderline significance. In the response to the Delegate's overview, the sponsor is asked to comment on this "statistical significance" given the alpha for this comparison was set at 0.005.

Cardiovascular death rate was similar on both drugs (3.38% versus 3.79%), with the majority being sudden death (1.38% versus 1.42%) and noting that fatal stroke was less on apixaban (0.42% versus 0.72%). Non-cardiovascular death was also similar between the two groups (2.15% versus 2.29%) with bleeding being a similar cause (0.16% versus 0.19%).

The data were analysed by median warfarin INR values, which showed the primary endpoint result was similar for study sites with INR control below and above the median TTR. The evaluator has indicated this shows there was an efficacy benefit even in subjects with the best INR control.

During the 30 day follow-up period at the end of treatment, there were 27 strokes/SEs in the apixaban group compared with 10 events in the warfarin group. The majority of these patients (23 versus 7) were not on apixaban or warfarin at the time. The majority of the strokes occurred in patients who had moved from apixaban to a VKA (n=16 strokes).

Summary of AVERROES (Study CV185048)

This was a pivotal, Phase III, multinational, multicentre, randomised, double blind, double dummy, parallel design, superiority trial comparing apixaban 5 mg bid (2.5 mg bid for 6.4% of subjects at increased risk of bleeding; namely those with at least two of the following criteria: age >80 years, body weight ≤60 kg or serum creatinine ≥133 μmol/L) and ASA 81-324 mg once daily (dose at discretion of the investigator, 64% on 81 mg, 27% on 162 mg) in 5,598 patients with AF (documented permanent, paroxysmal or persistent AF; not currently receiving warfarin therapy) and one additional risk factor for stroke (61% had ≥2 risk factors: hypertension 86%, heart failure or ≤35% left ventricular ejection fraction (LVEF) 34%, age ≥75 years 34%, diabetes mellitus 20%, prior stroke/TIA 14%, mean $CHADS_2$ score of 2.0) for a mean 1.1 years of follow up for the prevention of stroke or SE in AF patients who have failed or are unsuitable for warfarin treatment (40% had previously used warfarin).

Key exclusion criteria were: AF due to reversible causes; valvular disease requiring surgery; ALT/AST >2 times ULN or bilirubin >1.5 times ULN; creatinine clearance <25 mL/min; platelet count <100,000; and planned AF ablation to be performed within 3 months.

Baseline characteristics were similar between the groups (mean age 70 years, 59% male, 79% White, 34% normal renal function, 38% mild renal impairment, 17% moderate renal impairment and 2.1% severe renal impairment). Concomitant medications were similar in both groups.

Study discontinuation was 20% on apixaban and 23% on ASA with similar reasons for both groups (6.2-9.3% due to AEs). Protocol deviations were small, similar (5.9% versus 6%) and balanced between the groups.

The study had 90% power to detect a 35% relative risk reduction (RRR) of apixaban versus ASA for the primary endpoint. The study was terminated early following a planned interim analysis because of superior efficacy in the apixaban group.

The primary efficacy endpoint of prevention of the composite of stroke or SE in AF patients with at least one additional risk factor for stroke and who failed or were unsuitable for warfarin therapy showed apixaban was significantly superior to ASA (HR 0.45, 95% CI 0.32-0.62, p<0.00001), NNT=45.

The unadjusted 95% CI is 0.32-0.62. The yearly event rate for stroke/SE for apixaban was 1.62% versus 3.63% for ASA which was primarily driven by the number of ischaemic strokes. Haemorrhagic strokes were similar (0.21% versus 0.32%) but SEs were less on apixaban (n=2 versus n=13). These data are summarised in Table 15.

Table 15. AVERROES: Summary of adjudicated stroke or systemic embolism during the intended treatment period – randomised subjects

	Apixaban N=2807	ASA N=2791
STROKE/SYSTEMIC EMBOLISM, n (%)	51 (1.82)	113 (4.05)
EVENT RATE (%/yr)	1.62	3.63
HAZARD RATIO (APIXABAN/ASA)	0.45	
95% CI FOR HAZARD RATIO	(0.32, 0.62)	
2-SIDED P-VALUE FOR SUPERIORITY TEST	<0.00001	
FIRST EVENT, n (%)		
ISCHEMIC OR UNSPECIFIED STROKE	43 (1.53)	95 (3.40)
HEMORRHAGIC STROKE	6 (0.21)	7 (0.25)
SYSTEMIC EMBOLISM	2 (0.07)	11 (0.39)
CENSORED, n (%)	2756 (98.18)	2678 (95.95)
DEATH DURING INTENDED TREATMENT PERIOD	92 (3.28)	110 (3.94)
WITHDREW CONSENT TO BE FOLLOWED-UP	8 (0.29)	5 (0.18)
LOST TO FOLLOW-UP	5 (0.18)	2 (0.07)
COMPLETED INTENDED TREATMENT PERIOD	2651 (94.44)	2561 (91.76)
FIRST EVENT AFTER COMPLETING INTENDED TREATMENT PERIOD	14 (0.50)	16 (0.57)
STROKE, n (%)	49 (1.75)	105 (3.76)
ISCHEMIC STROKE	31 (1.10)	86 (3.08)
ISCHEMIC STROKE WITH HEMORRHAGIC CONVERSION	4 (0.14)	9 (0.32)
HEMORRHAGIC STROKE	6 (0.21)	9 (0.32)
STROKE OF UNCERTAIN TYPE	9 (0.32)	4 (0.14)
SYSTEMIC EMBOLISM, n (%)	2 (0.07)	13 (0.47)

Subgroup analysis showed that the HR results were <1 in all apixaban subgroups and that the majority of subgroups had a 95% CI also below a HR of 1, suggesting a benefit for apixaban in these groups over ASA. Analysis of the primary endpoint by $CHADS_2$ score showed HRs all <1, but the 95% CI crossing 1 for the lowest group (score ≤1: HR=0.63, 95% CI 0.31-1.30, score=2: HR=0.49, 95% CI 0.29-0.81, score ≥3: HR=0.35, 95% CI 0.20-0.61). For the secondary endpoints the following were seen:

- Reduction in major vascular events (stroke, SE, MI, vascular death): HR=0.66, 95% CI 0.53-0.83, p=0.00026.
- All-cause death: HR=0.79, 95% CI 0.62-1.02, p=0.068
- Net clinical benefit (stroke, SE, MI, vascular death and major bleeding): HR=0.73, 95% CI 0.60-0.90, p=0.0028, yearly event rate 5.23% versus 7.13%.

Summary of Study CV185067

This Phase IIb supportive study was randomised, partially blinded (double blind apixaban and open label warfarin), active controlled of apixaban (2.5 mg bid and 5 mg bid) versus warfarin (INR 2-3) for 12 weeks in 222 Japanese subjects with non-valvular AF. The primary endpoint was safety but efficacy was a secondary endpoint and showed 3 subjects with stroke on warfarin versus no subjects on apixaban.

