Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Rivaroxaban

Proprietary Product Name: Xarelto

Sponsor: Bayer Australia Ltd

October 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 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
Decision:	Approved
Date of decision:	27 June 2013
Active ingredient:	Rivaroxaban
Product name:	Xarelto
Sponsor's name and address:	Bayer Australia Ltd 875 Pacific Highway Pymble NSW 2073
Dose form:	Tablet
Strengths:	15 and 20 mg
Container:	Blister
Pack sizes:	7, 14, 28, 42, 84, 98, 100
New approved therapeutic use:	Treatment of pulmonary embolism.
Route of administration:	Oral
Dosage (abbreviated):	For treatment of PE: 15 mg twice daily for three weeks, followed by 20 mg once daily
ARTG Numbers:	181185 and 181186

Product background

Rivaroxaban is a highly selective, competitive, direct inhibitor of Factor Xa (FXa). Factor Xa catalyses the conversion of prothrombin to thrombin. Inhibition of FXa blocks the generation of thrombin, and thus reduces thrombin-mediated activation of coagulation and platelets.

Xarelto tablets containing 15 and 20 mg rivaroxaban are currently registered for the following indications:

- *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).*

This AusPAR describes the application by Bayer Australia Ltd (the sponsor) to extend the approved indications for Xarelto 15 and 20 mg tablets to include, in addition to the above, the treatment of pulmonary embolism (PE).

Regulatory status

Xarelto 15 and 20 mg tablets received initial registration on the Australian Register of Therapeutic Goods (ARTG) in April 2012.[1]

At the time this application was considered by the TGA, a similar application, for the treatment of PE, has been approved in the European Union (EU, November 2012) and USA (November 2012) and was under consideration in Canada and Switzerland.

Product Information

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

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

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

Introduction

Clinical rationale

Standard treatment for acute deep vein thrombosis (DVT) or PE usually involves initial use of parenteral anticoagulants such as low molecular weight heparin (LMWH; such as enoxaparin), unfractionated heparin (UFH) or fondaparinux. Per oral administration of vitamin K antagonists (VKA) such as warfarin is then started in overlap with the parenteral anticoagulants. Parenteral anticoagulants may be discontinued when the international normalised ratio (INR) is equal or above 2.0 for two or more measurements. Treatment with VKAs requires ongoing coagulation laboratory monitoring and dose adjustments to keep the INR in the optimal therapeutic window of 2.0 to 3.0.

[1] Xarelto 10 mg rivaroxaban tablets have been registered since November 2008 *for the 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).* The current application does not involve changes to the indications for the 10 mg tablet.

The sponsor had stated that rivaroxaban was developed as an alternative anticoagulant to the parenteral anticoagulant/VKA treatment regimen, as it is an oral, direct-acting antithrombotic agent with a predictable dose-response relationship, and can be administered without the need for laboratory monitoring of its anti-coagulant effect and subsequent dose-adjustments.

Scope of the clinical dossier

The submission contains the following clinical information:

Module 5

- 1 biopharmaceutics study (Study 15921; unrelated to the proposed extension of indication)
- 3 population PK/PD analyses (unrelated to the proposed extension of indication)
- 1 pivotal efficacy/safety study (Study Einstein-PE)
- 12 meta-analysis study reports and 1 technical report

The biopharmaceutics study evaluates the effect of a Japanese diet on the bioavailability of rivaroxaban in healthy Japanese male subjects. The population PK/PD studies were conducted to characterise the PK and evaluate the PK/PD relationship in patients co-medicated with strong cytochrome P450 3A (CYP3A4) inducers, and to provide PK simulations for patients with severe renal impairment or are co-medicated with strong CYP3A4 inhibitors or inducers. One pivotal efficacy/safety study, Study Einstein-PE, was submitted to support the application for extension of indication. The 13 meta-analysis and technical reports evaluated various efficacy and safety parameters.

Paediatric data

The submission does not include paediatric data.

The sponsor had stated that the use of rivaroxaban in paediatric population (children under the age of 18) is not the subject of this application.

Good clinical practice

The clinical studies reviewed in this evaluation were in compliance with the *Note for Guidance on Good Clinical Practice* (CPMP/ICH/135/95, adopted by the TGA with annotations).

Pharmacokinetics

Studies providing pharmacokinetics data

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	Primary aim of study
PK in healthy adults	Food effect	15921	To investigate the effect of a Japanese meal on the bioavailability of rivaroxaban 15 mg tablets in healthy Japanese male subjects
Population PK analyses	Target population	13238 (Einstein-CYP cohort study)	To characterise the population PK/PD of an adapted rivaroxaban dosing regimen in subjects with acute proximal DVT or

PK topic	Subtopic	Study ID	Primary aim of study
			acute PE and concomitant use of a strong CYP3A4 inducer.
		13812	To define structural PK and PK/PD models for rivaroxaban in the Einstein-CYP cohort study by using rivaroxaban plasma concentrations and prothrombin time
	Other	15539	Simulations to describe the expected exposure of various modified dosing regimens in special populations: · severe renal impairment (CrCl 15-30 mL/min) · concomitant medication with a strong inhibitor of both CYP3A4 and P-gp (such as ketoconazole) · concomitant medication with a strong CYP3A4/P-gp inducer (such as rifampicin)
	Healthy Subjects	PH36685	Pooled analysis of PK and PD of rivaroxaban in subjects in Phase I clinical trials

DVT: Deep vein thrombosis; PE: Pulmonary embolism; CrCl: creatinine clearance

The biopharmaceutics study (Study 15921) and 3 population PK/PD studies (Studies 13238, 13812 and 15539) do not provide any data relevant to the evaluation of this submission for the extension of indication for rivaroxaban. The sponsor is not proposing to make any changes to the recommended dosing regimen in patients with severe renal impairment or who are co-medicated with strong CYP3A4 inhibitors or inducers. The sponsor is also not proposing to include any of the results from these studies in the proposed PI, or make any changes to the PK and PD sections of the currently approved PI.

In addition, a study report PH 36685 was submitted, but this was an exploratory pooled PK/PD analysis of subjects in 64 Phase I studies with no efficacy or safety endpoints. The sponsor is also not proposing to make any changes to the PK and PD sections of the currently-approved PI based on this study report.

Study 13238 (Study Einstein-CYP) was conducted to characterise the population PK/PD of an adapted rivaroxaban dosing regimen (rivaroxaban 30 mg twice daily (b.i.d.) for 3 weeks followed by 20 mg b.i.d.) in subjects with acute proximal DVT or acute PE and concomitant use of a strong CYP3A4 liver enzyme inducer, compared to the usual dose regimen of 15 mg b.i.d. for 3 weeks followed by 20 mg once daily (o.d.) for subjects without concomitant use of a strong CYP3A4 inducer. Results showed that during initial treatment (30 mg b.i.d.), the median rivaroxaban rivaroxaban area under the concentration-time curve over zero to 24 h at steady state ($AUC_{0\text{-}24\,h,\,ss}$) in this study was approximately 36% lower than that of the pooled study results from subjects of the Phase II studies treated with the usual 15 mg b.i.d. / 20 mg o.d. dosing regimen. During extended treatment (20 mg b.i.d.), the median $AUC_{0\text{-}24\,h,\,ss}$ in this study was approximately 15% lower than that of the pooled results from the Phase II studies. The median maximum concentration at steady state (Cmax, ss) was also lower in this study (approximately 27% and 35% lower during initial and extended treatments, respectively).

Pharmacodynamics

No pharmacodynamics data were provided.

Dosage selection for the pivotal studies

The rivaroxaban dose regimen used in the pivotal study (Einstein-PE) is the same as the currently registered dose regimen of rivaroxaban for the treatment of DVT and the prevention of recurrent DVT and PE. The sponsor had stated in the clinical study report (CSR) of Study Einstein-PE that previous Phase II studies (Studies 11223 and 11528, performed in subjects with acute symptomatic DVT for a treatment duration of 3 months) showed that 20 mg rivaroxaban total daily dose had been the lowest effective dose associated with a safety profile at least as good as a treatment regimen starting with LMWH followed by VKA. The sponsor stated that the combined analyses of both dose-finding studies had indicated that the optimal regimen consists of administration of rivaroxaban 15 mg b.i.d. for an initial 3-week treatment phase followed by 20 mg o.d. for the subsequent treatment period.

Efficacy

Studies providing evaluable efficacy data

Pivotal study

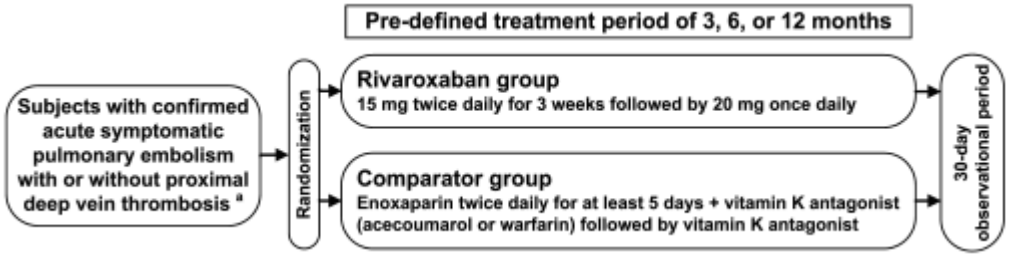
For the proposed additional indication for treatment of PE, the pivotal efficacy study to be evaluated is the Einstein-PE Study.

The rivaroxaban Phase III clinical development program consisted of 3 studies: the Einstein-DVT Study and Einstein-PE Study, which evaluated the treatment and prevention of DVT and of PE, respectively, and the Einstein Extension Study, which evaluated the benefit of continued treatment in subjects who had reached "equipoise" (that is, a state of clinical uncertainty) about the need for continued anticoagulation after the completion of initial anticoagulation treatment. The Einstein-DVT Study evaluated subjects with confirmed acute proximal symptomatic DVT without symptomatic PE, while the Einstein-PE Study evaluated subjects with confirmed acute symptomatic PE with or without symptomatic DVT.

The sponsor had stated that both Einstein-DVT and Einstein-PE Studies were integrated into a single study protocol, as the subject groups were complementary and were recruited at the same centres, the essential study design features were identical, and both evaluations were supervised and guided by the same study committees. Due to differences in recruitment rates for the target populations, the Einstein-DVT Study was completed earlier than the Einstein-PE Study, and had been used in a previous submission to the TGA to include the new indication of rivaroxaban 15 mg and 20 mg for the treatment of DVT and for the prevention of recurrent DVT and PE (approved in April 2012). The current submission presents the Einstein-PE Study results to support the additional indication for treatment of PE.

In the Einstein-PE Study, subjects were randomised to receive either rivaroxaban or enoxaparin/VKA. Subjects allocated to the rivaroxaban group received rivaroxaban per oral 15 mg b.i.d. for 3 weeks followed by rivaroxaban 20 mg o.d. for a total treatment duration of 3, 6, or 12 months. An overview of the study design is shown in Figure 1.

Figure 1. Einstein-PE: Overview of study design.



The primary efficacy objective for the Einstein-PE Study was to evaluate whether rivaroxaban is at least as effective as enoxaparin/VKA (either warfarin or acenocoumarol) in the treatment of subjects with acute symptomatic PE with or without symptomatic DVT, for the prevention of recurrent venous thromboembolism (VTE) events. The principal safety objective was the evaluation of major and clinically relevant non-major bleeding events.

Other studies

Study PH36746 is a pooled meta-analysis of Studies Einstein-PE and Einstein-DVT and was evaluated with regards to whether the results were consistent with those in Study Einstein-PE.

The other efficacy studies (PH36749, PH36705, PH36718, PH36706 and PH36711) were exploratory studies, and were briefly summarised and evaluated with regards to whether the results are pertinent to the evaluator's recommendations for this submission. These are described in the attached Extract from the Clinical Evaluation Report (CER; Attachment 2 of this AusPAR) and in the Delegate's Overview, below (see *Overall conclusion and risk/benefit assessment*).

Evaluator's conclusions on clinical efficacy for the proposed additional indication for treatment of pulmonary embolism

Overall, in the pivotal study, Einstein-PE, the study design and study inclusion and exclusion criteria were appropriate and consistent with the TGA-adopted European Medicines Agency (EMA) Committee for Proprietary Medicinal Products (CPMP) guideline *Note for guidance on clinical investigation of medicinal products for the treatment of venous thromboembolic disease* (CPMP/EWP/563/98, December 1999). The comparator active control drug combination and regimen of enoxaparin/VKA is a currently accepted drug combination regimen used in the clinical management of PE.

The primary and secondary endpoints of this non-inferiority study are appropriate and consistent with these recommendations of the above-mentioned TGA-adopted EMA guidelines. The statistical methods are appropriate for a non-inferiority study. The rationale and justification for the inferiority margin are in line with the recommendations of the *ICH E 9 Statistical principles for clinical trials; Note for guidance on statistical principles for clinical trials* (CPMP/ICH/363/96, September 1998), as well as the EMA Committee for Medicinal Products for Human Use (CHMP) *Guidelines on the choice of the non-inferiority margin* (EMEA/CPMP/EWP/2158/99, July 2005). The baseline demographic and disease characteristics of the study population were comparable between treatment groups, and also consistent with those in the target patient population.

The efficacy results in the pivotal study showed non-inferiority of rivaroxaban compared with enoxaparin/VKA across all primary and secondary efficacy outcomes. Analyses on the individual components of the efficacy outcomes showed that the incidence rates of recurrent PE, recurrent DVT and all-cause deaths were comparable between treatment groups, but the incidence rate of major bleeding event was lower in the rivaroxaban group

(1.4%) compared to the enoxaparin/VKA group (2.4%). The p-values for superiority were not statistically significant across all efficacy endpoints. However, this study was designed as a non-inferiority study, and not powered for test of superiority. Efficacy results of the pooled analysis using data from Studies Einstein-PE and Einstein-DVT were consistent with those in Study Einstein-PE alone, showing non-inferiority of rivaroxaban compared to enoxaparin/VKA across the primary and secondary efficacy outcomes.

Overall, interpretation of subgroup analyses on the primary efficacy endpoint and the secondary efficacy endpoint of net clinical benefit 1[2] in Study Einstein-PE was difficult due to the low event rates and/or small sample sizes in some subgroups, but did not raise significant concerns that rivaroxaban was less effective in certain subgroups. The p-values for interaction tests for the primary efficacy endpoint were ≥ 0.05 for all the subgroups. Subgroup analyses on net clinical benefit 1 initially triggered a more detailed look at the subgroup categories of age groups, but overall, when evaluated together with the subgroup analysis results in the pooled analysis, did not raise significant concerns.

