Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for dabigatran etexilate

Proprietary Product Name: Pradaxa

Sponsor: Boehringer Ingelheim Pty Ltd

January 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

Contents

Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ACS	Acute Coronary Syndrome
AE	Adverse Event
AF	Atrial fibrillation
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
aPTT	Activated Partial Thromboplastin Time
ASA	Australian Specific Annex
AST	Aspartate aminotransferase
AUC	Area Under the plasma concentration time Curve
aVTEt	Acute VTE treatment
BD	Twice daily
BI	Boehringer Ingelheim
BMI	Body Mass Index
CI	Confidence interval
CL	Clearance
C_{max}	Peak (or maximum) plasma concentration
CMI	Consumer Medicines Information
CRBE	Clinically Relevant Bleeding Event
CrCl	Creatinine Clearance
CRP	C-Reactive Protein
CT	Computerised axial tomography
CUS	Compression Ultrasonography
CV	Coefficient of Variation
DE	Dabigatran etexilate

Abbreviation	Meaning
DTI	Direct Thrombin Inhibitors
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
ECT	Ecarin Clotting Time
ESUS	embolic stoke of undetermined source
FAS	Full analysis set
GCP	Good Clinical Practice
GDSD	Global Drug Safety Database
gMean	Geometric Mean
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICSR	Individual Case Safety Reports
INR	International Normalised Ratio
KM	Kaplan-Meier
LFT	Liver function test
LMWH	Low Molecular Weight Heparin
MedDRA	Medical Dictionary for Drug Regulatory Activities
MBE	Major Bleeding Event
NOAC	new oral anticoagulant, novel oral anticoagulant
NSAID	Non-Steroidal Anti-Inflammatory Drug
NVAF	Non valvular atrial fibrillation
OR	Odds Ratio
PE	Pulmonary Embolism
PD	Pharmacodynamic
P-gp	P-glycoprotein
PI	Product Information

Abbreviation	Meaning
PIP	Paediatric Investigational Plan
PK	Pharmacokinetic
PMSB	Post Market Surveillance Branch (TGA)
POC	Point-of-Care (testing)
PPI	Proton Pump Inhibitor
PPS	Per Protocol Set
PT	Preferred Term
RMP	Risk Management Plan
SAE	Serious adverse event
SD	Standard Deviation
sec	seconds
SPAF	Stoke prevention in atrial fibrillation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
sVTEp	Secondary VTE prevention
T½	terminal half-life (of drug elimination)
TDTC	total dabigatran trough concentrations
Tmax	The time after administration of a drug when the maximum plasma concentration is reached
TIMI	Thrombolysis in Myocardial Infarction
TS	treated set
TT	Thrombin time
UFH	Unfractionated heparin
ULN	Upper Limit of Normal
US	United States
VKA	Vitamin K antagonist

Abbreviation	Meaning
VTE	venous thromboembolism, venous thromboembolic event
WF	Warfarin

I. Introduction to product submission

Submission details

Type of submission:	Major variation – extension of indications
Decision:	Approved
Date of decision:	24 August 2015
Date of entry onto ARTG	27 August 2015
Active ingredient:	Dabigatran etexilate (as dabigatran etexilate mesilate)
Product name:	Pradaxa
Sponsor's name and address:	Boehringer Ingelheim Pty Ltd PO Box 1969 North Ryde NSW 2113
Dose form:	Capsule, hard
Strengths:	75 mg, 110 mg and 150 mg
Containers:	Bottle, blister pack
Pack sizes:	10, 30, 60 (blister pack) 60 (bottle)
Approved therapeutic use:	Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE in adults.
Route of administration:	Oral
Dosage:	Treatment of acute DVT and/or PE: 150 mg twice daily following treatment with a parenteral anticoagulant for at least 5 days. Treatment should be continued for up to 6 months. Prevention of recurrent DVT and/or PE: 150 mg twice daily life long depending on the patient risk. For a full description of dosage please see the Product Information.
ARTG numbers:	137832, 138415, 138402, 138421, 168211, 168215

Product background

This AusPAR describes the application by Boehringer Ingelheim Pty Ltd (the sponsor) to register Pradaxa for the following indications:

> *Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of related death.*

and

Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and related death.

Pradaxa (dabigatran etexilate [DE]) is an inactive pro-drug. After oral administration it is converted to dabigatran by esterase hydrolysis in the plasma and liver. Dabigatran is a direct thrombin inhibitor, which competitively and reversibly inhibits both free and fibrin bound thrombin, preventing the conversion of fibrinogen to fibrin, thereby preventing thrombus formation. In addition, thrombin induced platelet aggregation is inhibited.

Concern was raised in a previous submission regarding dose adjustment in renal impairment, ability to monitor anticoagulation, lack of an antidote, gastrointestinal bleeding and myocardial infarction risk.

Dabigatran has a number of contraindications, precautions, drug interactions and dosage adjustments for various groups that relate to its increased risk of bleeding. These groups include those with renal impairment, the elderly and other factors that may increase the risk of bleeding such as concomitant use with P-gp inhibitors. These patient groups are of particular interest in this submission. Dabigatran has no specific antidote for the treatment of overdose and no specific ongoing monitoring of anticoagulation levels.

This submission is to extend the indication into treatment and prevention of DVT and PE based on two pivotal studies for treatment and two pivotal studies for prevention of recurrence. No changes to the formulation or presentation of the product are proposed.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on November 2008 for the indication:

Prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement).

The indications were extended in April 2011 to include:

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke.