Summary of ADOPT (Study CV185036)

During the course of evaluation, the sponsor submitted a study report for the ADOPT Study, which was a Phase III, randomised, double blind, active controlled trial of 2.5 mg bid apixaban compared with 40 mg enoxaparin once daily for the prophylaxis of VTE in 6,758 acutely ill medical patients. Apixaban did not show superiority to enoxaparin for the primary efficacy endpoint of total VTE and VTE-related death but was numerically lower. However major bleeding was higher, at 0.47% versus 0.19% on enoxaparin.

This study was in a different population and apixaban was used for approximately 30 days compared with 7 days for enoxaparin. However the clinical evaluator has indicated that the overall frequency of bleeding, bleeding related AEs, SAEs, deaths, marked laboratory abnormalities and hepatic events were low and comparable in the apixaban groups in all studies and that no safety signals in this study impact on the safety conclusions from the ARISTOTLE trial.

Safety

According to the clinical evaluator, overall patient exposure was up to 2.1 years from the pivotal studies, with 15,534 patient-years of exposure for apixaban for an average exposure of 1.7 years in the ARISTOTLE study and 3,193 patient-years of apixaban exposure for an average exposure of 1.1 years in the AVERROES study.

Adverse events were mostly mild to moderate across the two pivotal studies. In ARISTOTLE, AEs occurred in 82% of both apixaban and warfarin groups with similar distribution of events (infections and infestations 38% versus 39%, gastrointestinal disorders 27% versus 29%, respiratory 23% versus 25%, cardiac 23% versus 22%, musculoskeletal 22% versus 23%, neurological 22% versus 23%, general and administration site 21% versus 21%, and injury, poisoning and procedural 17% versus 20%). Of these, the most common were nasopharyngitis, dizziness, dyspnoea, peripheral oedema, diarrhoea and epistaxis. In AVERROES, the frequency of AEs was also similar at 66% versus 69%, with the most common being dizziness and dyspnoea and the distribution similar between apixaban and warfarin. There were no cases of amyotrophic lateral sclerosis or GBS. In the Japanese study, AEs were higher on apixaban at 59% for 5 mg bid versus 47% for warfarin.

Major bleeding was defined based on an adaptation from the ISTH as clinically overt bleeding with one of the following: a decrease in haemoglobin of 2 g/dL or more over 24 h, a two unit or more transfusion of packed red blood cells, bleeding into at least one critical site, or fatal bleeding. Clinically relevant non major bleeding was defined as acute clinically overt bleeding that is not major bleeding and with one of the following: hospital admission for bleeding, medical or surgical treatment for bleeding, or change in anticoagulant or antiplatelet therapy. The results for the two pivotal studies showed:

- ARISTOTLE showed major bleeding, CRNM bleeding, all-bleeding and intracranial bleeding were significantly less on apixaban than warfarin and the evaluator has commented that this was also demonstrated for GUSTO and TIMI criteria:
  - Adjudicated ISTH major bleeding: 3.6% on apixaban versus 5.1% on warfarin (HR 0.69, 95 %CI 0.60-0.80, p<0.0001). NNT=67. Similar results seen for sites with INR control below and above the median TTR.
    - Fatal haemorrhage: 0.11% versus 0.41%
    - Gastrointestinal haemorrhage: 1.3% versus 1.44%
    - Bleeding into a critical site: 1% versus 1.75% (all sites less or similar on apixaban except for serious intraocular bleeds (28 versus 19 events), which the evaluator has noted from a post hoc analysis occurred in those with risk

factors). Minor intraocular bleeds were lower on apixaban (20 versus 40 events).

§ Decrease in haemoglobin of ≥2g/dL over 24 h: 1.82% versus 2.45%

§ Transfusion of ≥2 units of packed red blood cells: 0.77% versus 1.12%

– Intracranial bleeding: 0.57% versus 1.35%, HR 0.42, 95% CI 0.30-0.58, p<0.0001.

– Major or CRNM bleeding: 6.75% on apixaban versus 9.69% on warfarin (HR 0.68, 95% CI 0.61-0.75, p<0.0001)

– All bleeding: 25.92% on apixaban versus 33.8% on warfarin (HR 0.71, 95% CI 0.68-0.75, p<0.0001)

· AVERROES showed bleeding was higher on apixaban than ASA and significantly for major or CRNM bleeding and all-bleeding:

– Major bleeding was higher on apixaban: 1.61% on apixaban versus 1.04% on ASA, HR=1.54, 95% CI 0.96-2.45, p=0.07, NNT (or harm, H)=175

§ Fatal bleeding: 0.18% versus 0.18%

§ Bleeding into a critical site: 0.79% versus 0.43%

– Major or CRNM bleeding was higher on apixaban: 5.00% on apixaban versus 3.63% on ASA (HR 1.38, 95% CI 1.07-1.78, p=0.0144)

– All-bleeding was higher on apixaban: 11.62% on apixaban versus 8.99% on ASA (HR 1.30, 95% CI 1.10-1.53, p=0.0017)

In the Japanese study, major or CRNM bleeding was 1.4% on apixaban 2.5 mg or 5 mg bid compared with 5.3% on warfarin.

Deaths were less on apixaban in ARISTOTLE (% of AEs that resulted in death 4.7% versus 5.2% on warfarin; adjudicated all-cause deaths 6.6% versus 7.4%). The most common Serious AEs resulting in death for apixaban subjects were: sudden death (0.6%), then cardiac failure, MI, sudden cardiac death, cardiac arrest, pneumonia, death and ischaemic stroke. Death was also less on apixaban in AVERROES (adjudicated all-cause 3.3% versus 4.1%). Serious AEs were similar in frequency in ARISTOTLE (35% versus 36.5%, mostly cardiac, infections and nervous system) and less in AVERROES for apixaban (23.5% versus 28.9%).

Adverse events leading to discontinuation were lower on apixaban in ARISTOTLE (7.6% versus 8.4%) and in AVERROES (9.5% versus 13%). In Study CV185030, liver function test elevations were low and similar on apixaban and warfarin (ALT >3 times ULN and total bilirubin >2 times ULN was 0.3% on both drugs(of these with <2 times ULN for alkaline phosphatise with a possible relationship to study drug was 1 event on apixaban, versus 3 events on warfarin). In the pooled pivotal studies, liver related deaths occurred in 7 patients on apixaban versus 6 patients on warfarin/aspirin. In Study CV185030, marked elevation in renal function were low and similar in both groups with significant elevations in serum creatinine (6.1% on apixaban versus 6.3% on warfarin[21]). Laboratory abnormalities were infrequent and similar in both groups and haematology parameters were also similar in both groups. No significant differences were seen in ECG findings or vital signs.

Clinical evaluator's recommendation

The clinical evaluator recommended approval of apixaban 2.5 mg bid or 5 mg bid for the proposed additional indication:

[21] Figures provided by sponsor.

to reduce the risk of stroke, systemic embolism and death in patients with non-valvular AF with at least one additional risk factor for stroke.