Subgroup analyses in Study Einstein-PE of the efficacy outcome of net clinical benefit 1, which is a composite evaluation of symptomatic recurrent VTE and major bleeding events, showed that the upper limit of the 95% confidence interval (CI) of the hazard ratio (HR) for the subgroup of subjects aged < 60 years was above 2.0, suggesting that in this subgroup of younger subjects, rivaroxaban was not non-inferior to enoxaparin/VKA, and that there was a 1.3 times higher risk of having a composite outcome of symptomatic recurrent VTE or major bleeding events compared to subjects on enoxaparin/VKA. In addition, the p-value for interaction was < 0.05 in this age subgroup category, suggesting that rivaroxaban was less effective in younger subjects < 60 years in terms of net clinical benefit 1, compared to older subjects ≥ 60 years.

When the endpoint of major bleeding events was not factored in (that is, primary efficacy endpoint of symptomatic recurrent VTE), subgroup analyses in Study Einstein-PE again showed that the upper limits of the 95% CIs of the HRs for younger subjects (subjects aged < 60 years, those aged< 65 years and those aged 65 to 75 years) were again above the pre-specified inferiority margin of 2.0, suggesting that in these subgroup of younger subjects, rivaroxaban was not non-inferior to enoxaparin/VKA, and that there was a 1.3 to 1.5 times higher risk of having an outcome of symptomatic recurrent VTE compared to subjects on enoxaparin/VKA. However, the p-values for the interactions tests were now ≥ 0.05 for these subgroup categories, suggesting that that there was no statistically significant difference between the younger and older age groups for the efficacy endpoint of symptomatic recurrent VTE. Interpretation of these results was confounded by the relatively low event rates in these subgroups.

Subgroup analyses on the efficacy outcome of net clinical benefit 1 in the pooled analysis of Studies Einstein-PE and Einstein-DVT, with overall bigger sample sizes and event rates, showed that although p-values for interaction tests were < 0.05 in the age group subgroup categories (suggesting that rivaroxaban was less effective in subjects who were < 60 years old (compared to those ≥ 60 years old), and in those who were < 65 years old or between 65-75 years old (compared to those > 75 years old)), the upper limits of the 95% CI of the HRs for these younger age subgroups were all below the pre-specified non-inferiority margin of 1.75, indicating rivaroxaban was non-inferior compared to enoxaparin/VKA in these younger subjects.

Subgroup analyses on the primary efficacy endpoint of symptomatic recurrent VTE in the pooled analysis of Studies Einstein-PE and Einstein-DVT suggested non-inferiority of rivaroxaban compared to enoxaparin/VKA in these subgroups for the primary efficacy endpoint (upper limits of the 95% CIs of the HRs for pooled subjects aged < 60 years,

[2] The secondary efficacy outcome of 'net clinical benefit 1' was the composite of the primary efficacy outcome and major bleeding events.

those aged< 65 years and those aged 65 to 75 years were all below the pre-specified inferiority margin of 1.75), and that there was no statistically significant difference between the younger and older age groups for the primary efficacy endpoint (p-values for the interaction of ≥ 0.05).

Overall, using the subgroup analysis results in the pooled Studies Einstein-PE and Einstein-DVT in view of the larger sample sizes and event rates, the subgroup analyses suggested that rivaroxaban was non-inferior compared to enoxaparin/VKA across all age groups for the endpoint of symptomatic recurrent VTE, and that there was also no statistically significant difference between the younger and older age groups for this efficacy endpoint. Rivaroxaban was also non-inferior compared to enoxaparin/VKA across all age groups when major bleeding events were factored in (that is, net clinical benefit 1), but rivaroxaban appeared to be less effective in the younger age groups compared to the older age groups.

Safety

Studies providing evaluable safety data

Pivotal study providing evaluable safety data

· Einstein-PE Study

Non-pivotal efficacy studies/meta-analyses study reports providing safety data

· Study PH 36746

This was a meta-analysis of Studies Einstein-DVT and Einstein-PE.

· Studies PH36705 and PH36718

Both studies were identical in objectives and design except that Study PH36705 evaluated data from Study Einstein-PE only, while Study PH36718 was a meta-analysis of the respective data from Studies Einstein-PE and Einstein-DVT.

· Studies PH36706 and PH36711

Both studies were identical in objectives and design except that Study PH36706 evaluated data on Study Einstein-PE only, while Study PH36711 is a meta-analysis of Studies Einstein-PE and Einstein-DVT.

Other studies/meta-analyses study reports evaluable for safety only

· Study PH36715

Study PH 36715 presented the results of an integrated analysis of the safety profile of the rollover subjects from Study Einstein-DVT or Study Einstein-PE to the Einstein-Extension Study.

· Studies PH36707 and PH36708

Both studies were identical in objectives and design except that Study PH36707 evaluated data from Study Einstein-PE only, while Study PH36708 was a meta-analysis of the respective data from Studies Einstein-PE and Einstein-DVT.

· Study PH36709 and PH36710

Both studies were identical in objectives and design except that Study PH36709 evaluated data from Study Einstein-PE only, while Study PH36710 was a meta-analysis of the respective data from Studies Einstein-PE and Einstein-DVT.

Clinical pharmacology study

· Study PH36686

This report presented a pooled safety analysis of rivaroxaban in subjects included in 64 Phase I clinical trials.

Post marketing data

The sponsor has also provided post-marketing data from spontaneous reports received by Bayer Global Pharmacovigilance cumulatively from the approval of rivaroxaban in Canada on 15 September 2008 and in Europe on 30 September 2008 through to the cut-off date of this submission of 31 December 2011.

Patient exposure

The median duration of treatment in the Einstein-PE Study was similar between the 2 treatment groups (183 days and 182 days in the rivaroxaban and enoxaparin /VKA groups, respectively). Overall, 73.7% of the subjects in the rivaroxaban group and 70.0% of the subjects in the enoxaparin/VKA group were treated for ≥6 months.

Drug exposure in the pooled analysis of Studies Einstein-DVT and Einstein-PE (applicable for Studies PH 36746, PH36708, PH36710 and PH36718) was similar between the 2 treatment groups (183 days and 182 days in the rivaroxaban and enoxaparin /VKA groups, respectively). Overall, 71.7% of the subjects in the pooled rivaroxaban group and 67.1% of the subjects in the pooled enoxaparin/VKA group were treated for ≥6 months.

In Study PH 36715, which presented the results of an integrated safety analysis for 172 rollover subjects who participated in Studies Einstein DVT or Einstein PE and then in Study Einstein Extension, and who took rivaroxaban in both parts, the172 subjects had a median treatment duration with rivaroxaban of 364 days (range: 183 to 644 days). Of these, 132 (76.7%) had a cumulative rivaroxaban treatment duration of at least 12 months, 43 (25.0%) of at least 15 months, 24 (14.0%) of at least 18 months and 3 (1.7%) of at least 21 months. In terms of actual treatment duration, 23.3% (40/172) had a rivaroxaban treatment duration of >0 months to < 12 months, 62.8% (108/172) of ≥ 12 months to < 18 months, and 14.0% (24/172) of ≥ 18 months.

The extent of exposure to rivaroxaban in the Phase I clinical trials (applicable for Study PH36686) is shown in Table 2.

Table 2. Extent of exposure to rivaroxaban (all subjects valid-for-safety, n=1419)

		Rivaroxaban					
		All n=1419	< 10 mg n=77	10 mg n=539	15 mg n=123	20 mg n=338	> 20 mg n=342
1 day	n(%)	1135 (80.0)	70 (90.9)	480 (89.1)	81 (65.9)	227 (67.2)	277 (81.0)
2-7 days	n(%)	247 (17.4)	7 (9.1)	39 (7.2)	42 (34.1)	111 (32.8)	48 (14.0)
8-10 days	n(%)	37 (2.6)	0 (0.0)	20 (3.7)	0 (0.0)	0 (0.0)	17 (5.0)
> 10 days	n(%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Overall, the study drug exposure in the Einstein-PE Study is adequate to assess if the safety profile is consistent with that reported in the Product Information.

Evaluator's overall conclusions on clinical safety

Overall, in Study Einstein-PE, the incidences of all-causality treatment emergent adverse events (TEAEs), treatment-related TEAEs, all-causality treatment emergent serious AEs (TESAEs) and treatment-related TESAEs were comparable between the 2 treatment groups (Table 3).

Table 3. Incidence of AEs and most commonly-reported AEs in Study Einstein-PE and pooled analysis of Studies Einstein-PE and DVT, safety population

	Study Einstein-PE		Pooled analysis (Studies Einstein-PE and Einstein-DVT)	
	Rivaroxaban N=2412	**Enoxaparin/VKA N=2405**	**Pooled rivaroxaban N=4130**	**Pooled enoxaparin/VKA N=4116**
Incidence of all-causality TEAEs	80.3%	79.0%	73.0%	72.4%
Incidence of treatment-related TEAEs	32.2%	32.6%	28.5%	28.6%
Incidence of all deaths	2.6%	2.1%	2.5%	2.5%
Incidence of all-causality SAEs	19.5%	19.3%	16.4%	16.9%
Incidence of treatment-related TESAEs	4.6%	4.9%	3.7%	4.1%
Most commonly reported all-causality TEAEs in the rivaroxaban group	epistaxis (9.0% in the rivaroxaban group versus (vs.) 8.2% in the enoxaparin/VKA group) headache (8.0% vs. 7.2%) chest pain (7.6% vs. 7.7%) nasopharyngitis (7.5% vs. 7.9%) dyspnoea (6.7% vs. 5.7%).		epistaxis (7.4% vs. 6.6 % in the pooled enoxaparin/VKA group) headache (6.9% vs. 5.9%) nasopharyngitis (6.8% vs. 6.8%) cough (5.5% vs. 5.3%) chest pain (5.3% vs. 5.2%).	
Most commonly reported treatment-related TEAEs in the rivaroxaban group	epistaxis (7.2% vs. 6.6% in the enoxaparin/VKA group) haemoptysis (2.6% vs. 1.9%) menorrhagia (2.5% vs. 1.4%) contusion (2.2% vs. 3.6%).		epistaxis (5.8% vs. 5.2% in the pooled enoxaparin/VKA group) menorrhagia (2.4% vs. 1.2%) contusion (2.0% vs. 3.1%) gingival bleeding (1.9% vs. 2.1%).	
Most commonly reported all-causality TESAEs in the rivaroxaban group	chest pain (0.8% vs. 1.1% in the enoxaparin/VKA group) pneumonia (0.8% vs. 0.8%) dyspnoea (0.7% vs. 0.5%).		chest pain (0.6% vs. 0.7% in the pooled enoxaparin/VKA group) pneumonia (0.6% vs. 0.7%) anaemia (0.5% vs. 0.3%).	
Most commonly reported treatment-related TESAEs in the rivaroxaban group	menorrhagia (0.4% vs. <0.1 % in the enoxaparin/VKA group) anaemia (0.3% vs. <0.1%) haematuria (0.3% vs. 0.4%).		menorrhagia (0.3% vs. <0.1 % in the pooled enoxaparin/VKA group) anaemia (0.3% vs. 0.1%) haematuria (0.3% vs. 0.4%).	

The safety results of the study were also consistent with the known AEs of rivaroxaban. The AEs elicited in this pivotal study are known AEs of rivaroxaban stated in the currently-approved Australian PI for rivaroxaban.

Safety results in the pooled analysis of Studies Einstein-PE and Einstein-DVT were consistent with those of Study Einstein-PE. Safety results in the pooled Phase I studies

(Study PH36686) did not show any obvious dose-related increase in incidences of all-causality TEAEs and treatment-related TEAEs. Analyses of the rollover subjects from the Einstein-DVT or Einstein-PE Studies to the Einstein Extension Study (Study PH 36715) did not show any obvious increase in incidences of TESAEs with duration of treatment.

The most commonly occurring treatment-related TEAEs in the rivaroxaban group in Study Einstein-PE were bleeding-related AEs of epistaxis, haemoptysis and menorrhagia. The most commonly occurring treatment-related TESAEs in the rivaroxaban group were menorrhagia and anaemia. These were known AEs of rivaroxaban stated in the currently-approved Australian PI for rivaroxaban. The incidence rates of these treatment-related TEAEs and TESAEs were higher in the rivaroxaban group than in the enoxaparin/VKA group (Table 3, above).

However, analyses of the AE of interest of bleeding events in both study Einstein-PE and the pooled analysis of Studies Einstein-PE and Einstein-DVT showed that the overall incidence of clinically relevant bleeding events (composite of major and clinically relevant non-major bleeding events) was slightly lower in the rivaroxaban group compared to the enoxaparin/VKA group. The incidence of the component of major bleeding events was lower in the rivaroxaban group compared to the enoxaparin/VKA group, yielding HRs of about 0.5, and statistically significant p-values for superiority (rivaroxaban over enoxaparin/VKA) in both Study Einstein-PE and the pooled analysis. The incidence of the component of clinically relevant non-major bleeding events was comparable between treatment groups in both Study Einstein-PE and the pooled analysis. In addition, the majority of major bleeding events in the rivaroxaban group (in both Study Einstein-PE and the pooled analysis of Studies Einstein-PE and Einstein-DVT) were in the category of non-fatal non-critical organ bleeding events. The number of fatal major bleeding events in the rivaroxaban group was numerically lower compared to the enoxaparin/VKA treatment group (Study Einstein-PE: 2 [< 0.1%] versus 3 [0.1%] in the enoxaparin/VKA treatment group; pooled analysis: 3 [< 0.1%] versus 8 [0.2%]).

Subgroup analyses of the principal safety outcome and of major bleeding events in both Study Einstein-PE and the pooled analysis showed similar results to that in the overall safety population, with HRs below or close to 1.00, except for certain subgroups with low sample sizes and/or low event rates, which makes interpretation difficult. Treatment interactions p-values were not statistically significant for the majority of the subgroups.

Subgroup analyses in Study Einstein-PE showed that for major bleeding events, the HRs of rivaroxaban versus enoxaparin/VKA in the younger age groups (age < 65 years and age 65 to 75 years) were all < 1.0 (that is, in favour of rivaroxaban over enoxaparin/VKA), although treatment interaction p-values were statistically significant (this was supported by subgroup analyses in the pooled analysis of Studies Einstein-PE and Einstein-DVT for major bleeding events, showing that the HRs of rivaroxaban versus enoxaparin/VKA in the age groups of < 60 years was < 1.0, although treatment interactions p-value was statistically significant for this age subgroup category (age < 60 years versus ≥ 60 years). These suggested that although there was a statistically significant difference between the younger and the older age groups, subjects on rivaroxaban nonetheless had a lower risk of major bleeding events compared to those on enoxaparin/VKA across the age groups.