Risk management plan

The TGA's OPR has accepted the Apixaban RMP, Version 1 (Data Lock Point 1 April, 2011, Document date 9 September 2011) plus the Australian specific Annex (Version 1, Data lock Point 1 April 2011) and recommended further changes as outlined above under Section V *Pharmacovigilance findings*, *Summary of recommendations.*

The Delegate requested the sponsor, in the response to this overview, address matters raised by the OPR and follow up where appropriate with the OPR.

Risk-benefit analysis

Delegate considerations

Efficacy: Apixaban has demonstrated superiority to ASA and non-inferiority to warfarin in two large, well designed, Phase III trials in patients with AF and at least one additional risk factor for stroke for the reduction of stroke or SE. This benefit was almost all in reduction in stroke with little events of SE, however this is not unexpected. The total number of strokes or SE was 2.32% on apixaban compared with 2.92% on warfarin in ARISTOTLE (absolute risk reduction (ARR)=0.60%, relative risk reduction (RRR)=21%), compared with 1.82% on apixaban and 4.05% on ASA in AVERROES (ARR=2.23%, RRR=55%). The yearly event rate for stroke or SE in ARISTOTLE was 1.27% on apixaban versus 1.60% on warfarin, compared with the yearly event rate in AVERROES of 1.62% on apixaban versus 3.63% on ASA (although the early termination of the AVERROES trial may have inflated the primary endpoint result).

In ARISTOTLE, apixaban appeared to be superior to warfarin for the primary efficacy endpoint and of borderline superiority for all-cause death, however the sponsor, in the response to the Delegate's overview, is requested to comment on the "statistical significance" of the results given the alpha value set for these endpoints was a one sided 0.005.

All-cause death was non-significantly less on apixaban compared to ASA. The main type of stroke contributing to the primary endpoint was ischaemic stroke which occurred in almost the same number of people on both apixaban and warfarin (1.54% versus 1.5%), however the reduction in the primary endpoint for apixaban was mainly driven by a reduction in haemorrhagic stroke, which was reduced by 49% in ARISTOTLE compared with warfarin (0.44% versus 0.86%). The results were closer in AVERROES (6 versus 9 events). Fatal or disabling strokes were reduced by 29% in ARISTOTLE. Subgroup analysis showed a consistent benefit in most groups, although the lack of power and multiple comparisons for individual groups means this cannot be conclusively stated.

To calculate an AF patient's risk of stroke and bleeding, risk scores have been developed with the most common being the $CHADS_2$ score. Analysis by $CHADS_2$ score for stroke risk (less sensitive for low risk patients) showed HRs all <1 in both pivotal studies but CIs crossing unity for some groups. A recent publication by Lopes *et al*.[22] examined the primary endpoint by $CHADS_2$ score, CHA_2DS_2VASc score (a newer and more sensitive

[22] Lopes RD et al. Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. Lancet 2012;380:1749-1758.

score for stroke risk, especially in low risk patients[23]) and HAS-BLED score (which estimates the risk of bleeding for patients on anticoagulants) and found no significant difference by stroke risk or bleeding risk, although some CIs were broad and had HRs >1. The benefit of apixaban also appeared to be seen in different INR control groups based on their TTR. In summary, the NNT to prevent a stroke compared to warfarin was 167 in ARISTOTLE over an average 1.7 years, and compared to aspirin the NNT was 45 in AVERROES for an average 1.1 years.

Safety and RMP: The safety profile of apixaban appears similar to warfarin for the majority of safety signals identified in ARISTOTLE. Exposure was for a reasonable period (mean 1.7 years) and the number of subjects exposed was large, as expected for this type of indication and duration of use. Bleeding is the main safety signal of interest for an anticoagulant and ARISTOTLE showed that this was significantly less on apixaban than warfarin for major bleeding (3.6% versus 5.1%, ARR=1.5%, RRR=31%), CRNM bleeding, all-bleeding and intracranial bleeding. Fatal haemorrhage was less on apixaban than warfarin and gastrointestinal haemorrhage was similar to warfarin. However, when compared with ASA in AVERROES, bleeding was higher on apixaban and significantly so for major or CRNM bleeding combined and all-bleeding, but not for major bleeding alone (1.61% versus 1.04%, absolute risk increase=0.57%, relative risk increase=54%). However, given the pharmacology of the drug, this may not be unexpected. Bleeding into a critical site was less on apixaban than warfarin except possibly for serious intraocular bleeding, but higher on apixaban than ASA. Fatal bleeding was similar on apixaban and ASA.

Apixaban's safety profile was similar in subgroups and there was no increased risk of MI in either pivotal study. The recent publication by Lopes RD *et al*, examined major bleeding by $CHADS_2$ score, CHA_2DS_2VASc score and HAS-BLED score and found no significant difference by stroke risk or bleeding risk, with all HRs <1, including most CIs.

The RMP has outlined a number of matters that require further consideration by the sponsor as outlined above, especially an Australian-specific patient and health professional education program. In summary, the number needed to treat to prevent a major bleed compared to warfarin was 67 in ARISTOTLE for an average 1.7 years and compared to aspirin was a number needed to treat to harm of 175 in AVERROES for an average 1.1 years.

Indication: The indication proposed by the sponsor is:

> *Eliquis is indicated to reduce the risk of stroke, systemic embolism, and death in patients with non-valvular atrial fibrillation with at least one additional risk factor for stroke.*
>
> *Eliquis also reduced the risk of major bleedings when compared to warfarin (see Clinical Trials).*

The inclusion of death in the indication is not supported as it is a secondary endpoint in the pivotal study and of questionable significance. The indication should be focussed on the primary endpoint. This information would be better placed in the *Clinical Trials* section of the PI. The second statement regarding *'Eliquis also reduced the risk of major bleedings when compared to warfarin (see Clinical Trials)'* is also not supported in the Indications as it is also a secondary endpoint from the study, makes a comparative claim and, as noted by the RMP evaluator, appears to be more of a marketing claim for the product. Given the indication is aimed at adults and the clinical evaluator's comment regarding use in children (see above discussion of Study CV185066), then it should be considered whether the indication be restricted to adults only.

[23] In addition to risk factors assigned in the CHADS2 score, the CHA2DS2VASc score assigns points to additional risk factors, such as female sex, age 65–75 years, and vascular disease.

Dispensing errors: The dispensing errors which were initially thought to be much higher on apixaban than warfarin were subsequently found in a sample of 40% of subjects checked to be much lower at <0.1% of study medication dispensations in <1% of subjects, and was balanced between the apixaban and warfarin groups. Given the small number of errors reported, the similar rate of error on apixaban and warfarin, the sensitivity analysis conducted by the sponsor to demonstrate that these errors did not impact the primary efficacy endpoint or major bleeding or all-cause death, and the subsequent checking of 40% of the dispensations, then the results from the ARISTOTLE study should still be valid.

Warfarin dosing: The clinical evaluator has commented that warfarin provides effective protection against stroke but is not prescribed in up to 50% of AF patients due mainly to bleeding concerns, low risk of embolus, difficulty of use or patient refusal. The evaluator notes that INRs are only in the therapeutic range for approximately 60% of the time during chronic warfarin therapy. The recent *Review of Anticoagulation Therapies in Atrial Fibrillation*[24] notes that in Australia, the TTR varies significantly amongst individuals with estimates of 50-68% in Australian community practice. In the ARISTOTLE trial, the TTR was 60.5% median time (66% if exclude first 7 days of titration and warfarin interruptions) which is consistent with the Australian community practice figures cited in the Review. The Review also notes that the average TTR in the warfarin arms for the pivotal dabigatran trial (see PI for Pradaxa) was 64%, for rivaroxaban it was 55% (noting that rivaroxaban recruited higher risk stroke patients) and for apixaban it was 62.2%. Patients in the dabigatran pivotal trial, Randomised Evaluation of Long-term anticoagulant therapy (RELY), had a mean $CHADS_2$ score of 2.1, which is the same as the $CHADS_2$ score in this trial for apixaban of a mean 2.1. Therefore the TTR seen for apixaban in the pivotal ARISTOTLE trial is within the range seen in the Australian community. The data from ARISTOTLE were also analysed by median warfarin INR values which showed the primary endpoint result was similar for study sites with INR control below and above the median TTR, suggesting an efficacy benefit even in subjects with the better INR control.

End of treatment strokes: It is noted that during the follow up period for the trial there were 27 strokes in the apixaban group versus 10 in the warfarin group. Of these, 23 original apixaban patients were not on apixaban and had either transitioned to other drugs or no drug. Of these, 16 strokes occurred in patients who had transitioned from apixaban to a VKA. This is a concerning finding and it is unclear whether this represents a problem with apixaban in terms of rebound or a delayed effect of the drug once ceased, or whether this represents a problem with maintaining anticoagulation when transferring patients. Patients will for various reasons and at various times need to cease medication and transfer to alternative medication. If these strokes are predominantly due to a transition problem then the sponsor will need to ensure that this is completely addressed in the PI. This matter will need a robust education program and clear guidance to health professionals on the importance of maintaining adequate anticoagulation. This should also be included in the RMP. The sponsor must address this issue in their response to this overview. However if this is due to a rebound phenomenon or some delayed effect of the drug, then the mechanism to address the matter is unclear and raises doubts on the safe use of apixaban.

Data deficiencies: The breach of GCP in China is a concern which the sponsor has responded to, but the potential effect would only have been up to 37 patients out of the total ARISTOTLE trial of nearly 20,000. Therefore this breach of GCP is unlikely to affect the results. However, it is not clear whether other sites were audited to determine that this was not a more widespread occurrence.

[24] Australian Government. Department of Health and Ageing. Review of anticoagulation therapies in atrial fibrillation. 2012, pp 13-14. Available at <http://www.pbs.gov.au/reviews/atrial-fibrillation-files/report-anticoagulation.pdf>

Data is lacking in severe renal impairment.

Summary: Overall at present the submission appears approvable, with demonstrated efficacy and an acceptable safety profile.

Proposed action

The Delegate proposed to approve the registration of Eliquis (apixaban) 5 mg tablet and to register a new indication, below, based on the quality, safety and efficacy of the product being satisfactorily established for the indication (below) and for the reasons stated above in the *Risk/Benefit Discussion*:

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

In its response to the Delegate's overview, the sponsor was requested to address the following issues in particular:

a. Given that the dosing instructions allow for a 2.5 mg dose, please provide a biowaiver justification that compares the 5 mg strength with the 2.5 mg strength.

b. Given the GCP concerns at two sites in China, have further audits been conducted of the other sites to determine that this was not a more widespread matter?

c. The outstanding matters raised by the RMP evaluator, as detailed above in the PV section of this document, should be addressed.

d. The two-sided p-value for superiority in the ARISTOTLE trial was 0.0114 however the statistical plan indicates that the one sided alpha value was set at 0.005 for superiority. Please provide comment on whether the p-value of 0.0114 is therefore strictly above the threshold for statistical significance and that apixaban is not superior to warfarin.

e. Similarly, in the ARISTOTLE trial, the one sided alpha value was set at 0.005 for all cause death however the p-value for the result was 0.0465. Please provide comment on the statistical significance of this result and whether it is considered that apixaban is superior to warfarin for this endpoint.

f. What is the likely explanation for the increased number of strokes seen in patients who had changed therapy at the end of the study from apixaban to warfarin, and how will this be addressed in the PI, RMP and education to healthcare professionals? How can it be assured that that this is not a rebound phenomenon or other delayed effect of the drug and, if this is the case, how can this risk be mitigated?

g. Were patient's risk of stroke calculated using the CHA_2DS_2VASc score? If so, please provide these scores for patients in this trial using a median and mean approach and a distribution for each score level.

h. Confirm the unadjusted and adjusted HR and 95% CI for the primary endpoint in the AVERROES study.

i. Comment on whether there were any cases of liver dysfunction that met the definition for Hy's law in the ARISTOTLE or AVERROES studies.

j. Discuss the rationale for why the lower dose of 2.5 mg bid was chosen as the appropriate dose for patients with two of the following characteristics: age ≥80 years, body weight ≤60kg or serum creatinine ≥133 µmol/L.

k. Provide a table comparing the primary endpoint result, major bleeding, all-bleeding and CRNM bleeding in patients aged <75 years and ≥75 years and comment on any differences.

l. Discuss any plans for development of an antidote to apixaban and of any assays for monitoring the level of anticoagulation of the patient.

m. Provide an analysis of major bleeding events by concomitant medication use in ARISTOTLE.

Conditions of Registration:

The Delegate proposed the following as conditions of registration:

- The implementation in Australia of the apixaban RMP version 1, (Data Lock Point 1 April, 2011, Document date 9 September 2011) plus the Australian specific Annex (Version 1, Data lock Point 1 April 2011), and the changes agreed to in the sponsor's correspondence to the TGA, included with submission PM-2011-03165-3-3, and any subsequent revisions, as agreed with the TGA.
- The development and implementation of an Australian-specific patient and health professional education program as part of the risk minimisation plan that aims to ensure the safe use of apixaban in Australia. Specific details of the education program and associated materials should be agreed with OPR prior to supply.

Advice requested from ACPM

The Delegate sought general advice on this application from the ACPM, and requested the committee address the following issues in particular:

1. Should the indication be modified to: remove reference to a reduction in death; remove the claim of a reduction in risk of major bleeding; and to add “adults” to the indication?
2. Does the ACPM consider that the data integrity issues are unlikely to effect the overall results and that the investigations by the sponsor into this matter are satisfactory?
3. Is the increase in strokes seen following cessation of apixaban of concern and has this been adequately addressed by the sponsor?