When clinically relevant non-major bleeding events were factored in (that is, principal safety outcome which was a composite of major and clinically relevant non-major bleeding events), subgroup analyses in both Study Einstein-PE and the pooled analysis of Studies Einstein-PE and Einstein-DVT suggested that subjects aged <60 years and on rivaroxaban had about 1.1 times higher risk of major or clinically relevant non-major bleeding events compared to those on enoxaparin/VKA. In the pooled analysis, the treatment interactions p-value was statistically significant for this age subgroup category (age < 60 years versus ≥ 60 years), suggesting that there was a statistically significant difference between the

younger and older age groups. However, in Study Einstein-PE, the p-value was not statistically significant for this age subgroup category.

Analyses of bleeding events in 172 rollover subjects to Study Einstein Extension showed that in these subjects, who had a median treatment duration with rivaroxaban of 364 days and among whom about 75% had a cumulative rivaroxaban treatment duration of at least 12 months, and about 25% of at least 15 months, the majority of clinically relevant bleeding events were non-major bleeding events and only a minority were major bleeding events. The majority of these bleeding events occurred within the first 12 months, and no bleeding events were reported after 15 months of treatment, suggesting the incidence of these bleeding events did not increase with duration of treatment.

Analyses on the incidence of multiple bleeding events showed that in both Study Einstein-PE and the pooled analysis of Studies Einstein-PE and Einstein-DVT, the majority of subjects with clinically relevant bleeding events, major bleeding events, or all confirmed bleeding events had single bleeding event. The incidence rate of multiple bleeding events affecting the principal safety outcome and all confirmed bleeding events were also comparable between treatment groups.

Analyses on the effect of co-medications on the incidence of bleeding events (Studies PH36705 and PH36718) suggested that subjects on 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), acetylsalicylic acid (ASA, aspirin), non-steroidal anti-inflammatory drugs (NSAIDs) or CYP3A4 inhibitors at baseline had a higher incidence of major bleeding events, clinically relevant bleeding events, and all confirmed bleeding events compared to those who were not. The interactions of NSAIDs and CYP3A4 inhibitors with rivaroxaban are known drug interactions stated in the currently approved PI for rivaroxaban. The currently approved PI stated that "No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid" although it was also stated under the *Precaution* section of the PI that "Care should be taken if patients are treated concomitantly with platelet aggregation inhibitors (for example, clopidogrel and acetylsalicylic acid) as it may lead to an increased bleeding risk". No mention of drug interaction with statins are stated in the PI except that "There were no mutual pharmacokinetic interactions between rivaroxaban and midazolam (substrate of CYP 3A4), digoxin (substrate of P-gycoprotein (P-gp) transporter) or atorvastatin (substrate of CYP3A4 and P-gp)." The sponsor is not currently proposing to make any changes to the PI using data derived from Studies PH36705 and PH36718, but had stated that these analyses were exploratory and that results and conclusions will be described in a separate report. It is not critical that the separate report be provided now in order that a recommendation can be made with regards to this submission (see also *List of Questions and Second round evaluation of clinical data submitted in response to questions*, below).

The potential use of prothrombin time as a PD marker for bleeding events was explored in Studies PH36706 and PH36711, but results had not been analysed with statistical tests and were exploratory at the time of submission. The sponsor had stated that results and conclusions will be described in a separate report. It is not critical that the separate report be provided now in order that a recommendation can be made with regards to this submission (see also *List of Questions and Second round evaluation of clinical data submitted in response to questions*, below).

Analyses of liver laboratory test results and of hepatic disorder AEs and SAEs in both Study Einstein-PE and the pooled analysis of Studies Einstein-PE and Einstein-DVT yielded results consistent with the known adverse effect of rivaroxaban in causing liver laboratory test abnormalities, and did not raise additional significant concerns on the risk of hepatic injury with rivaroxaban use. The incidence rates of post-baseline increases in liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (AP) were lower or comparable in the rivaroxaban treatment group versus

those in the enoxaparin/VKA group. Incidence rates of post-baseline elevations in total and direct bilirubin levels were higher in the rivaroxaban group compared to the enoxaparin/VKA group at lower thresholds of elevations (>1.5 times the upper limit of normal (ULN) for total bilirubin; >1.5 times ULN and > 2 times ULN for direct bilirubin), but were similar between treatment groups for the higher thresholds. Analyses of hepatic disorder AEs and SAEs in both Study Einstein-PE and the pooled analysis of Studies Einstein-PE and Einstein-DVT showed lower incidence rates in the rivaroxaban treatment group than in the enoxaparin/VKA treatment group.

Analyses of cardiovascular events and cardiovascular deaths showed that while overall incidence of on-treatment cardiovascular events was similar between treatment groups, the incidence of on-treatment cardiovascular deaths, off-treatment cardiovascular events and off-treatment cardiovascular deaths were higher in the rivaroxaban group compared to the enoxaparin/VKA group. However, the event rates were low, making interpretation difficult.

First round benefit-risk assessment

The benefit of rivaroxaban in the proposed usage is:

- Potential treatment of PE and prevention of recurrent DVT and PE

According to a report by the Australia and New Zealand Working Party on the Management and Prevention of Venous Thromboembolism (2008), an estimated 15000 to 23000 Australians experienced VTE in 2008.[3] Retrospective studies report mortality rates following VTE of 5–23%.[4] Worldwide, PE is the third most common cause of death from cardiovascular disease after heart attack and stroke.[5]

Standard treatment for acute DVT or PE usually involves initial use of parenteral anticoagulants such as LMWH (such as enoxaparin), unfractionated heparin or fondaparinux. Per oral administration of VKA such as warfarin is then started in overlap with the parenteral anticoagulants. As VKAs can interact with various other drugs and food, treatment with VKAs requires ongoing coagulation laboratory monitoring and dose adjustments to keep the INR in the optimal therapeutic window of 2.0–3.0. The sponsor had stated that rivaroxaban was developed as an alternative anticoagulant to the parenteral anticoagulant/VKA treatment regimen. As it is an oral, direct-acting antithrombotic agent with a predictable dose-response relationship, it can be administered without the need for laboratory monitoring of its anti-coagulant effect and subsequent dose-adjustments. As the currently approved PI for rivaroxaban does not make any reference to a need for anticoagulation laboratory monitoring with the use of rivaroxaban, and as this submission does not include any data on this benefit of rivaroxaban over current treatment regimen, this evaluation will only comment on the efficacy claim of rivaroxaban for the treatment of PE and prevention of recurrent DVT and PE without reference to the benefit of rivaroxaban in not requiring anticoagulation laboratory monitoring.

The study design of the submitted pivotal study, Study Einstein-PE, was good. The design elements, including efficacy endpoints, were consistent with the TGA-adopted *Note for guidance on clinical investigation of medicinal products for the treatment of venous thromboembolic disease* (CPMP/EWP/563/98, December 1999). This TGA-adopted EMA guideline recommends that VTE Phase III trials should primarily address clinical outcome in the form of recurrent, symptomatic VTE (non-fatal DVT and/or non-fatal PE), deaths

[3] Access Economics, The burden of venous thromboembolism in Australia: Report for the Australian and New Zealand Working Party on the Management and Prevention of Venous Thromboembolism. 2008
[4] Goldhaber SZ, Pulmonary embolism. *Lancet* 2004:363:1295–305.
[5] Goldhaber SZ, Bounameaux H, Pulmonary embolism and deep vein thrombosis. *Lancet* 2012:379:1835-1846.

and bleeding episodes. The study primary efficacy endpoint was the composite endpoint of recurrent DVT/PE or deaths from PE. The main secondary endpoint evaluated the composite outcome of recurrent DVT/PE or all-cause deaths. The secondary endpoint labelled 'net clinical benefit 1' evaluated the composite outcome of recurrent DVT/PE, deaths from PE, or major bleeding events. The secondary endpoint labelled 'net clinical benefit 2' evaluated the composite outcome of recurrent DVT/PE, deaths from PE, major bleeding events, or cardiovascular events/deaths.

Overall, the efficacy results in the pivotal study showed non-inferiority of rivaroxaban compared with enoxaparin/VKA, a currently accepted standard treatment regimen for PE, across all these primary and secondary efficacy outcomes. In addition, the incidence rates of the individual components of recurrent PE, recurrent DVT and all-cause deaths were comparable between treatment groups and the incidence rate of major bleeding event was lower in the rivaroxaban group compared to the enoxaparin/VKA group. The efficacy results in Study Einstein-PE were supported by similar efficacy results in the pooled analysis of Studies Einstein-PE and Einstein-DVT.

First round assessment of risks

The main risks of rivaroxaban in the proposed usage are:

- Bleeding
- Hepatic laboratory abnormalities

The potential risks of rivaroxaban listed above were all known adverse effects of rivaroxaban. The safety results of the pivotal study were consistent with the known adverse effects of rivaroxaban stated in the currently-approved Australian PI.

The most commonly occurring treatment-related TEAEs in the rivaroxaban group were bleeding-related AEs of epistaxis, haemoptysis and menorrhagia. These are known adverse effects of rivaroxaban stated in the currently-approved Australian PI for rivaroxaban and are consistent with the known pharmacodynamic of rivaroxaban.

When compared to enoxaparin/VKA, a currently accepted standard treatment regimen for PE, the incidence rate of major bleeding events was lower in subjects on rivaroxaban group with clinically relevant non-major bleeding events comparable between treatment groups. Taking both major and clinically relevant non-major bleeding events together as a composite endpoint, the overall incidence was lower in subjects on rivaroxaban. In addition, the majority of major bleeding events in the rivaroxaban group were in the category of non-fatal non-critical organ bleeding events. Analyses of bleeding events in rollover subjects to Study Einstein Extension showed no evidence that the incidence of these bleeding events increased with duration of treatment. Analyses on the incidence of multiple bleeding events showed that the majority of subjects with bleeding events had a single bleeding event instead of multiple bleeding events and that the incidence rate of multiple bleeding events was comparable with that in the enoxaparin/VKA group.

Subgroup analyses for major bleeding events in both Study Einstein-PE and the pooled analysis of Studies Einstein-PE and Einstein-DVT suggested that there was a statistically significant difference between the younger and the older age groups. Subjects on rivaroxaban had a lower risk of major bleeding events compared to those on enoxaparin/VKA across the age groups.

Analyses of hepatic laboratory test results and of hepatic disorder AEs and SAEs in the Study Einstein-PE and the pooled analysis of Studies Einstein-PE and Einstein-DVT yielded results consistent with the known adverse effect of rivaroxaban in causing hepatic laboratory test abnormalities and did not raise additional significant concerns on the risk of hepatic injury with rivaroxaban use.

First round assessment of benefit-risk balance

The benefit-risk balance of rivaroxaban, given the proposed usage, is favourable.

The efficacy results in the pivotal study showed non-inferiority of rivaroxaban compared with enoxaparin/VKA across all efficacy endpoints which included the composite endpoint of recurrent VTE or deaths from PE, composite endpoint of recurrent VTE or all-cause deaths, composite endpoint of recurrent VTE, deaths from PE, or major bleeding events, and composite endpoint of recurrent VTE, deaths from PE, major bleeding events, or cardiovascular events/deaths. In addition, the incidence rates of the individual components of recurrent PE, recurrent DVT and all-cause deaths were comparable between rivaroxaban and enoxaparin/VKA.

The potential risks of rivaroxaban elicited in Study Einstein-PE were bleeding and hepatic laboratory test abnormalities, which are all known adverse effects of rivaroxaban. When compared to enoxaparin/VKA, the incidence rate of major bleeding events was lower in subjects on rivaroxaban group and that of clinically relevant non-major bleeding events was comparable between patients treated with rivaroxaban or enoxaparin/VKA. When both major and clinically relevant non-major bleeding events were taken together as a composite endpoint, the overall incidence was lower in subjects on rivaroxaban than in subjects treated with enoxaparin/VKA. Routine laboratory assessment of liver abnormalities indicated no evidence suggesting potential liver injury by rivaroxaban.

The benefit-risk balance in the younger or older age groups in subgroup analyses in Study Einstein-PE were difficult to interpret due to low event rates/sample sizes in some subgroups but no interaction test p-value for any subgroup analyses on the primary efficacy endpoint of symptomatic recurrent VTE was statistically significant. Subgroup analyses on the safety endpoint of major bleeding events showed that there was a statistically significant difference between younger and older subjects (with the risk being lower in older subjects). Nevertheless, there was a lower risk of major bleeding events in younger subjects on rivaroxaban compared to those on enoxaparin/VKA.

First round recommendation regarding authorisation

It is recommended that the application for extension of indication of rivaroxaban for treatment of pulmonary embolism be approved subject to a satisfactory response to the clinical questions (see *List of Questions and Second round evaluation of clinical data submitted in response to questions*, below).

List of questions and second round evaluation of clinical data submitted in response to questions

The clinical evaluator's questions to the sponsor following the first round assessment phase and the evaluator's assessment of the sponsor responses to these appear below.

Overall, the sponsor adequately addressed all the questions posed in the first round of evaluation.

Pharmacokinetics Question 1

Please provide comments on the results of Study 15921 which appear to differ from the currently approved PI regarding the effect of food on rivaroxaban.

The response by the sponsor adequately clarified the reason for the recommendation in the proposed PI that the 15 mg dose be taken with food.

Overall, the rationale provided by the sponsor for the recommendation in the proposed PI that the 15 mg dose be taken with food is reasonable. The pooled analyses suggested a possible food effect on rivaroxaban 15 mg. In the absence of any confirmatory food effect study for rivaroxaban 15 mg, it is reasonable to recommend that 15 mg dose be taken with food.

(See Attachment 2 of this AusPAR for full details of the rationale for this question and the assessment of the response.)

Pharmacokinetics Question 2

Please provide justification for the conclusion for Study 13238 that "a comparable exposure was observed in subjects with CYP induction receiving an adapted dosing regimen and subjects without CYP induction receiving the usual 15 mg b.i.d. / 20 mg o.d. dosing regimen".

This question was raised because the PK results of this study showed that the median rivaroxaban $AUC_{0\text{-}24\ h,\ ss}$ and median Cmax, ss were both lower in this study compared to those of the pooled study results from subjects of the Phase II studies (who were not on strong CYP3A4 inducers and treated with the usual15 mg b.i.d./20 mg o.d. dosing regimen), as well as those predicted by the simulations in study 15539.

The sponsor provided an acceptable response to this question, which included reference to demographic differences between the study populations which had to be taken into account.

(See Attachment 2 of this AusPAR for full details of the rationale for this question and the assessment of the response.)

Efficacy Question 1

Please provide details on the protocol violations in Study Einstein-PE.

Rationale for question: The sponsor stated in the CSR of Einstein-PE that, among all randomised subjects, 12 subjects (0.5%; 12/2420) and 5 subjects (0.2%; 5/2413) in the rivaroxaban group and the enoxaparin/VKA group, respectively, had protocol violations. No further details were given on the nature of the protocol violations, although a listing of all protocol deviations, and protocol deviations that were reasons for exclusions from analysis sets were provided.

The sponsor provided the requested details on the nature of the protocol violations for these subjects. The additional data provided did not raise any concerns impacting the recommendation for this submission.

The additional data for the 12 subjects in the rivaroxaban group indicated that 7 of these subjects did not have confirmed acute symptomatic PE with or without symptomatic DVT, 3 subjects had concomitant use of strong CYP3A4 inhibitors or strong CYP3A4 inducers, 1 subject had other indication for VKA than DVT and/or PE, and 1 subject whose pre-randomisation local laboratory haematology results were not received prior to randomisation. Out of the 5 subjects in the enoxaparin/VKA group 3 subjects did not have confirmed acute symptomatic PE with or without symptomatic DVT, 1 subject was treated with anticoagulant therapy other than specified in the protocol, and 1 subject had creatinine clearance (CrCl) less than 30 mL/min.

Efficacy Question 2

Please provide a timeline as to the availability of finalised results for Studies PH36705, PH36718, PH36706, PH36711, PH36707, PH36708, PH36709, PH36710 and PH36686.

The evaluator later clarified to the sponsor that the question was raised because in each of the 9 studies the sponsor had stated that they were "technical reports" and that "After medical review of the data, results and conclusions will be described under separate cover". The question was therefore seeking for the timeline when these "separate cover" reports describing the results and conclusions would be available.

In the response, the sponsor satisfactorily clarified that these study reports were "technical reports" as they were exploratory and the results were intended to generally support, "for exploratory and supplementary purposes", the conclusions presented in the summary documents in Module 2 of the submission. Hence, no individual conclusions were presented for the individual study reports. This was the intended meaning of the generic statement of "After medical review of the data, results and conclusions will be described under separate cover".

The summary documents in Module 2 of the submission, which included these 9 study reports, had been reviewed in the first round clinical evaluation and did not raise any concerns impacting the recommendation for this submission.

Second round benefit-risk assessment

Second round assessment of benefits

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

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of rivaroxaban in the proposed usage are unchanged from those identified in the *First round assessment of risks*.

Second round assessment of benefit-risk balance

The benefit-risk balance of rivaroxaban, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

It is recommended that the application for extension of indication of rivaroxaban for treatment of pulmonary embolism be approved.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP, version: 1.0, dated 29 May 2012) which was reviewed by the TGA's Office of Product Review (OPR). This is summarised in Table 4.

Table 4. Summary of the Risk Management Plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Important identified risks		
Haemorrhage	Routine pharmacovigilance activities Additional information from clinical trials	Contraindication in CCDS section 4.3 "*Contraindication*" Warning in CCDS section 4.4 "*Special warnings and precautions for use*" Warning in CCDS section 4.5 "*Interaction with other medicinal products and other forms of interactions*" Haemorrhage is listed in CCDS section 4.8 "*Undesirable effect*"
Important potential risks		
Embryo-fetal toxicity	Routine pharmacovigilance activities	CCDS section 4.3 "*Contraindication*" CCDS section 4.6 "*Pregnancy and lactation*"
Important missing information		
Patients undergoing major orthopaedic surgery other than elective hip or knee replacement surgery	Routine pharmacovigilance activities	CCDS (10 mg) section 4.4. "*Special warnings and precautions for use*"
Patients with severe renal impairment (CrCl < 30 mL/min	Routine pharmacovigilance activities	CCDS section 4.2.7 SPAF (4.2.14 DVT-T, 4.2.11 for VTE-P +ACS) "*Additional information on special population*" and section 4.4. "*Special warnings and precaution for use*"
Remedial procoagulant therapy for excessive haemorrhage	Routine pharmacovigilance activities Additional information from clinical trials	CCDS section 4.9 "*Overdose*"
Patients receiving systemic treatment with Cyp3A4 and P-gp inhibitors other than azole antimycotics (e.g. ketokonazole) and HOV-protease inhibitors (e.g. ritonavir)	Routine pharmacovigilance activities	CCDS section 4.4 "*Special warnings and precaution for use*" and 4.5 "*Interaction with other medicinal products and other forms of interaction*"
Pregnant or breast-feeding women	Routine pharmacovigilance activities	CCDS section 4.3 "*Contraindication*" CCDS section 4.6 "*Pregnancy and lactation*"
Patients with AF and prosthetic valve	Routine pharmacovigilance activities	CCDS (15/20 mg) section 4.4 "Special warnings and precaution for use" (Patients with prosthetic valves)

CCDS: Company Core Data Sheet

Safety specification

Subject to the evaluation of the clinical aspects of the safety specifications (SS) by the TGA Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows (Table 5):

Table 5. Summary of the Ongoing Safety Concerns

Important identified risks	• Haemorrhage
Important potential risks	• Embryo-fetal toxicity
Important missing information	• Patients undergoing major orthopaedic surgery other than elective hip or knee replacement surgery • Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic inhibitors of CYP3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Remedial pro-coagulant therapy for excessive haemorrhage • Pregnant or breast-feeding women • Patients with AF and a prosthetic heart valve

Pharmacovigilance plan

The sponsor stated that routine pharmacovigilance activities, consistent with the activities outlined in *3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03),* are proposed to monitor all the specified ongoing safety concerns, including the use of SAE questionnaires for the important identified risk: 'Haemorrhage' and the important missing information: 'Patients with severe renal impairment (CrCl < 30 mL/min)' and 'Patients receiving concomitant systemic inhibitors of CYP3A4 or P-gp other than azole antimycotics (for example, ketoconazole) and human immunodeficiency virus (HIV)-protease inhibitors (for example, ritonavir)'. Copies of the proposed specific questionnaires are listed in Annex 2 of the Australian (AU)-RMP, but this annex does not appear to have been provided.

Risk minimisation activities

The sponsor has concluded that, at the present routine, risk minimisation activities are sufficient for all the specified ongoing safety concerns. However, the sponsor has proposed additional risk minimisation activities to minimise medication error.

Routine risk minimisation activities will comprise labelling, including indications, contraindications, special warning and precaution statements, instructions for use, overdose statements, notification of interactions and/or notification of undesirable effects for all the specified ongoing safety concerns.

The sponsor states: *"At present no additional risk minimisation measures are planned for important identified or potential risks."*

Advisory committee considerations

At the 14th meeting of Australian Committee on the Safety Of Medicines (ACSOM), the committee considered whether the printed materials associated with the Xarelto education program and the Product Familiarisation Program (PFP) for the existing indications, which aimed to highlight the important identified risk: 'Haemorrhage' and to minimise medication error, were adequate in addressing these issues.

In summary, ACSOM advised that the printed materials provided were not adequate. The committee expressed concern that the PFP documents were overly promotional and not

presented clearly or logically. In particular, the statement that monitoring was unnecessary was considered misleading and the emotive aspects such as smiling faces were not considered appropriate. The materials were not of the same standard as the PI and Consumer Medicines Information (CMI), and there was not enough emphasis on education and safety.

Consequently all printed materials associated with the Xarelto education program and the PFP must be revised in the light of this advice and provided to the TGA for review before this application can be approved, given that such activity is the subject of specific conditions of registration for these products.

Summary of recommendations and assessment of sponsor responses

This section describes the recommendations issued by the OPR and the assessment of the sponsor's responses to these recommendations:

The OPR provides these recommendations in the context that the submitted AU-RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the draft PI and CMI documents should not be revised until the Delegates Overview has been received:

1. Safety considerations may be raised by the nonclinical and clinical evaluators. It is important to ensure that the information provided in response to these will include a consideration of the relevance for the AU-RMP, and any specific information needed to address this issue in the AU-RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the AU-RMP.

   The sponsor has stated that no safety considerations have been raised by the nonclinical and clinical evaluators as a result of assessment. This is acceptable.

2. In comparison to the RMP documents previously reviewed for these products, the important potential risk: 'Embryo-foetal toxicity' has now been added based on pre-clinical data. This is acceptable. However, the important potential risk: 'Increases in liver enzymes, including bilirubin' has now been excluded without any apparent explanation. The sponsor should provide compelling justification as to why this ongoing safety concern was excluded.

   The sponsor has provided justification and concluded that deletion of the important potential risk: 'Increases in liver enzymes, including bilirubin' is supported by the data. The clinical evaluator agreed with this and therefore it is acceptable.

3. The sponsor's correspondence, dated 7 August 2012, reports that the current EU-RMP is Version: 7.2. In comparison the proposed AU-RMP includes the same ongoing safety concerns, except for the important missing information: 'Long term therapy with rivaroxaban in VTE treatment and SPAF[6] under real-life conditions'. The sponsor should provide compelling justification as to why this ongoing safety concern is not included in the AU-RMP.

   The sponsor agreed that the important missing information: 'Long term therapy with rivaroxaban in VTE treatment and SPAF under real-life conditions' is relevant to Australia and therefore will adopt the EU-RMP Version: 7.2 and an Australia Specific Annex (ASA) Version 1. This is acceptable.

4. Notwithstanding the evaluation of the non-clinical and clinical aspects of the SS, it is recommended that the sponsor include the important missing information: 'Paediatric population' as an ongoing safety concern when the AU-RMP is next

[6] SPAF: stroke prevention in atrial fibrillation.

updated. The AU-RMP states there are no data available to support appropriate dosing, safety or efficacy in this population (subjects aged < 18 years) but recognises that prescribers may make use of rivaroxaban in a paediatric population, either in a population undergoing major orthopaedic surgery, in those receiving conservative treatment of fractures by plaster cast, in those being treated for acute thrombosis, or in those with atrial fibrillation (AF).

The sponsor agreed that the important missing information: 'Paediatric population' should be included as an ongoing safety concern and this has been captured in the ASA Version 1. This is acceptable.

5. The sponsor should provide Annex 2 of the AU-RMP, which contain copies of the proposed specific questionnaires regarding the proposed pharmacovigilance activities.

   The sponsor has provided copies of the questionnaires to monitor the important identified risk: 'Haemorrhage' as attachments to the EU-RMP Version: 7.2 under Annex 6.1 and Annex 6.2. This is acceptable.

6. In comparison to the RMP documents previously reviewed for these products and the current EU-RMP (Version: 7.2), additional pharmacovigilance activities have now been excluded without any apparent explanation. The sponsor should provide compelling justification as to why these additional pharmacovigilance activities have now been excluded.

   With the adoption of the EU-RMP Version: 7.2 and an ASA Version 1, additional pharmacovigilance activities to be conducted in Europe will now be captured. This is acceptable.

7. The current EU-RMP (Version: 7.2) also includes other additional pharmacovigilance activities. The sponsor should provide compelling justification as to why these additional pharmacovigilance activities have not been included in the AU-RMP. Alternatively the sponsor should provide all relevant information in the AU-RMP, including at least a draft study protocol, for any post-marketing safety study agreed to be conducted in the EU.

   With the adoption of the EU-RMP Version: 7.2 and an ASA Version 1, additional pharmacovigilance activities to be conducted in Europe will now be captured. This is acceptable.

8. The sponsor's conclusion that at present routine risk minimisation activities are sufficient for all the specified ongoing safety concerns does not appear to be consistent with the current EU-RMP (Version: 7.2), which the sponsor reports as stating:

   – "Routine Risk Minimization Activities sufficient except for haemorrhage".
   – "Patient alert card is introduced as an additional risk minimisation activity for haemorrhage to reinforce patient counselling about the important safety information during treatment with rivaroxaban."
   – "Prescriber guide is introduced to increase awareness about the risk of bleeding during treatment with rivaroxaban and to provide guidance on how to manage that risk."

   In addition the AU-RMP states: "The Prescriber Guide gives prescribing physicians an overview of Xarelto (rivaroxaban) in a booklet for future reference including dosing recommendations, identifying patients at an increased risk of bleeding and management of bleeding." and "All the above measures (proposed additional risk minimisation activities) have been put in place to minimise medication errors and the

key messages from these activities will ensure appropriate patient selection, compliance and management of bleeding."

Notwithstanding the evaluation of the non-clinical and clinical aspects of the SS, it is recommended the sponsor should conclude that at present routine risk minimisation activities are sufficient for all the specified ongoing safety concerns, except for the important identified risk: 'Haemorrhage' and amend the relevant sections of the AU-RMP accordingly.

The sponsor agreed that at present routine risk minimisation activities are sufficient for all the specified ongoing safety concerns, except for the important identified risk: 'Haemorrhage' for which additional risk minimisation activities are proposed. With the adoption of the EU-RMP Version: 7.2 and an ASA Version 1, these additional risk minimisation activities will now be captured. This is acceptable.

9. Section 3.1: 'Summary table of planned actions' and Section 5: 'Summary of the risk management plan' of the AU-RMP should refer to details of routine risk minimisation in the Australian PI, not the Company Core Data Sheet (CCDS).

   In response the sponsor has now attached the approved and proposed Australian PI to the ASA. This is not entirely satisfactory and it is reiterated that a short description, including the location within the Australian PI, of routine risk minimisation for all of the specified ongoing safety concerns should be provided in the ASA when it is next updated.

10. The sponsor should provide for review copies of the printed materials associated with each element of the proposed additional risk minimisation activities and be included as an annex to the AU-RMP. If such printed materials are not yet available, the sponsor should indicate when it is anticipated they will become available and provide an assurance that they will be provided to the TGA for review once they become available.

    The sponsor has provided copies of the printed materials (Doctor PFP Guides and Patient Alert Cards) associated with the Xarelto education program and the PFP for the existing indications as Appendices 5-8 of the ASA. This is acceptable, although as previously noted these materials, including Patient Guides and Enrolment Packs, will require extensive revision in the light of ACSOM advice as to the suitability of these materials to highlight the important identified risk: 'Haemorrhage' and to minimise medication error (see *Advisory Committee Considerations*, above).

11. It is apparent that the results reported in the first edition of 3 monthly report on prescriber education program and PFP for Xarelto are purely qualitative and subjective. The sponsor's correspondence, dated 14 December 2011, provided an assurance that a post-market periodic schedule for the prescriber and patient survey testing would be proposed and implemented for as long as these additional risk minimisation activities were considered necessary. No such survey testing program appears to have been proposed or implemented, and it appears this assurance was not honoured. Furthermore the sponsor's correspondence, dated 28 October 2011, stated that to measure the success of these additional risk minimisation activities, the sponsor proposed to conduct a prescriber, patient and pharmacist survey to test stakeholder understanding of the key aspects in the prescriber guide to aid correct use of Xarelto. The feedback would then be used to refine the prescriber guide and patient information. Consequently the sponsor must honour these assurances and specify the quantitative criteria, suitably justified, to be used to verify the success of the proposed risk minimisation activities.