Response from the Sponsor

Executive Summary

- **Indication:** The sponsor proposes a revised indication (see below), consistent with the Delegate’s proposed indication. The sponsor maintains that the secondary outcome of all-cause death is statistically significant, clinically relevant and hence provides Health Care Providers (HCPs) with important information when prescribing apixaban. The sponsor acknowledges the Delegate’s view that a secondary endpoint cannot be included as an indication, and maintains that given the clinical trial findings, the data on all-cause death should be included in the *Clinical Trials* section of the PI.
- **Data Integrity:** The sponsor maintains that the data integrity issues identified during the evaluation do not affect the overall results. The sponsor has kept the TGA updated on the investigations and outcomes. These conclusions have also been accepted by the Delegate (in the overview).
- **Post Treatment Events:** A careful analysis of events that occurred following cessation of apixaban therapy in ARISTOTLE suggest that there was an excess of thromboembolic and bleeding events in this treatment arm at end of the trial. These excess events in the apixaban arm were associated with the new initiation of a VKA rather than the discontinuation of apixaban treatment. This highlights the importance of monitoring anticoagulation status during initial titration of warfarin therapy to reduce the risk of stroke and bleeding. Therefore, the sponsor has updated the PI on the need for INR monitoring when switching therapy.

Recommendations from the RMP evaluations are addressed in a separate document (details of this are beyond the scope of this AusPAR). Of note, the sponsor has committed to:

- ensuring appropriate safety-related information is incorporated in the planned Eliquis educational program, which focuses on the identified and potential risks and appropriate prescribing of Eliquis
- including "management of severe bleeding" as important missing information in the Australian Specific Annex
- an additional PV activity, a targeted questionnaire for severe bleeding.

The sponsor provided a copy of these responses to the OPR and will work with OPR to finalise these before approval. An updated apixaban Core Company RMP plus the Australian Specific Appendix will be provided to the TGA following confirmation of the acceptability of the above following the ACPM meeting and the sponsor's discussion with OPR.

Changes have been made to the PI in response to requests from various evaluators and the Delegate. Details of these are beyond the scope of this AusPAR. A corresponding CMI document is also provided.

Sponsor's comments on the Delegate's request for ACMP advice

1) Should the indication be modified to remove reference to a reduction in death, remove the claim of a reduction in risk of major bleeding and to add "adults" to the indication?

The sponsor accepts the recommendation to remove the comparison to warfarin and to remove reference to death. With the removal of reference to death, the sponsor proposes to change the associated text "reduce the risk" to "prevention of", which is supported by the findings from the pivotal clinical trials. This wording is in harmony with the current Xarelto (rivaroxaban) and Pradaxa (dabigatran) PI documents.

The sponsor has not added reference to adults because the lack of data in paediatric patients is appropriately and adequately described under the *Precautions* section in the PI.

Therefore, the proposed revised wording for the indication is as follows:

> *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.*

2) Does the ACPM consider that the data integrity issues are unlikely to effect the overall results and that the investigations by the sponsor into this matter are satisfactory?

The Sponsor does not believe that the data integrity issues have affected the overall results. The TGA was provided with an identical copy of the comprehensive response to the FDA's CRL, which concluded from an extensive audit of the data that the analysis of the Combined Random Sample provided a robust and reliable assessment of the rate of medication errors in the ARISTOTLE study. Three sets of analyses were performed on various samples collected at different points in time in response to the FDA and EMA requests. While the methodologies have become more rigorous with each analysis, the results remain highly consistent. The FDA-requested analysis addressed all known sources of uncertainty to estimate the dispensing error so as to maximise the count of incorrect dispensations. An alternative analysis used other reliable sources of information to obtain a more likely, and perhaps more reliable estimate. Sensitivity analyses confirmed that the finding of superiority of apixaban over warfarin was preserved over this range of dispensation error estimates, hence the results remain valid. This response has since been deemed acceptable by the FDA and approval was granted for Eliquis on 28 December 2012.

The GCP issues in China have also been addressed satisfactorily for both the FDA and EMA and further details of the isolated incident can be found against point b) below where specific issues raised in the Delegate's overview are addressed.

3) Is the increase in strokes seen following cessation of apixaban of concern and has this been adequately addressed by the sponsor?

End of Treatment Events in ARISTOTLE: Concerns regarding the switching and discontinuation of anticoagulant therapy center around the safety of interrupting treatment, the possibility of over- or under-anticoagulation as treatments are changed (for example, from warfarin to apixaban or from apixaban to low molecular weight heparin (LMWH)), and the possibility of a rebound or hypercoagulable state following discontinuation of therapy. The sponsor has done a careful analysis of events that occurred after switching from double blind therapy in ARISTOTLE. The results of this analysis have been presented publically (European Society of Cardiology meeting, 2012) and a manuscript is in preparation. The findings of this analysis (presented below) suggest:

- There was an excess of both thromboembolic and bleeding events in the apixaban arm upon discontinuation at end of the trial
- The benefit of apixaban over warfarin following discontinuation of blinded study drug during the trial was preserved, as evidenced by sensitivity analysis
- Excess events in the apixaban arm were likely due to an increased risk associated with the new initiation of a VKA, and not a liability of the discontinuation of apixaban treatment:
  - The majority of excess events occur more than one week after discontinuation, which makes a hypercoagulable state an unlikely explanation
  - Increased events were noted in both stroke/SE and in major bleeding outcomes (the latter could not be explained by apixaban discontinuation)
  - A similar pattern of excess events was noted in warfarin-naïve patients with warfarin initiation at the time of randomisation. This is consistent with that described in studies of warfarin initiation in the clinic.

Proper interpretation of events occurring after the efficacy cut-off date requires an understanding of how patients were switched to open label therapy and of end of trial conduct. The end of the trial involved switching patients from blinded apixaban to open label warfarin, or from blinded warfarin to open label warfarin (few patients received dabigatran, some did not receive open label therapy). Since this was a "one way switch" (apixaban to warfarin, but not warfarin to apixaban), patients in the warfarin treatment group would have demonstrated an ability to tolerate titration and long term treatment with a VKA; those on apixaban would not, especially if they entered the trial as warfarin naïve. Warfarin assigned patients would likely have warfarin dosing continued at the same initial strength, without the need for titration, but with additional INR monitoring following the switch. Moreover, additional complexity was incurred by the need to preserve the double blind while switching (which would not be an issue in clinical practice), and by the fact that many patients were also switching treatment physicians - for example, returning to their primary care physician from the investigation site for management of their antithrombotic therapy.