    The sponsor was reminded of its previous assurances that a post-market periodic schedule for the prescriber and patient survey testing would be proposed and

implemented for as long as additional risk minimisation activities were considered necessary and the feedback would then be used to refine the prescriber guide and patient information. However, the sponsor has now advised that such survey testing will not commence until February 2013, and then 6 and/or 12 months after Pharmaceutical Benefits Scheme (PBS) listing.

This response is considered to be inadequate in the light of previous assurances and the fact that supply of these products has commenced in Australia, presumably since 4 June 2012, via the PFP. The sponsor has reported that as of 28 September 2012 almost 4,000 prescribers and almost 3,000 patients have enrolled in the PFP. Furthermore no quantitative criteria, suitably justified, to be used to verify the success of the proposed additional risk minimisation activities have been specified. Consequently this remains an outstanding recommendation which the sponsor must address in an appropriate and adequate manner before this application is approved, given that such activity is the subject of specific conditions of registration for these products.

12. Section 4: 'Risk Minimisation Plan' of the AU-RMP will need to extensively revised to include additional risk minimisation activities for the important identified risk: 'Haemorrhage' as per the EMA Annex C: Template for EU Risk Management Plan (EU – RMP).

    The sponsor agreed that at present routine risk minimisation activities are sufficient for all the specified ongoing safety concerns, except for the important identified risk: 'Haemorrhage' for which additional risk minimisation activities are proposed. With the adoption of the EU-RMP Version: 7.2 and an ASA Version 1, these additional risk minimisation activities will now be captured. This is acceptable.

Final recommendation to the Delegate

The outstanding issues in relation to the RMP aspects of this application are described at points 9, 10 and 11, above.

If this application is approved the following specific conditions of registration should be applied:

- The EU-RMP identified as Version: 7.2, dated 29 March 2012, and an ASA identified as Version 1, dated September 2012, with revised details of a Risk Minimisation Plan within the ASA as agreed with the TGA, must be implemented.
- Post marketing reports are to be provided in line with the current published list of EU reference dates and frequency of submission of periodic safety update reports (PSURs) until the period covered by such reports is not less than three years from the date of this approval letter. The reports are to meet the requirements in accordance with ICH E2C (R2) guideline on Periodic Benefit-Risk Evaluation Reports and Module VII of the EMA Guideline on Good Pharmacovigilance (GPV) Practices relating to PSURs. Submission of the report must be within the 70 days of the data lock point for PSURs covering intervals up to and including 12 months and within 90 days of the data lock point for PSURs covering intervals in excess of 12 months. The submission may be made up of PSURs each covering six months.

VI. Overall conclusion and risk/benefit assessment

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

In the Overview, the Delegate raised several matters that the sponsor was requested to address in the sponsor's response to the Delegate's Overview. These matters, below, are presented in bolded text.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Rivaroxaban is a selective, direct acting Factor Xa inhibitor. The currently approved indications for rivaroxaban tablets (Xarelto) are:

> *"Xarelto is indicated for*
>
> *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 new indication which will result from approval of this submission will read as follows (the only amendment is to the third dot point):

> *"Xarelto is indicated for*
>
> *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 pulmonary embolism (PE)*** *and for the prevention of recurrent DVT and PE."*

According to the clinical evaluation report (CER), the clinical data in Module 5 consisted of the clinical study report of a Phase III pivotal study, EINSTEIN-PE or Study 11702-PE, related directly to the proposed extension of indications, 12 meta-analysis study reports, 1 technical report as well as several study reports not directly related to the proposed extension of indication (one biopharmaceutics food study, Study 15921, which evaluated the effect of a Japanese diet on the bioavailability of rivaroxaban in healthy Japanese male subjects and 3 population PK/PD studies).

Relevant EU Guidelines (beside general guidelines) are as follows:

- CPMP/EWP/563/98 (pdf,45kb)
  Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Venous Thromboembolic Disease

- CPMP/EWP/2330/99 (pdf,51kb)
  Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study
  Adopted by the TGA with the following notation: "Sponsors are reminded that they should submit all available new safety data that are relevant to the intended treatment population."
- pp. 127 - 132 of Rules 1998 (3C) - 3CC6a (pdf,27kb)
  Clinical Investigation of Medicinal Products for Long-Term Use
  See also: pp. 121 - 125 of Rules 1998 (3C) - 3CC5a (Adopted by TGA with conditions)
- CHMP/EWP/185990/06 (pdf,64kb)
  Guideline on Reporting the results of Population Pharmacokinetic Analysis

Pharmacokinetics

Influence of food: Study 15921 which evaluated the effect of Japanese meal on safety, tolerability and PK of 15 mg rivaroxaban given orally to Japanese healthy male subjects showed that the AUC and Cmax of rivaroxaban after single administration of 15 mg rivaroxaban were similar in the fasted state and the fed state. However, the time to Cmax (tmax) for rivaroxaban administered with the Japanese meal was prolonged by 1.5 h in comparison to tmax in the fasted state (4.0 h compared to 2.5 h). As noted by the clinical evaluator, in the currently approved PI, it states that Xarelto 15 mg and 20 mg tablets should be taken with food, implying that food had been found to have an effect on the bioavailability of Xarelto 15 mg tablets. The clinical evaluator's question regarding this issue and the sponsor's response are discussed later in this overview.

Pharmacokinetic interactions: Although Study 13238 is described in the CER as a population PK/PD study, it was in fact an open-label, cohort study. Study 13238 (Study Einstein-CYP) was conducted to characterise the population PK/PD of an adapted (higher) rivaroxaban dosing regimen (rivaroxaban 30 mg b.i.d. for 3 weeks followed by 20 mg b.i.d.) in subjects with acute proximal DVT or acute PE and with concomitant use of a strong CYP3A4 inducer. This is compared to the usual dose regimen of 15 mg b.i.d. for 3 weeks followed by 20 mg o.d. for subjects without concomitant use of a strong CYP3A4 inducer. This Einstein-CYP Study was integrated into the framework of the Einstein-DVT and Einstein-PE Studies, with the subjects recruited in the same centres and with similar study design and eligibility criteria except for the concomitant use of strong CYP3A4 inducers (concomitant use of strong CYP3A4 inducers was expected to decrease rivaroxaban plasma concentrations, and was an exclusion criterion in the Einstein-DVT and Einstein-PE Studies). The total duration of study treatment was 3 months.

Results showed that during initial treatment (30 mg b.i.d.), the median rivaroxaban $AUC_{0\text{-}24\ h,\ ss}$ in this study was approximately 36% lower than that of the pooled study results from subjects of the Phase II studies treated with the usual 15 mg b.i.d. / 20 mg o.d. dosing regimen. During extended treatment (20 mg b.i.d.), the median rivaroxaban $AUC_{0\text{-}24\ h,\ ss}$ in this study was approximately 15% lower than that of the pooled results from the Phase II studies. The median Cmax, ss was also lower in this study (approximately 27% and 35% lower during initial and extended treatments, respectively). Although 50 subjects were planned for enrolment in Study 13238 (Einstein-CYP), only 25 subjects were actually enrolled due to difficulties in recruiting subjects and all were enrolled at 3 study centres in South Africa. Of these 25 patients, only 14 completed the study. The majority of patients were Black (92.0%), HIV-positive (56.0%) and with a medical history of tuberculosis (TB, 80.0%) which would limit the ability to extrapolate the results from these patients. The results of Study 13238 (Einstein-CYP) suggested that a dosing regimen of rivaroxaban 30 mg b.i.d. for 3 weeks followed by 20 mg b.i.d. for a total of 3 months of treatment in a study population on strong CYP3A4 inducers did not lead to a drug exposure profile significantly in excess of that seen in a study population on the usual

15 mg b.i.d. / 20 mg o.d. dosing regimen and not on strong CYP 3A4 inducers. Given the limitations of Study 13238, the higher dose regimen is a dosing regimen that could be further explored in other studies.

Other PK data: In the dossier there were 2 other population PK/PD studies, the first, Study 13812 whose primary objective was to define the structural PK and PK/PD models for rivaroxaban in Study 13238 (Einstein-CYP); and the second, Study 15539 in which simulations were carried out to describe the exposure of various modified dosing regimens in patients with severe renal impairment, in those on concomitant medications which are strong inhibitors of both CYP3A4 and P-gp and in those on concomitant medications which are strong CYP3A4/P-gp inducers. Both were exploratory in nature. As well there was a study, PH 36685 which was an exploratory pooled analysis of the subjects in 64 Phase I studies. The Delegate had nothing further to comment about these studies except to request that the **sponsor, in the response to this Overview, provide a summary of the principal findings of these exploratory studies and whether they have triggered any further or confirmatory studies.**

Pharmacodynamics

No new data.

Efficacy

Pivotal efficacy study

Study 11702-PE (Einstein-PE): In the context of the treatment and prevention of DVT and PE there were a total of 3 studies: Einstein-DVT, Einstein-PE and Einstein Extension. The Einstein-DVT Study evaluated subjects with confirmed acute proximal symptomatic DVT without symptomatic PE, while the Einstein-PE Study evaluated subjects with confirmed acute symptomatic PE with or without symptomatic DVT. Both Einstein-DVT and Einstein-PE Studies were integrated into a single study protocol, as the subject groups were complementary and were recruited at the same centres, the essential study design features were identical, and both evaluations were supervised and guided by the same study committees. Due to differences in recruitment rates for the target populations, the Einstein-DVT Study was completed earlier than the Einstein-PE Study, and was used in a previous submission for the new indication of rivaroxaban 15 mg and 20 mg for the treatment of DVT and for the prevention of recurrent DVT and PE. This submission was approved in April 2012. The current submission presents the Einstein-PE clinical Study results to support the additional indication for treatment of PE.

The primary efficacy objective for the Einstein-PE Study was to evaluate whether rivaroxaban is at least as effective as enoxaparin/VKA (either warfarin or acenocoumarol) in the treatment of subjects with acute symptomatic PE with or without symptomatic DVT, for the prevention of recurrent VTE events. The principal safety objective was the evaluation of major and clinically relevant non-major bleeding events.

Einstein-PE was a multi-centre[7], randomised, open-label, parallel-group, active-controlled, event-driven non-inferiority study with a treatment duration of 3, 6, or 12 months. It ran between March 2007 and December 2011.

Subjects in the study were male or female adults above country-specific legal age limit, who had confirmed acute symptomatic PE with or without symptomatic DVT.

[7] There were 263 centres in 38 countries: Andorra (1), Australia (23), Austria (6), Belgium (12), Brazil (2), Canada (4), China (15), Czech Republic (7), Denmark (1), Estonia (1), Finland (2), France (34), Germany (25), Hong Kong (2), Hungary (10), India (1), Indonesia (1), Ireland (1), Israel (10), Italy (13), Lithuania (2), Latvia (1), Malaysia (1), Netherlands (6), New Zealand (5), Norway (3), Philippines (1), Poland (7), Singapore (1), South Africa (10), South Korea (4), Spain (8), Sweden (5), Switzerland (6), Taiwan (3), Thailand (3), United Kingdom (3), United States (23).

Subjects were randomised to receive either rivaroxaban or enoxaparin/VKA. Subjects allocated to the rivaroxaban group received rivaroxaban per oral 15 mg b.i.d. for 3 weeks followed by rivaroxaban 20 mg o.d. for a total treatment duration of 3, 6, or 12 months. Subjects allocated to the enoxaparin/VKA group received 1 mg/kg enoxaparin b.i.d. subcutaneously for at least 5 days in combination with VKA (warfarin or acenocoumarol; overlap 4-5 days), administered orally at individually titrated doses to achieve a target INR of 2.5 (range:2.0-3.0) for a total treatment duration of 3, 6, or 12 months. The decision to treat a subject for 3, 6, or 12 months was at the investigator's discretion, based on his/her assessment of the period during which anticoagulant treatment was expected to have a potentially favourable risk-benefit ratio.

The primary efficacy outcome was symptomatic recurrent VTE (that is, the composite of recurrent DVT or non-fatal or fatal PE). There were 3 secondary efficacy outcomes assessed in this study as outlined in the CER (Attachment 2).

The statistical analysis plan defined 4 analysis populations. The intent-to-treat (ITT) population consisted of all randomised subjects and were analysed according to the randomised treatment groups. The ITT on treatment population also consisted of all randomised subjects who were analysed according to the randomised treatment groups, but was restricted to subjects who had received at least one dose of study treatment after randomisation. The valid-for-safety analysis population consisted of all randomised subjects who had received at least one dose of study treatment after randomisation, and were analysed according to the treatment they actually received. The per protocol (PP) population consisted of all randomised subjects without any major deviations from the protocol.

This was an event-driven study. The sponsor assumed equal efficacy between treatment groups, and calculated that a total of 88 confirmed symptomatic recurrent VTE events was needed to give a power of 90% to demonstrate that rivaroxaban is non-inferior to the comparator, considering a relative non-inferiority margin for the HR of 2.0 (2-sided α=0.05). The sponsor assumed an overall incidence rate for the primary efficacy outcome of 3% for both treatment groups, and at least 1465 subjects per group were determined to be needed.

A dose confirmation analysis was planned in the first 400 subjects based on the composite endpoint of symptomatic recurrent VTE (that is, primary efficacy outcome) and asymptomatic deterioration at repeat lung imaging at 3 weeks. A later protocol amendment permitted the inclusion of these 400 subjects in the primary analysis rather than having to recruit an additional 400 subjects at the end of the study.

For the primary efficacy analysis, the time to the first event of the composite primary efficacy outcome was analysed using a stratified Cox proportional hazards model with intended treatment duration (3, 6, or 12 months) as stratum and adjusted for the baseline presence of cancer. The rivaroxaban-to-comparator HR was computed with 2-sided 95% CI. Based on this model, rivaroxaban was to be considered non-inferior to the comparator if the upper limit of the CI was less than 2.0 (non-inferiority margin). If non-inferiority for the primary efficacy outcome was demonstrated, superiority for the primary efficacy outcome was to be tested utilising the 2-sided 95% CI interval for the HR. The clinical evaluator judged that the statistical methods were appropriate for a non-inferiority study. The rationale and justification for the inferiority margin of 2.0 was presented by the sponsor in an appendix to the CSR, and were in line with the recommendations of the ICH E 9 *Statistical Principles for Clinical Trials* as well as of the EMA Guidelines on the choice of the non-inferiority margin, which involved identifying the maximally acceptable treatment differential assessed as the difference between the currently recommended and approved standard of care, and placebo or no-treatment. This quantification of the effect of active control relative to placebo was derived from historical studies.