Table 16. Sensitivity analyses for stroke/SE, first dose through 2, 7, 30 days after last dose of blinded study drug (evaluable subjects)

Time Period	HR (Apixaban/Warfarin)	95% CI	P-value (2-sided for superiority)
Up to 2 days after last dose	0.69	0.56, 0.86	0.0009
Up to 7 days after last dose	0.69	0.56, 0.85	0.0006
Up to 30 days after last dose	0.77	0.63, 0.94	0.0086

Source: Table 7.1.1.2 of CV185030 CSR

Discontinuation events on apixaban were not an issue during the trial (that is, prior to the efficacy cut off date), as sensitivity analyses at 2, 7, and 30 days following discontinuation of apixaban blinded therapy confirm the robust reduction in stroke and SE persists across these time periods, with highly significant reductions in hazard from 23% to 31%.

During the period from the end of intended treatment period (that is, after the efficacy cut off date of 31 January 2011) up to 30 days after the last dose of study medication, a total of 27 stroke/SE events in the apixaban group and 10 events in the warfarin group occurred. A small and similar number of these events occurred in subjects remaining on apixaban or warfarin at the time of the event (4 versus 3 events, respectively). A majority of apixaban (23) and warfarin (7) subjects had started other therapies. Of these subjects, 7 of the apixaban but only 2 of the warfarin-treated were not switched to either a VKA or dabigatran as their open-label stroke prevention treatment; they were therefore receiving either less effective treatment (antiplatelet agents) or no therapy. Of the remaining 16 apixaban subjects who received warfarin or a VKA as their open-label therapy, 4 had events within 10 days of switching, compared with 2 from the warfarin treatment group. The remaining 12 subjects in the apixaban group had their events late- from 18 to 29 days after switching.

A hypercoagulable state has not been described often with FXa inhibitors. In situations where it has been described, it tends to occur early - within 7 days of therapy. That the majority of apixaban treated patients in ARISTOTLE who had events after the efficacy cut off date had occurrences 18 or more days after switching is strongly against hypercoagulability as a cause. It also suggests that further bridging (up to 7-10 days) is unlikely to address the issue.

A further analysis of events reveals a similar pattern of increased major bleeding in apixaban treated patients after switching following the efficacy cut off date (Table 17).

Table 17. International Society on Thrombosis and Haemostasis major bleeding events in patients who completed treatment in ARISTOTLE, at time periods after last dose

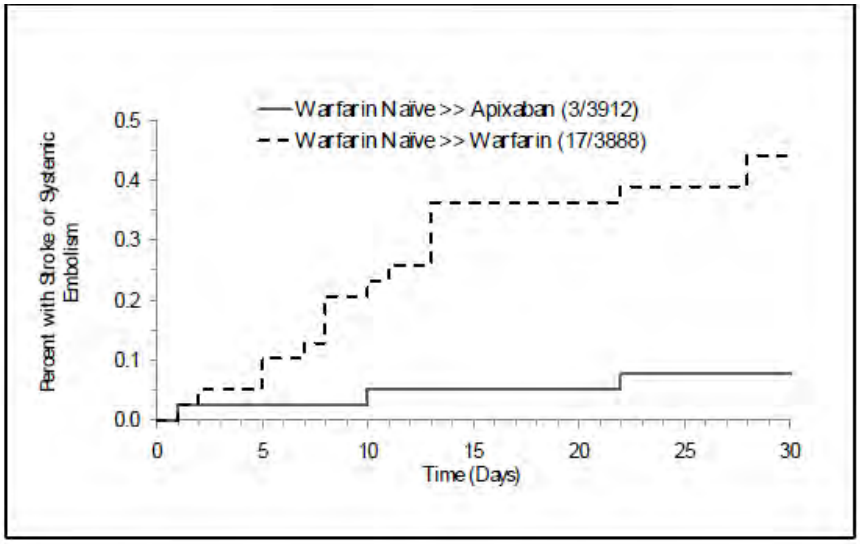
	Apixaban		Warfarin	
DaysAfter Last Dose	n/N	%/ yr	n/N	%/ yr
1 – 30	26 / 6791	4.97	10 / 6569	1.97
1 – 2	0 / 6791	–	2 / 6569	5.56
3 – 7	1 / 6787	1.08	3 / 6566	3.34
8 – 14	7 / 6780	5.39	0 / 6559	–
15 – 30	18 / 6771	6.84	5 / 6548	1.96

Patients were significantly more likely to bleed after discontinuation of apixaban during titration of warfarin/VKA therapy, with the majority of events (25/26) occurring 8 or more days after the last dose of apixaban (>16 half-lives (t½) later). This pattern, that mirrors that of the stroke/SE in the same period, strongly suggests that the liability that accompanies switching is related to initiation of VKA, not to apixaban. Again, this goes

against the presence of a hypercoagulable state as such a scenario would not account for increased bleeding occurring weeks after drug discontinuation.

The first 30 days following initiation of warfarin therapy is known to be a time of particular concern for both stroke and bleeding, especially in warfarin naïve patients. To further understand the nature of this issue in ARISTOTLE, the sponsor examined the occurrence of stroke/SE following the initiation of study drug in the first 30 days after randomisation into the trial. The behaviour of warfarin (oral anticoagulation) naïve patients was of particular interest, so a comparison was performed of the rates of stroke/SE in this group by treatment assignment. These finding are shown in Figure 2, which shows that the two groups behave quite differently.

Figure 2. Stroke/SE events in warfarin naïve patients entering ARISTOTLE, from randomisation to day 30



The rate of stroke/SE for warfarin naïve patients randomised to apixaban is quite low in the 30 days following randomisation, and does not look much different from their behaviour at other time points during the trial, nor does it differ much from warfarin experienced patients entering the trial (data not shown). The behaviour of warfarin naïve patients randomised to warfarin looks quite different, with a steep increase in events in the first 30 days, behaviour that has been described in other studies of warfarin initiation in the clinic and is very similar to the event pattern seen after switching from apixaban to open label warfarin at the end of the trial. Hence, such patients randomised to apixaban do not show this increase in events in the 30 days following initiation of study drug, but they can be at risk for these events when switched to (or initially started upon) warfarin. A previous study (not shown here) indicates that warfarin naïve patients who are begun on warfarin or other VKA should be considered at risk during the first 30 days of titration, whether in the setting of a new warfarin start (from no previous therapy) or when switching from apixaban (or another novel oral anticoagulant such as rivaroxaban). The liability is associated with warfarin/VKA initiation, not with apixaban.

Based on the above analyses and consistent with what has been described in studies of warfarin initiation in the clinic, the sponsor concludes that there is an increased risk of stroke/SE and of bleeding when switching from apixaban to warfarin/VKA. This risk is associated with the initiation of warfarin, not the discontinuation of apixaban. Events tend to cluster late (>1 week after discontinuation), which makes a hypercoagulable state unlikely, and suggests that early bridging will be of little utility in reducing this risk. Prescribers should appreciate this early risk of warfarin treatment when selecting therapy, and should increase the role of INR monitoring during titration to reduce the risk

of stroke and bleeding, especially in patients at higher risk of stroke such as those with multiple $CHADS_2$ risk factors.