An initial 400 randomised subjects participated in the dose confirmation part of Einstein-PE with 205 and 195 in the rivaroxaban and enoxaparin/VKA groups, respectively. Altogether, 379 subjects had a baseline and a repeat lung scan at 3 weeks. The incidence rate of the combination of symptomatic recurrent VTE and asymptomatic deterioration at repeat lung imaging at 3 weeks was 1.7% (3/177 subjects) in the rivaroxaban group and 0.6% (1/174) in the enoxaparin/VKA group. The upper limit of the 1-sided 95% CI of the absolute difference between observed incidence rates was 3.7%. As this did not exceed the pre-specified value of 8.0%, the Dose Confirmation Committee recommended continuing the study as planned without the need to change the study conditions.

In the overall study, a total of 4843 subjects were screened, and 4833 subjects were randomised: 2420 to rivaroxaban and 2413 to enoxaparin/VKA.

Overall, 5.2% of the randomised subjects had an intended treatment duration of 3 months, 57.4% had an intended treatment duration of 6 months, and 37.4% had an intended treatment duration of 12 months.

The baseline demographic characteristics were comparable between treatment groups in the ITT analysis population and the PP analysis population. In the ITT analysis population, the majority of subjects in each treatment group were male (54.1% [1309/2419] and 51.7% [1247/2413] in the rivaroxaban and enoxaparin/VKA groups, respectively), and White (65.5% [1585/2419] and 65.8% [1587/2413], respectively). The mean (standard deviation [SD]) age was 57.9 (17.3) and 57.5 (17.2) years in the rivaroxaban group and the enoxaparin/VKA group, respectively. The age range was 18 to 97 years in each of the treatment groups. In the ITT analysis population, 39.6% and 38.7% of subjects in the rivaroxaban and enoxaparin/VKA groups, respectively, were aged ³ 65 years, and 18.2% and 16.7% of subjects, respectively, were aged > 75 years.

The baseline disease characteristics were also comparable between treatment groups in the ITT and PP analysis populations. The baseline risk factors for thromboembolism were comparable between treatment groups, and the most commonly reported risk factor was idiopathic DVT/PE (ITT dataset: 49.4% [1196/2419] and 49.2% [1186/2413] in the rivaroxaban and enoxaparin/VKA groups, respectively; PP dataset: 49.4% [1099/2224] and 49.3% [1103/2238], respectively).

In the ITT population, the percentage of subjects with events for the primary efficacy outcome until the end of intended treatment duration was 2.1% (50/2419) in the rivaroxaban group and 1.8% (44/2413) in the enoxaparin/VKA group. These results are shown in Table 6 below. In the Cox's proportional hazard model, the comparison of rivaroxaban with enoxaparin/VKA treatment yielded a HR of 1.123 (95% CI of 0.749-1.684). The upper limit of the CI was below the pre-defined non-inferiority margin of 2.0, showing non-inferiority of rivaroxaban over enoxaparin/VKA for the primary efficacy outcome. The test for superiority of rivaroxaban versus enoxaparin/VKA was not statistically significant ($p_{superiority} = 0.5737$). The Kaplan-Meier cumulative incidence rate plot in the ITT population (Figure 2) shows quite close overlap of the two curves, particularly up to day 180 when there were still reasonable numbers of subjects being followed. Analyses of the primary efficacy endpoint in the ITT on treatment population and the PP population yielded similar results (see Table 6).

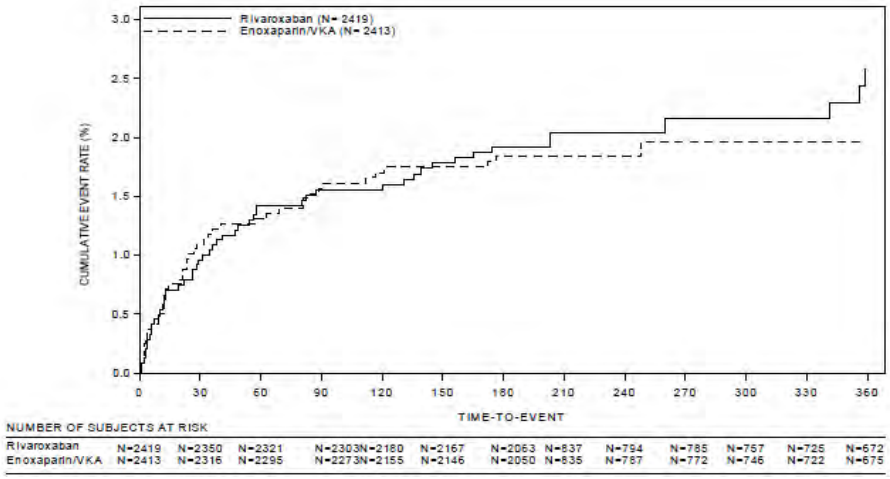
Table 6. Summary of results for primary efficacy outcome, Study Einstein-PE

Population	ITT	ITT on treatment	PP (on treatment)
Incidence rate of primary efficacy outcome			
Rivaroxaban group	50 / 2419 (2.1%)	44 / 2412 (1.8%)	38 / 2224 (1.7%)
Enoxaparin / VKA group	44 / 2413 (1.8%)	39 / 2405 (1.6%)	36 / 2238 (1.6%)
Cox proportional hazard model for rivaroxaban versus enoxaparin / VKA			
Hazard ratio	1.123	1.115	1.045
Confidence interval	0.749 - 1.684	0.725 - 1.717	0.662 - 1.648
p-value for non-inferiority	0.0026	0.0040	0.0026
p-value for superiority	0.5737	0.6194	0.8504

Note: p-value and hazard ratio estimates based on stratified proportional hazards model, with stratification based on intended treatment duration, using events after randomization up to the end of intended treatment (ITT population) or events after the first dose of study treatment up to the last dose of study treatment plus 2 days within the intended treatment duration (ITT on treatment and PP populations). The asymptotic 1-sided p-value for non-inferiority was calculated based on the log-hazard ratio estimated for rivaroxaban versus comparator, on its standard error and on the logarithm of the non-inferiority margin of 2.0.

ITT = intent to treat; PP = per protocol; VKA = vitamin K antagonist

Figure 2. Kaplan-Meier cumulative incidence rate of primary efficacy outcome until the intended end of study treatment (time point: event or censoring up to the intended treatment duration) (ITT population), Study Einstein-PE



Analyses of the individual components of the primary efficacy outcome yielded incidence rates which were comparable between treatment groups.

The main secondary efficacy outcome was a composite of recurrent DVT, non-fatal PE and all-cause mortality. The incidence rates of this main secondary efficacy outcome until the end of intended treatment duration were 4.0% (97/2419) in the rivaroxaban group and 3.4% (82/2413) in the enoxaparin/VKA group. In the Cox's proportional hazard model, the comparison of rivaroxaban with enoxaparin/VKA treatment yielded a HR of 1.156 (95% CI of 0.862-1.552). The upper limit of the CI was below the pre-defined non-inferiority margin of 2.0, showing non-inferiority of rivaroxaban over enoxaparin/VKA for the main secondary efficacy outcome. The test for superiority of rivaroxaban versus enoxaparin/VKA was not statistically significant ($p_{superiority}$ = 0.3333). The one imbalance that does strike the eye under the secondary efficacy outcome concerns the differential rates of cardiovascular death, viz. 10/2419 (0.4%) for the rivaroxaban group versus 3/2413 (0.1%) in the enoxaparin/VKA group. **Admittedly the numbers are small but the sponsor should comment on this observed difference.**

The secondary efficacy outcome of 'net clinical benefit 1' was the composite of the primary efficacy outcome and major bleeding events. The secondary efficacy outcome of 'net clinical benefit 2' was the composite of the primary efficacy outcome, major bleeding events, and cardiovascular events/deaths (cardiovascular deaths, myocardial infarctions, strokes, and non-CNS systemic embolisms). For both net clinical benefits 1 and 2, the

incidence rates were comparable in the rivaroxaban and enoxaparin/VKA groups, respectively. The trend to a more favourable result for net clinical benefit 1 for rivaroxaban appears to be driven by the lower rate of major bleeding [33/2419, 1.4% for rivaroxaban versus 57/2413, 2.4% for enoxaparin/VKA]. The trend to a more favourable result for net clinical benefit 2 for rivaroxaban appears once again to be driven by the lower rate of major bleeding and also by the lower rate of non-ST segment elevation myocardial infarction (NSTEMI, 2/2419, <0.1% for rivaroxaban versus 11/2413, 0.5% for enoxaparin/VKA). Interestingly there was a higher rate of STEMI in the rivaroxaban group although the numbers were very small [5/2419, 0.2% for rivaroxaban versus 2/2413, <0.1% for enoxaparin/VKA].

Sub-group analyses of the primary efficacy endpoint by baseline and demographic factors did not reveal any significant interactions.

Sub-group analyses of the secondary endpoint of net clinical benefit 1 by baseline and demographic factors did reveal some results worthy of comment, For the age group of subjects < 60 years, the comparative rates of this endpoint were 36/1204 or 3.0% in the rivaroxaban group versus 27/1211 or 2.2% in the enoxaparin/VKA group while for the subjects ≥ 60 years, the comparative rates were 47/1215 or 3.9% in the rivaroxaban group versus 69/1202 or 5.7% in the enoxaparin/VKA group. The test of interaction was statistically significant [p-value = 0.024]. The 95% CI for the HR for the older age group was located entirely below unity whereas that for the younger age group spanned unity. There may be a slight advantage to the use of rivaroxaban in the older age group although it should be noted that both 95% CIs did overlap each other. A similar situation obtained when one compared the rate of net clinical benefit 1 in the group of subjects aged > 75 years with the corresponding rates in younger age groups. In fact for the group aged > 75 years, the comparative rates of net clinical benefit 1 were 19/441 or 4.3% in the rivaroxaban group versus 37/402 or 9.2% in the enoxaparin/VKA group. This resulted in a HR of 0.437 with a 95% CI of [0.251, 0.760]. Again a similar result was obtained when one compared incidence rates in so-called fragile subjects with those in non-fragile subjects. There appeared to be a distinct advantage to the use of rivaroxaban in the fragile subjects. The Delegate considered the possibility that these 3 sets of results are driven by a common underlying factor such as lower relative bleeding rates on rivaroxaban compared with being on enoxaparin/VKA for the more elderly and the more fragile. **The sponsor was asked to comment on this issue;** the Delegate also proposed to seek comment on this issue from the Advisory Committee on Prescription Medicines (ACPM) particularly in the light of what the sponsor may have to say in the response to the Overview. **The sponsor was also asked to comment on the apparently better performance of rivaroxaban versus enoxaparin/VKA for those with moderate impairment of renal function (CrCl between 50 and 80 mL/min) compared with those with normal renal function (and also with those with severe impairment of renal function) and also on the apparently better performance of rivaroxaban versus enoxaparin/VKA for those with cardiac disease compared with those with no cardiac disease.**

The Delegate was not able to find any comment on sub-group analyses of net clinical benefit 2 in the CER. Were any such analyses carried out? **If so, the sponsor was asked to provide a brief report of the most important results.**

Analyses performed across trials (pooled analyses and/or meta-analyses)

Study PH36746

This pooled analysis of the Studies Einstein-DVT and Einstein-PE followed the statistical analysis plan and approach previously described for Einstein-PE except for a more conservative non-inferiority margin of 1.75 (as opposed to 2.0).

In the pooled studies, there were a total of 8282 randomised subjects: 4151 in the rivaroxaban group and 4131 in the enoxaparin/VKA group.

The baseline demographic characteristics were comparable between the pooled treatment groups in the ITT analysis population and the PP analysis population.

The primary efficacy outcome was the same in both Studies Einstein-DVT and Einstein-PE (that is, symptomatic recurrent VTE). In the pooled ITT population, the percentage of subjects with events for the primary efficacy outcome until the end of intended treatment duration was 2.1% (86/4150) in the rivaroxaban group and 2.3% (95/4131) in the enoxaparin/VKA group. The Cox's proportional hazard model of rivaroxaban versus enoxaparin/VKA treatment yielded a HR of 0.886 (95% CI of 0.661-1.186). The upper limit of the CI was below the pre-defined non-inferiority margin of 1.75, showing non-inferiority of rivaroxaban over enoxaparin/VKA for the primary efficacy outcome in the pooled analysis. The test for superiority of rivaroxaban versus enoxaparin/VKA was not statistically significant ($p_{superiority} = 0.4143$). The p-value for interaction of treatment effect by index event was not statistically significant at 0.097.

The results for all of the secondary outcomes (main, net clinical benefit 1 and net clinical benefit 2) were all consistent with the primary outcome. The incidences of the components of the efficacy outcomes were comparable between the pooled treatment groups except for that of major bleeding event, which occurred in 1.2% (48/4150) of subjects in the pooled rivaroxaban group and 1.9% (80 /4131) in the pooled enoxaparin/VKA group.

In the pooled sub-group analysis of the primary efficacy outcome by baseline and demographic factors, there was one result of note. For those subjects with a previous episode of DVT/PE, the comparative rates of the primary endpoint were 11/791, 1.4% in the rivaroxaban group versus 25/819, 3.1% in the enoxaparin/VKA group [HR = 0.445, 95% CI {0.219, 0.905}] while for those with no previous episode of DVT/PE, the comparative rates were 75/3359, 2.2% in the rivaroxaban group versus 70/3312, 2.1% in the enoxaparin/VKA group [HR = 1.044, 95% CI {0.754, 1.446}]. **The 95% CIs do overlap. The sponsor was asked to comment on this finding.**

Once again in the sub-group analyses of net clinical benefit 1 by baseline and demographic factors, there was an apparent benefit of rivaroxaban over enoxaparin in older age groups compared with younger and in those who were fragile versus those who were not fragile. Again, **is there a common driver here such as differential major bleeding rates? The sponsor was asked to comment.**

Study PH36749

The objective of this study was to evaluate the treatment effect of rivaroxaban compared to enoxaparin/VKA in Studies Einstein-DVT and Einstein-PE on patient-reported treatment satisfaction through analyses on two questionnaire responses: the Anti-Clot Treatment Scale (ACTS) and the Treatment Satisfaction Questionnaire for Medication (TSQM). The study population was the ITT analysis population in Studies Einstein-DVT and Einstein-PE in seven participating countries: United States, United Kingdom, Canada, Germany, France, Italy, and the Netherlands.

There were two primary endpoints: analysis on the Burdens subscale of ACTS and analysis on Benefits subscale of ACTS. For the former, there was a consistent treatment effect across all visits while for the latter, the treatment effect was not consistent across visits.

Studies PH36705 and PH36718

Both studies were identical in objectives and design except that Study PH36705 evaluated data on Study Einstein-PE only, while Study PH36718 was a meta-analysis of Studies Einstein-PE and Einstein-DVT. These studies were analyses of the effect of rivaroxaban on bleedings and efficacy with selected co-medication categories in Study Einstein-PE (Study PH36705) and in pooled Studies Einstein-PE and Einstein-DVT (Study PH36718). The main objectives of the analyses in these studies were to investigate the effect of

concomitant use of CYP3A4 inducers, statins, NSAIDs, ASA and platelet aggregation inhibitors on the primary efficacy outcome (that is, symptomatic recurrent VTE), and the effect of concomitant use of NSAIDs, ASA, platelet aggregation inhibitor, clopidogrel/ticlopidine, strong CYP3A4 inhibitors, P-gp inhibitors and statins (and steroids for Study PH36718 only) on the risk of adjudicated and confirmed treatment-emergent bleeding events.

The analyses were purely exploratory. Results from the Cox proportional hazard model with covariate co-medication use for the primary efficacy outcome are provided for Einstein PE and for the pooled Studies Einstein-DVT and Einstein-PE. The most notable result concerns ASA use in the at-risk period for > 50% of the time where the rate of the primary endpoint in the rivaroxaban group was 4/298, 1.3% versus 11/244, 4.5% in the enoxaparin/VKA group.

Studies PH36706 and PH36711

Both studies were identical in objectives and design except that Study PH36706 evaluated data on Study Einstein-PE only, while Study PH36711 was a meta-analysis of Studies Einstein-PE and Einstein-DVT. The objective of the studies was to evaluate the relationship between the pharmacodynamic marker for rivaroxaban, prothrombin time (PT; measured with Neoplastin reagent), and efficacy and safety outcomes. The efficacy outcome analysed was the incidence of the primary efficacy outcome (that is, symptomatic recurrent VTE). The safety outcomes were bleeding events (treatment-emergent major bleeding, treatment-emergent major or non-major clinically relevant bleeding [that is, the principal safety outcome in Studies Einstein-DVT and Einstein PE], and any treatment-emergent bleeding). Again the analyses were designed to be exploratory only and there would appear to be no conclusions. For instance, there appears to be a partial result in that the numbers of rivaroxaban subjects with primary efficacy outcome and bleeding events in Einstein-PE and in the pooled Studies Einstein-PE and Einstein-DVT are presented in the dossier. However, there is no comparable table showing the numbers of enoxaparin/VKA subjects. **The sponsor was asked to clarify this apparent discrepancy or missing information.**

There were a number of exploratory analyses, 9 in fact, conducted and reported in the dossier and the clinical evaluator asked a question as to when the conclusions would be available. The sponsor replied that these study reports were described as "technical reports" as they were exploratory and their results were intended to support "for exploratory and supplementary purposes" the conclusions presented in the summary documents in Module 2 of the submission and hence no individual conclusions were presented for the individual study reports. The Delegate considered this explanation needed to be clarified. In the response to the Overview, **the sponsor was requested to explain, succinctly and accurately, the nature and objectives of each of the exploratory studies and to explain, again succinctly and accurately precisely how the results of each supported "for exploratory and supplementary purposes" the conclusions presented in the summary documents in Module 2. The sponsor was requested to detail, for each study, how the results of each exploratory study may have changed the way in which the conclusions were presented in the summary documents in Module 2**.

Safety

Studies providing evaluable safety data are described in detail in the CER (see Attachment 2 of this AusPAR). The most important of these are the pivotal Study Einstein-PE, the various non-pivotal efficacy studies and meta-analyses (Study PH36746 (the most important of these) and a meta-analysis of Einstein-DVT and Einstein-PE, PH36705, PH36718, PH36706, PH36711) and the other studies/meta-analyses evaluable for safety

only (Studies PH36707 and PH36708). In the latter category there were two studies, PH36709 and PH36710, which were purely exploratory. **The sponsor was requested to give a brief summary of the latter two studies and whether there are any results/conclusions to be drawn from them.**

Also there was a pooled safety analysis of rivaroxaban in subjects enrolled in 64 Phase I clinical trials. The latter analysis appears also to have been an exploratory analysis presented without any conclusions. Once again **the sponsor was asked to prepare a summary of the data in that analysis and present what conclusions, if any, may be drawn from it.**

For the pivotal study, Einstein-PE, the median duration of treatment was similar between the 2 treatment groups (183 days and 182 days in the rivaroxaban and enoxaparin /VKA groups, respectively). Overall, 73.7% of the subjects in the rivaroxaban group and 70.0% of the subjects in the enoxaparin/VKA group were treated for ≥6 months. For the pooled analysis of Studies Einstein-DVT and Einstein-PE, the median duration of treatment was similar between the 2 treatment groups (183 days and 182 days in the rivaroxaban and enoxaparin /VKA groups, respectively). Overall, 71.7% of the subjects in the pooled rivaroxaban group and 67.1% of the subjects in the pooled enoxaparin/VKA group were treated for ≥6 months.

In the pivotal study, Einstein-PE, the percentages of subjects with any AEs were comparable between treatment groups (81.2% [1959/2412] and 80.2% [1928/2405] in the rivaroxaban and enoxaparin/VKA groups, respectively). The percentages of subjects with any TEAEs (that is, AEs in the period from randomisation until 2 days after the last dose of study drug) were comparable between treatment groups (80.3% [1937/2412] and 79.0% [1901/2405], respectively). The most commonly reported TEAEs in the rivaroxaban group were epistaxis (9.0% versus 8.2% in the enoxaparin/VKA group), headache (8.0% versus 7.2%), chest pain (7.6% versus 7.7%), nasopharyngitis (7.5% versus 7.9%), and dyspnoea (6.7% versus 5.7%). TEAEs with higher incidence rates in the rivaroxaban treatment group by ≥1% compared to the enoxaparin/VKA group were menorrhagia (3.0% versus 1.9%), dyspnoea (6.7% versus 5.7%), and pruritus (2.2% versus 1.1%). Similar results were observed for the pooled analysis of Einstein-DVT and Einstein-PE (Study PH36746).

In the pivotal study, Einstein-PE, the incidences of any treatment-related TEAEs were comparable between treatment groups (32.2% [776/2412] and 32.6% [784/2405] in the rivaroxaban and enoxaparin/VKA groups, respectively). The most commonly reported treatment-related TEAEs in the rivaroxaban group were epistaxis (7.2% versus 6.6% in the enoxaparin/VKA group), haemoptysis (2.6% versus 1.9%), menorrhagia (2.5% versus 1.4%), and contusion (2.2% versus 3.6%). TEAEs with higher incidence rates in the rivaroxaban treatment group by ≥1% compared to the enoxaparin/VKA group were menorrhagia (2.5% versus 1.4%) and headache (1.5% versus 0.5%). The majority of treatment-related TEAEs were assessed as being either mild (21.4% [516/2412] in the rivaroxaban group versus 23.3% [561/2405] in the enoxaparin/VKA group) or moderate 8.3% [200/2412] versus 6.7% [160/2405]). The incidences of treatment-related TEAEs which were assessed as being severe were 2.5% [60/2412] in the rivaroxaban group and 2.6% [63/2405] in the enoxaparin/VKA group. Again, similar results were observed for the pooled analysis of Einstein-DVT and Einstein-PE (Study PH36746).

In the pivotal study, Einstein-PE, the total number of deaths reported and adjudicated was 63 (2.6%) in the rivaroxaban group and 51 (2.1%) in enoxaparin/VKA group. The most frequently reported primary causes for death in the rivaroxaban group were cancer (0.9% [22/2412] in rivaroxaban group versus 1.0% [23/2405] in enoxaparin/VKA group), infectious disease (0.4% [9/2412] versus 0.2% [6/2405]), and unexplained death for which PE could not be ruled out (0.3% [8/2412] versus 0.2% [6/2405]). The incidence rate of treatment-emergent death (that is, deaths between treatment randomisation and 2

days after stopping the study drug) was 1.2% (28/2412) in the rivaroxaban group and 0.8% (20/2405) in the enoxaparin/VKA group. The most frequently reported primary causes for death (by CIAC) in this period in the rivaroxaban group were cancer (0.4% [10/2412] in rivaroxaban group versus 0.2% [4/2405] in enoxaparin/VKA group), unexplained death for which PE could not be ruled out (0.3% [8/2412] versus 0.2% [5/2405]), and infectious disease (<0.1% [2/2412] versus 0.2% [4/2405]). Similar results were observed for the pooled analysis of Einstein-DVT and Einstein-PE.

Overall in the pivotal study, 20.9% of subjects (504/2412) in the rivaroxaban group and 20.7% of subjects (497/2405) in the enoxaparin/VKA group reported any SAEs. The percentages of subjects with any treatment-emergent SAEs (TESAEs) (that is, SAEs in the period from randomisation until 2 days after the last dose of study drug) were 19.5% (471/2412) and 19.3% (463/2405) in the rivaroxaban and enoxaparin/VKA groups, respectively. The most frequently reported TESAEs in the rivaroxaban treatment group were chest pain (0.8% versus 1.1% in the enoxaparin/VKA group), pneumonia (0.8% versus 0.8%), and dyspnoea (0.7% versus 0.5%). The incidence rates of the foregoing SAEs, both overall and individually, were lower in the pooled analysis of Einstein-DVT and Einstein-PE which implies that these rates were even lower in the Einstein-DVT Study. **The sponsor was requested, in its response to the Overview, to give a detailed summary of the differential rates of SAEs in Einstein-DVT and in Einstein-PE, highlighting the most significant differences.**

In the pivotal study, the incidence rate of any AEs resulting in permanent discontinuation of study drug was 5.1% (123/2412) in the rivaroxaban group and 4.1% (99/2405) in the enoxaparin/VKA group. The most frequently reported AEs resulting in permanent discontinuation of study drug in the rivaroxaban group were anaemia (0.2% versus <0.1%% in the enoxaparin/VKA group), ischaemic stroke (0.2% versus 0%), and rash (0.2% versus 0.1%). Comparable results were observed in the pooled analysis.

In the pivotal study, the incidence rate of any AEs resulting in hospitalisation or prolonged hospitalisation was 17.6% (425/2412) in the rivaroxaban group and 17.9% (430/2405) in the enoxaparin/VKA group. The most frequently reported AEs resulting in hospitalisation or prolonged hospitalisation in the rivaroxaban group were chest pain (0.9% versus 1.1% in the enoxaparin/VKA group), pneumonia (0.8% versus 0.8%), dyspnoea (0.7% versus 0.5%), sepsis (0.5% versus <0.1%), and pleural effusion (0.4% versus 0.5%). The incidence rates of the foregoing events involving hospitalisation, both overall and individually, were lower in the pooled analysis of Einstein-DVT and Einstein-PE which implies that these rates were even lower in the Einstein-DVT Study. **The sponsor was requested, in its response to the Overview, to give a detailed summary of the differential rates of these events in Einstein-DVT and in Einstein-PE, highlighting the most significant differences.**

There were no significant abnormalities of concern with regard to liver-related laboratory parameters. **The sponsor was asked to confirm whether or not there were any suspected or confirmed Hy's Law[8] cases in either the Einstein-PE database or the Einstein-DVT database.**

With regard to post-marketing experience, the most current report available to the clinical evaluator was that until the data lock point of 31 December 2011. Until the latter, 3404 spontaneous case reports (including 156 consumer reports) had been identified, and this included 6144 AEs, of which 3573 were SAEs. The most frequently reported SAEs were PE (n=339), DVT (n=318), haematoma (n=185), and haemorrhage (n=120). Until 31 December 2011, 91 death cases had been reported through spontaneous reporting. The most frequently reported AE associated with a fatal outcome was PE (n=39). Bleeding-related AEs were identified through a search of the AE database for the preferred terms

[8] Hy's law provides prognostic rules for identifying drug induced liver injury

included in the Standardised Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQ) for Haemorrhages. A total of 1518 cases with at least one bleeding-related event were identified, of which 1108 cases were considered serious. The most frequent bleeding-related SAEs were haematoma (n=185), post-procedural haemorrhage (n=97), haemorrhage (n=120), gastrointestinal haemorrhage (n=90), and post procedural haematoma (n=70). The clinical evaluator was satisfied that the post-marketing data supplied was consistent with the known safety profile of rivaroxaban. **The sponsor was asked to give, in the response to the Overview, a brief summary of the post-marketing experience up to the most recently available data lock point.**

In the pivotal study, Einstein-PE, the principal safety outcome was clinically relevant bleeding events (that is, the composite of major bleeding events or clinically relevant non-major bleeding events). The incidence rate of the principal safety outcome was slightly lower in the rivaroxaban group (10.3% [249/2412]) compared to the enoxaparin/VKA treatment groups (11.4% [274/2405]). The HR (rivaroxaban versus enoxaparin/VKA) was 0.900 (95% CI: 0.758 to 1.069; p-value for superiority: 0.2305). This result for the principal safety outcome was driven largely by that for the component of major bleeding events rather than that for clinically relevant non-major bleeding events. For the component of major bleeding events, the incidence rate was lower in the rivaroxaban treatment group (1.1% [26/2412]) compared to the enoxaparin/VKA treatment group (2.2% [52/2405]) whereas the incidence rate of the component of clinically relevant non-major bleeding events was similar between treatment groups (9.5% [228/2412]) and 9.8% [235/2405] in the rivaroxaban and the enoxaparin/VKA treatment groups, respectively). Similar results were observed for the pooled analysis.

The number of fatal major bleeding events in the rivaroxaban group was numerically lower compared to the enoxaparin/VKA treatment group (Study Einstein-PE: 2 [< 0.1%] versus 3 [0.1%] in the enoxaparin/VKA treatment group; pooled analysis: 3 [< 0.1%] versus 8 [0.2%]).