To ensure HCPs continue to monitor coagulation status during the switching period, the sponsor has updated the *Dosage and Administration* section of the PI with advice on INR monitoring when switching therapy; and the *Precaution* section has also been updated in this regard. Details of proposed revisions of text in the PI are beyond the scope of this AusPAR.

In addition, guidance regarding switching from or to apixaban treatment will be included in the planned HCP education program.

Sponsor's responses to specific issues raised in the Delegate's Overview

a) Given that the dosing instructions allow for a 2.5 mg dose, please provide a biowaiver justification that compares the 5 mg strength with the 2.5 mg strength.

Based on the favourable physical-chemical properties and PK characteristics of apixaban, along with the proportional similarity of the 2.5 mg and 5 mg commercial tablet formulations, comparative dissolution testing can be used to support apixaban dose-strength equivalence. Comparative dissolution testing met all criteria for establishing similar dissolution profiles between dose-strengths. Therefore, the sponsor has concluded that dose-strength equivalence between the apixaban 2.5 mg and 5 mg tablets is established and that a clinical bioequivalence study is not needed.

b) Given the GCP concerns at two sites in China, have further audits been conducted of the other sites to determine that this was not a more widespread matter?

The GCP concerns occurred at a single site (site 1200) in China after the study was completed during inspection preparation activities. As the reported misconduct occurred after data-lock, they did not impact data integrity. The sponsor's investigation of the reported misconduct included a review at site 1200 and also at site 1178 in China which was also inspected by FDA. No concerns were noted at site 1178 during the sponsor review or the FDA inspection.

During the study the sponsor and Contract Research Organisation (CRO) conducted audits at 56 sites; there were no issues of misconduct identified during those audits. As further follow-up to the investigation, the sponsor conducted targeted audits at four additional sites in China (1198, 1168, 1244, 1287) that were monitored by personnel involved with the monitoring of site 1200 and 1178. No evidence of misconduct was identified at any of the four sites. Lastly, the sponsor contacted all of the sites in China (36) to review the documentation practices that were in place during the trial, specifically regarding the source document worksheets that appeared to have been altered at site 1200. The follow-up established that adequate controls were in place during the study at the other sites, and that the activities at site 1200 were isolated.

c) Outstanding matters raised by the RMP evaluator.

The outstanding matters have been addressed in separate documents and communications with the OPR.

d) The two-sided p-value for superiority in the ARISTOTLE trial was 0.0114 however the statistical plan indicates that the one sided alpha value was set at 0.005 for superiority. Please comment on whether the p-value of 0.0114 is therefore strictly above the threshold for statistical significance and that apixaban is not superior to warfarin.

As per the CSR for the ARISTOTLE trial (CV185030), Statistical Analysis Plan Version 2, the one-sided alpha used for superiority is 0.02499. According to the pre-specified hierarchical testing procedure, non-inferiority for the primary endpoint of stroke and SE was tested first with a one-sided alpha of 0.005. The one-sided non-inferiority p-value of <0.0001 was less than the one-sided alpha level, so non-inferiority was established. Since,

as required by the hierarchical testing procedure, non-inferiority was established, superiority was tested. The two-sided alpha level for superiority corresponding to the one-sided alpha of 0.02499 is 2 times 0.02499=0.04998. Since non-inferiority was established and the two-sided superiority p-value of 0.0114 is less than two-sided alpha level of 0.04998 with an estimated HR favouring apixaban, it is concluded that apixaban is superior to warfarin for the combined endpoint of stroke and SE.

e) Similarly, in the ARISTOTLE trial, the one sided alpha value was set at 0.005 for all cause death however the p-value for the result was 0.0465. Please comment on the statistical significance of this result and whether it is considered that apixaban is superior to warfarin for this endpoint.

As per the CSR for the ARISTOTLE trial (CV185030), Statistical Analysis Plan Version 2, the critical value for all-cause death was set equal to the corresponding critical value for the primary endpoint. The critical value is determined by the alpha level, so the rest of the discussion is focused on alpha levels. As described in the response to point d) above, the alpha level used for superiority for stroke and SE was a one-sided alpha of 0.02499, so a one-sided alpha of 0.02499 was also used for all-cause death. According to the pre-specified hierarchical testing procedure, if and only if non-inferiority and superiority in stroke and SE were established, superiority for ISTH major bleeding is tested. As both of these were established and the two-sided p-value of <0.001 was less than the two-sided alpha of 0.05 (that is, 2 times 0.025) with an estimated HR favouring apixaban, it is concluded that apixaban is superior to warfarin in ISTH major bleeding. Finally, superiority for death was tested if only if the following were established: non-inferiority for stroke and SE, superiority for stroke and SE, and superiority for major bleeding. Since each of these was established and the two-sided p-value for all-cause death of 0.0465 was less than the two-sided alpha level of 0.04998 with an estimated HR favouring apixaban, it is concluded that apixaban is superior to warfarin for all-cause death.

f) What is the likely explanation for the increased number of strokes seen in patients who had changed therapy at the end of the study from apixaban to warfarin, and how will this be addressed in the PI, RMP and education to healthcare professionals? How can the sponsor be sure that this is not a rebound phenomenon or other delayed effect of the drug and therefore if so how could this risk be mitigated?

This is addressed at point 3 under Delegate's request for ACPM Advice, above.

g) Were patient's risk of stroke calculated using the CHA_2DS_2-VASc and if so, please provide these scores for patients in this trial using a median and mean approach and a distribution for each score level.

No, this scale was not a component of any of the conducted clinical trials, as this scale did not exist at the time the Statistical Analyses Plans were written (it would have only been available for the last 2 years). Furthermore, not all elements of the CHA_2DS_2VASc scoring scheme were collected for all patients in ARISTOTLE, so CHA_2DS_2VASc scores cannot be determined post-hoc.

h) Confirm the unadjusted and adjusted HR and 95% CI for the primary endpoint in the AVERROES study.

The unadjusted HR and 95% CI for stroke and system embolism was 0.45 (0.32, 0.62). These results are identical to the adjusted HR and 95% CI when all are rounded to two decimal places.

i) Comment on whether there were any cases of liver dysfunction that met the definition for Hy's law in the ARISTOTLE or AVERROES studies.

There were no cases that met the definition for Hy's law in the ARISTOTLE and AVERROES studies. An assessment report authored and endorsed by members of the external

independent hepatic panel for the apixaban programme was provided to support this assertion.

j) Discuss the rationale for why the lower dose of 2.5 mg bid was chosen as the appropriate dose for patients with 2 of the following characteristics: age 80 years, body weight ≤60 kg or serum creatinine 133 µmol/L.

The decision to require 2 or more factors listed in the algorithm (as detailed in the CSR) for dose reduction was based on clinical judgment together with available PK data at the time this algorithm was devised and the results from the programme fully support this adjustment.

k) Provide a table comparing the primary endpoint result, major bleeding, all bleeding and CRNM bleeding in patients aged <75 years and 75 years and comment on any differences.

ARISTOTLE: As expected from epidemiological data where older age predicts higher risk, in ARISTOTLE there were higher primary efficacy event rates in both treatment groups for subjects with age ≥75 years compared to those with age <75 years. Nevertheless, the treatment advantage of apixaban compared to warfarin was maintained.

Similarly, there were higher event rates in both treatment groups for subjects with age ≥75 compared to those with age <75 for all bleeding endpoints and the benefit-risk profile of apixaban compared to warfarin was maintained in these patients.

AVERROES: The primary efficacy event rates in AVERROES were higher in both treatment groups for older subjects; however, the comparative treatment effect of apixaban was maintained.

Again and as expected, bleeding event rates were generally higher in the older patients. For major bleeding, the HRs were similar. For the other types of bleeding, the HRs were somewhat elevated in the subjects with age ≥75 compared to those with age <75. The advantage of using apixaban in older subjects was maintained.

l) Discuss the sponsor's plans for development of an antidote to apixaban and of any assays for monitoring the level of anticoagulation of the patient.

The sponsor's overall strategy for developing an effective antidote includes the following complementary activities: (1) further characterisation of the reversal of apixaban's anticoagulant effects by haemostatic agents *in vitro* and in animal models; (2) a clinical study examining the reversal of apixaban's anticoagulant effects by prothrombin complex concentrate (PCC); (3) addition of a targeted bleeding questionnaire to the post-marketing authorisation PV activities that will collect information on serious bleeding events and interventions attempted to control the bleeding; and (4) pursuit of a clinical study examining the reversal of apixaban's anticoagulant effects by Portola Pharmaceutical's investigational antidote for FXa inhibitors.

m) Provide an analysis of major bleeding events by concomitant medication use in ARISTOTLE.

The addition of concomitant medications known to cause bleeding or bleeding diathesis (ASA, ASA and thienopyridine or NSAIDS) to study drug increased the risk of bleeding in both the apixaban and warfarin treatment groups. However, in all cases, the risk of bleeding was less on the apixaban treatment arm than the warfarin treatment arm.

Sponsor's conclusion

The sponsor supports the Delegate's recommendation to approve the application to register a new strength for Eliquis (apixaban) and to extend the indication to: *prevention of stroke and systemic embolism in patients with non-valvular AF and at least one additional risk factor for stroke.* The sponsor requested the Delegate consider the revised Eliquis PI (details of this are beyond the scope of this AusPAR).

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, taking into account the submitted evidence of efficacy, safety and quality, considered this product to have an overall positive benefit–risk profile for the modified indication;

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

In making this recommendation, the ACPM noted the outcomes from the audit of the pivotal trial data and do not have additional concerns about the study integrity. However, the ACPM expressed caution on the overall transferability of efficacy and safety outcomes into the broader population, as proposed in this indication. The ACPM does not support the reference to reduction in the secondary endpoints of death and bleeding risk in the indication as these were secondary endpoints and the test for statistical significance was borderline.

The ACPM had significant concern about incomplete and inconsistent analysis and consideration of the risk to patients aged over 75 years, especially in relation to the recommended dose adjustments. This population group frequently has significant renal function impairment and extreme caution is warranted; however dosage adjustment guidelines are absent or this is inadequately referenced in the PI / CMI for renal impairment, aged or low body weight patients.

The ACPM encouraged the TGA to examine data for the incidence of adverse effects of gastrointestinal and intraocular bleeding as this analysis appears incomplete and inconsistent with the safety profile for these products.

The ACPM agreed with the delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following;

- a statement in the *Dosage and Administration* and *Clinical Trials* sections of the PI and relevant sections of the CMI to ensure the removal of reference to risk of major bleeding in the indication and to include a full reference in the PI.
- a statement in the *Contraindications*, *Precautions* and *Dosage and Administration* sections of the PI and relevant section of the CMI to ensure that the products are not used in patients with significant renal impairment (below 25 mL/minute creatinine clearance, as in the clinical trial) and there are clear guidelines of dose adjustment in patients with renal impairment or, low body weight or aged 80 years or over.

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following;

- that the sponsor should be requested to provide further details of the rates of GI and ocular bleeding particularly for the very elderly, that is, aged 80 years and over.
- full implementation of the RMP to the satisfaction of the TGA.

The ACPM advised that the 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 these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved:

- the registration of the new strength ELIQUIS apaxiban 5 mg film-coated tablet and;
- the new indication:

  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 full indications are now:

> *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 and at least one additional risk factor for stroke*

This approval is based on the evaluation of the information and data provided with the original letter of application and with any subsequent correspondence and submissions relating to the application.

The approval letter to the sponsor indicated the following specific conditions of registration for these goods:

Specific conditions applying to these therapeutic goods

- The implementation in Australia of the apixaban Risk Management Plan (RMP) CCRMP version 2.0, dated 13 July 2012 and RMP - Australian Specific Annex (ASA) version 4 dated 26 March 2013, included with submission PM-2011-03165-3-3, and any subsequent updated versions, as agreed with the TGA.
- The sponsor formulate and implement an Australian-specific patient and health professional education program as part of the risk minimisation plan that aims to ensure the safe use of apixaban in Australia, including during transition to or from apixaban, raises patient awareness of and access to the apixaban Consumer Medicines Information leaflet and makes prescribers aware of apixaban's contraindications and precautions and risks applying to particular patient population groups prior to prescribing. Specific details of the education program and associated materials must be agreed with the TGA prior to supply for this indication. The sponsor is required to lodge with the TGA a report every 3 months summarising the success or otherwise of these particular aspects of the prescriber education program. In these reports particular attention is to be paid to any problems encountered in making prescribers aware of these factors. The first report is to be lodged no later than 3 months after the date of the approval letter and subsequent reports are to be lodged at 3-monthly intervals, the final report to be lodged 12 months after the first, making 5 reports in all.
- The sponsor is to provide the distribution rationale for use of the bleeding questionnaire within 3 months after the date of the approval letter, as agreed in the sponsor's pre-ACPM response (Appendix 2) and letter from the sponsor dated 25 February 2013.
- If there is any initiative such as a prescriber familiarization program or a patient familiarisation program involving the enrolment of patients for the purpose of commencing them on apixaban, then:
  - All patients involved must be provided with the latest version of the Consumer Medicines Information leaflet
  - Copies of the Consumer Medicines Information leaflet along with the Product Information document must be provided to those prescribers

  - There must be a focus on obtaining the participation of prescribers in pharmacovigilance monitoring, particularly the reporting of all events of bleeding in a patient with the aim of accurate data collection for analysis
  - The TGA is to be informed immediately upon the actual commencement of such a program and to be given a 3-monthly report of this program until such time as no longer required by the TGA

· The following studies must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission:

  - The study on the use of activated charcoal to treat bleeding in apixaban patients.
  - The study CV185087 in subjects on haemodialysis.
  - The population pharmacokinetic/pharmacodynamic study in patient with atrial fibrillation.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information, please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au