The sponsor was requested, in the response to the Overview, to provide a brief summary of the two exploratory studies, PH36707 and PH36708, analyses of multiple bleeding events. The sponsor was also requested to give in the same response a summary of the conclusions, if any, which may be derived from these studies. Analyses on the incidence of multiple bleeding events showed that in both Study Einstein-PE and the pooled analysis of Studies Einstein-PE and Einstein-DVT, the majority of subjects with clinically relevant bleeding events, major bleeding events, or all confirmed bleeding events had single bleeding event. The incidence rate of multiple bleeding events affecting the principal safety outcome and all confirmed bleeding events were also comparable between treatment groups. **The sponsor was requested to clarify what additional information, if any, was meant to be obtained from the exploratory analyses?**

Analyses on the effect of co-medications on the incidence of bleeding events (Studies PH36705 and PH36718) suggested that subjects on statins, ASA, NSAIDs or CYP3A4 inhibitors at baseline had a higher incidence of major bleeding events, clinically relevant bleeding events, and all confirmed bleeding events compared to those who were not. This is not an unexpected observation. For the pivotal study, Einstein-PE, the incidences of major bleeding events were lower in the rivaroxaban group compared to the enoxaparin/VKA group irrespective of the use of these co-medications (statins, ASA, NSAIDs and CYP3A4 inhibitors) at baseline. The incidences of clinically relevant bleeding events and of all confirmed bleeding events were higher in the rivaroxaban group compared to the enoxaparin/VKA group in subjects on statins or NSAIDs at baseline. **The sponsor was asked to comment on the latter observation.**

For the pivotal study, the overall incidence of on-treatment cardiovascular events was similar between treatment groups (1.5% [35/2412] in the rivaroxaban group and 1.5 %

[37/2405] in the enoxaparin/VKA group). The incidence of on-treatment cardiovascular deaths was higher in the rivaroxaban group compared to the enoxaparin/VKA group (0.3% [7/2412] versus 0.1 % [3/2405]). **The sponsor was asked to comment on this observation.**

The incidence rate of hepatic disorder AEs was lower in the rivaroxaban treatment group than in the enoxaparin/VKA treatment group (8.3% [199/2412] in rivaroxaban group versus 12.4% [299/2405] in enoxaparin/VKA group). The incidence rate of hepatic disorder SAEs was also lower in the rivaroxaban treatment group than in the enoxaparin/VKA treatment group (1.0% [23/2412] versus 1.5% [36/2405]). The incidence rates of hepatic disorder AEs resulting in permanent discontinuation of study drug were comparable between the rivaroxaban and enoxaparin/VKA groups (0.5% [11/2412] and 0.3% [7/2405], respectively).

There were no observations of concern with regard to the incidence rates of thrombocytopenia, acute pancreatitis, renal failure and anaphylactic reactions/severe cutaneous reactions.

First round risk-benefit balance

The clinical evaluator was of the opinion that the benefit-risk balance of rivaroxaban, given the proposed usage, is favourable and recommended that the application for the extension of indications for rivaroxaban for the treatment of pulmonary embolism be approved.

Clinical questions asked and Second round clinical evaluation

The clinical evaluator asked two questions about pharmacokinetics and two questions about efficacy in the round of clinical questions.

The first question sought clarity about the recommendation in the proposed PI that the 15 mg dose be taken with food. As noted, pooled analyses of a number of Phase I studies had suggested a possible food effect on rivaroxaban 15 mg. The sponsor's rationale is acceptable but there should be some brief statement in the PI that the relevant data is somewhat limited.

The clinical evaluator asked the sponsor to provide justification that, in Study 13238, a comparable exposure was observed in subjects with CYP induction receiving an adapted dosing regimen (a higher dosage regimen of 30 mg b.i.d./20 mg b.i.d.) and in subjects without CYP induction receiving the usual 15 mg b.i.d. / 20 mg o.d. dosing regimen. The sponsor provided data which showed that the patients in Study 13238 were younger, had a lower lean body mass and lower serum creatinine concentration than those in the Phase II studies. These factors would explain higher individual clearance and consequent lower AUC.

The sponsor was asked to supply details about the protocol violations in the pivotal study, Einstein-PE. The additional data does not raise any concerns.

The sponsor was asked by the clinical evaluator to clarify the status of the 9 exploratory studies, however, the response was not satisfactory. As noted above, **the Delegate requested the sponsor clarify the exact impetus of these studies and how or when "results and conclusions will be described under separate cover". In particular, the Delegate requested clarification of what is meant by "under separate cover"; the sponsor provide a succinct and accurate explanation of the purpose of each of these studies and of precisely what conclusions can or cannot be drawn from them; and to clarify whether the observations in these studies have any impact whatsoever on either the efficacy or safety profile of rivaroxaban in the treatment of PE and whether they have triggered or will trigger any further confirmatory studies.**

Clinical evaluator's recommendation

The clinical evaluator has recommended that the extensions of indication sought by the sponsor should be approved.

Risk management plan

The TGA OPR is of the view that the sponsor has adequately addressed all OPR recommendations except for some outstanding issues (see *Final recommendations to the Delegate* under section *V Pharmacovigilance findings*, above), which the sponsor was requested to address in the response to the Delegate's Overview.[9] In summary, the outstanding issues relate to:

- assurances that a post-market periodic schedule for the prescriber and patient survey testing would be proposed and implemented for as long as additional risk minimisation activities were considered necessary and the feedback would then be used to refine the prescriber guide and patient information.
- a short description, including the location within the Australian PI, of routine risk minimisation for all of the specified ongoing safety concerns should be provided in the ASA when it is next updated.
- ACSOM concerns over the printed materials associated with the Xarelto education program and the PFP.

The sponsor has said that it will consider the ACSOM's/OPR's comments regarding the clarity of the monitoring message in future materials to ensure that clinicians are advised that general patient monitoring should continue to be conducted given the potential for bleeding with Xarelto.

The Delegate is aware that ACSOM also had a number concerns about the various guides in existence for rivaroxaban.[10] There are 3 different guides, all apparently separate from the approved PI. They are the 'Patient Guide', the 'Prescriber Guide' and the 'PFP Guide'.

The Delegate requests the sponsor, in its pre-ACPM response, to explain succinctly and accurately the nature and role of each of the above 3 guides and to explain the difference(s) between the Patient Guide and the CMI. Also, the sponsor was requested to provide up-to-date copies of all "Guides" presently issued by the sponsor, no matter whether they refer to a specific indication or not.

If this application is approved, the OPR has recommended that the following specific conditions of registration should be applied:

- The EU-RMP identified as Version: 7.2, dated 29 March 2012, and an ASA identified as Version 1, dated September 2012, with revised details of a Risk Minimisation Plan within the ASA as agreed with the TGA, must be implemented.
- Post marketing reports are to be provided in line with the details stated above under *Final recommendations to the Delegate* under section *V Pharmacovigilance findings*, above.

The sponsor was requested to confirm that the RMP to be implemented in Australia is that identified in the previous paragraph.

[9] Matters relating to the RMP were subsequently addressed in separate correspondence (not detailed in this AusPAR) from the sponsor that was reviewed by the OPR.
[10] Details regarding product literature are beyond the scope of the AusPAR; therefore the specific concerns are not described in this AusPAR.

Risk-benefit analysis

Delegate considerations

As noted in the CER, the efficacy results in the pivotal study showed non-inferiority of rivaroxaban compared with enoxaparin/VKA, a currently accepted standard treatment regimen for PE, across all efficacy endpoints: composite endpoint of recurrent VTE or deaths from PE, composite endpoint of recurrent VTE or all-cause deaths, composite endpoint of recurrent VTE, deaths from PE, or major bleeding events, and composite endpoint of recurrent VTE, deaths from PE, major bleeding events, or cardiovascular events/deaths. In addition, the incidence rates of the individual components of recurrent PE, recurrent DVT and all-cause deaths were comparable between rivaroxaban and enoxaparin/VKA.

The potential risks of rivaroxaban elicited in Study Einstein-PE were bleeding and hepatic laboratory test abnormalities, which are all known adverse effects of rivaroxaban. When compared to enoxaparin/VKA, the incidence rate of major bleeding events was lower in subjects on rivaroxaban group and that of clinically relevant non-major bleeding events was comparable between rivaroxaban and enoxaparin/VKA. Taking both major and clinically relevant non-major bleeding events together as a composite endpoint, the overall incidence was lower in subjects on rivaroxaban. There was also no evidence suggesting potential liver injury by rivaroxaban. The sponsor has been requested to confirm whether or not there were any suspected or confirmed Hy's Law cases in either the Einstein-PE or the Einstein-DVT databases. However, the possibility of liver laboratory test abnormalities must continue to be monitored by appropriate laboratory assessment.

The sponsor has been requested to clarify a number of issues throughout this Overview, in particular the precise benefit-risk balance in younger versus older subjects. The requests are summarised as follows:

Summary of issues raised by the Delegate

The sponsor should address the following issues:

- Clarification of the exact purpose of the exploratory studies
- Clarification of the differential rates of cardiovascular death
- Clarification of the results of the sub-group analyses of net clinical benefit 1 by baseline and demographic factors, in particular those for older versus younger subjects, for fragile subjects versus non-fragile subjects, for those with moderate impairment of renal function versus those with normal renal function (and those with severe impairment of renal function) and for those with cardiac disease versus those with no cardiac disease
- Clarification as to whether there were any sub-group analyses of net clinical benefit 2 as there were for net clinical benefit 1
- Clarification of the results of the pooled sub-group analysis of the primary efficacy outcome by baseline and demographic factors for those with a previous episode of DVT/PE versus those with no previous episode of DVT/PE
- Clarification of the results of the pooled sub-group analysis of net clinical benefit 1 by baseline and demographic factors for the older versus younger subjects and for those who were fragile versus those who were not fragile
- Clarification regarding the differential rates of SAEs in Einstein-DVT versus those in Einstein-PE

- Clarification of the differential rates of AEs involving hospitalisation in Einstein-DVT versus those in Einstein-PE
- Clarification regarding any suspected or confirmed Hy's Law cases
- A summary of the most up-to-date post-marketing data
- Clarification regarding the higher incidences of clinically relevant bleeding events and of all confirmed bleeding events on rivaroxaban versus enoxaparin/VKA in subjects on statins or NSAIDs at baseline
- Clarification of outstanding issues involving the proposed RMP

Proposed action

The Delegate proposed to approve this submission by Bayer Australia Limited to extend the indications for Xarelto tablets (15 mg and 20 mg), based on the safety and efficacy of the product having been satisfactorily established for the indication below, for the reasons stated above in the risk-benefit discussion.

The indication proposed for approval is as follows (amendment in bold font)

> *Xarelto is indicated for*
>
> *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 pulmonary embolism (PE)*** *and for the prevention of recurrent DVT and PE.*

This approval will be contingent upon the provision, by the sponsor, of satisfactory answers to all questions asked of the sponsor in this Overview and also upon amendment of the PI document to the satisfaction of the TGA.

The Delegate intends to impose the following specific conditions of registration:

- The EU-RMP identified as Version: 7.2, dated 29 March 2012, and an ASA identified as Version 1, dated September 2012, with revised details of a Risk Minimisation Plan within the ASA as agreed with the TGA, must be implemented.
- Post marketing reports are to be provided in line with the details stated above under *Final recommendations to the Delegate* under section *V Pharmacovigilance findings*, above.

The Delegate also intends to frame a specific condition of registration which will require the sponsor to ensure that all information in the three Guides: the Patient Guide, the Prescriber Guide and the PFP Guide must be consistent with the information in the latest approved PI and that there must be no important safety information in the PI omitted from any of these three Guides.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM, and requested advice and comment specifically with regards to the following issues:

a. Is the ACPM of the view that the evidence presented in the dossier is sufficiently robust to support the proposed extension of indication?

b. Does the ACPM have any view concerning the type of educational programmes for intending prescribers of rivaroxaban which it would like to see implemented by the sponsor? That is to say what are the characteristics of an educational programme which gives practitioners confidence in being able to make a decision about the benefit-risk balance of the use of rivaroxaban in a particular patient? Is the ACPM of the opinion that all such educational programs should undergo the appropriate certification to be part of Continuing Professional Development (CPD) training for the relevant colleges, in particular for the Royal Australian College of General Practitioners (RACGP) CPD Program? Does the ACPM view the latter issue of sufficient concern to warrant a specific condition of registration?

c. The Delegate noted the existence of a number of documents produced by the sponsor, documents which are separate from the approved PI: the Patient Guide, the Prescriber Guide and the PFP Guide. The Delegate has requested that the sponsor provide up-to-date copies of all Guides presently issued by the sponsor, no matter whether they refer to a specific indication or not, and address concerns raised by the ACSOM in relation to these Guides. Does the ACPM have any remaining issues of concern?

Response from sponsor

The sponsor's responses to matters raised in the Delegate's overview, above, have not been included in 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, agreed with the Delegate and considered these products to have an overall positive benefit–risk profile for the proposed indication**;**

Xarelto is indicated for;

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 pulmonary embolism (PE) and for the prevention of recurrent DVT and PE.

Proposed PI/CMI amendments:

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- a statement in the *Precautions and Contraindications* sections of the PI and relevant sections of the CMI to more accurately reflect the data available on rivaroxaban use and patients on dialysis.
- a statement in the relevant section of the CMI to ensure patients are aware that there is no antidote.

Proposed conditions of registration:

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

- The reporting of the rates of bleeding seen in the user population, not just in the standard terms of "major or minor bleed" but also in more specific terms such as units of blood required.
- The alignment of any extra patient or prescriber educational material with the official PI and CMI, including more robust statements of risk.

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 Xarelto containing 15 or 20 mg rivaroxaban for the new indication:

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

The full indications are now:

Xarelto is indicated for:

- *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 arterial fibrillation and at least one additional risk factor for stroke*
- *Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for the prevention of recurrent DVT and PE*

Specific conditions applying to these therapeutic goods

- The implementation in Australia of the rivaroxaban European Risk Management Plan identified as Version: 7.10 dated 21 March 2013, with an Australian Specific Annex (ASA) identified as Version 2.1 dated June 2013 and any future versions as negotiated with and approved by the Office of Product Review.
- The information in any patient or prescriber educational or communication material for Xarelto, including the CMI, must be always consistent with and aligned with the approved PI document for Xarelto. As a guiding principle there must be no important safety-related information in the PI which is omitted from any patient or prescriber educational or communication material.
- If there is to be a product, patient or prescriber familiarisation programme, the details of that programme must be agreed with the OPR before the commencement of that programme and that any subsequent major revisions of the programme are to be agreed upon with the OPR.
- Provide to the OPR the final reports of the physician and patient surveys which will be conducted in Europe and which are described in the EU RMP v7.10 Annex 4.3.1 Risk Minimisation Plan Evaluation. These are to be provided to the OPR within 3 months of their becoming available to the EMA together with a summary of the important findings of each survey.

Provide to the OPR the final report of the patient CMI readability assessment currently being conducted, that is, the assessment mentioned on page 10 of the sponsor's response of 29 May 2013; and a summary of the important findings of this readability assessment. The final report and summary are to be submitted to the TGA within one month of the creation of the final report.

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

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