At the time the TGA considered this application, a similar application had been approved in more than 20 jurisdictions, with a summary of EU, New Zealand, Canada, Switzeralnd and the USA detailed in Table 1.

Table 1. Overseas regulatory status.

Country	Submission status; date	Approved indication
New Zealand	Approved; 17 July 2014	Treatment of acute deep vein thrombosis (DVT)and/or pulmonary embolism (PE) and prevention of related death Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and related death

Country	Submission status; date	Approved indication
Canada	Approved; 24 June 2014	Treatment of venous thromboembolism events (deep vein thrombosis (DVT), pulmonary embolism (PE)) and prevention of recurrent DVT and PE
European Union (Centralised Procedure)	Approved; 03 June 2014	Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.
Switzerland	Approved; 22 January 2015	Treatment of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in adult patients who have been treated with fractionated or unfractionated Heparin for 5 days and prevention of recurrent DVT and PE.
United States of America	Approved; 04 April 2014	For the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5 to 10 days. To reduce the risk of recurrence of DVT and PE in patients who have been previously treated.

There are ongoing submissions in about 20 countries for the extension of indications to include:

- Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of related death; and
- Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and related death.

Product information

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

II. Quality findings

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

Venous thromboembolism (VTE) is a common disorder which remains a major cause of morbidity and mortality in Australia, and internationally. It is estimated that the annual Australian incidence of VTE is 18,248 cases, comprised of 11,340 cases of PE and 6,908 cases of deep vein thrombosis (DVT) (Access Economics, 2008)[1]. The condition may clinically present as DVT, PE or both concurrently. DVT and PE are considered to be two different but overlapping clinical presentations of the same pathologic process. Thrombus extension, recurrence of disease and fatal PE are the most important sequelae of VTE. The incidence of VTE varies substantially with subject age. In those < 40 years of age, the incidence is approximately 1 in 1,000 but the disease occurrence rises with increasing age. It is estimated that 1 in 100 people over the age of 80 years will experience VTE. In those who have suffered a VTE episode the risk of recurrence within 8 years is approximately 30%. In general, the risk of recurrence decreases with time and is influenced by factors such as whether or not the index VTE event was provoked (for example recent surgery or immobilisation) or not, as well as the presence of risk factors for recurrence (for example thrombophilia).

Current acute management of patients with VTE usually consists of initial treatment for 5 to 7 days with a heparin based therapy such as unfractionated heparin (UFH) or Low Molecular Weight Heparin (LMWH), followed by 3 to 12 months of anticoagulant therapy, typically oral vitamin K antagonists such as warfarin (WF). Alternatively some patients may receive ongoing treatment with subcutaneously administered LMWH as an alternative to oral anticoagulation. Treatment with warfarin may be difficult for several reasons such as the drug's delayed onset of antithrombotic effect, narrow therapeutic index, variable pharmacological response, interaction with other medicines and the need for regular laboratory monitoring. Additionally, warfarin therapy may be complicated by clinically significant bleeding events in up to 7% of patients. Hence, there is clinical need for additional oral anticoagulant therapies to provide alternative therapeutic options.

[1] Deloitte Access Economics. The burden of venous thromboembolism in Australia. 1 May 2008.

Dabigatran etexilate is the oral pro-drug of dabigatran. The pro-drug has no anticoagulant activity. Dabigatran is a direct thrombin inhibitor with a relatively rapid onset of action, and an acceptable efficacy and safety profile in treating patients with two current approved indications in Australia, without the need for routine laboratory monitoring. These characteristics make it an appealing candidate to investigate further for potential use in the treatment and prevention of recurrence of VTE.

Guidance

There are two specific EU guidelines adopted by the TGA relevant to this submission, besides the general guidelines:

- CPMP/EWP/563/98: Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Venous Thromboembolic Disease. Effective: 25 January 2001.
- CPMP/EWP/6235/04: Guideline on Clinical Investigation of Medicinal Products for the Prophylaxis of Venous Thromboembolic Risk in Non-Surgical Patients. Effective: 29 September 2006.

Contents of the clinical dossier

The submission contained the following clinical information:

- 1 new clinical pharmacology sub-study (data derived from Study 1160.53) which provided pharmacokinetic (PK) and pharmacodynamic (PD) data in the target patient population.
- No new population PK analyses.
- 4 pivotal efficacy/safety studies.
- No new dose finding studies.
- Pooled efficacy analyses of the active controlled Studies 1160.53 and 1160.46, supporting the indication of acute treatment of VTE; and a pooled efficacy analysis of the 2 pivotal trials, supporting the prevention of recurrent VTE; Studies 1160.47 and 1160.63.

The submission also included a Clinical Overview, Summary of Clinical Pharmacology, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

All of the studies in the DE clinical development program for the treatment and prevention of VTE were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met.

Pharmacokinetics

Studies providing pharmacokinetic data

In support of this application, one of the pivotal studies (Study 1160.53) collected a limited quantity of PK data in the target patient population.

Evaluator's conclusions on pharmacokinetics

The PK properties of DE in healthy volunteers, and adult subjects undergoing orthopaedic surgery or with atrial fibrillation have been previously assessed. The sponsor has provided a limited quantity of new PK data (trough DE concentrations collected at Days 30 and 180 of treatment) in this submission for patients with the additional treatment indication of treatment of VTE. The sponsor is proposing two minor changes to the PK section of the current PI: insertion of PK data from Study 1160.53 regarding increased drug exposure in patients with renal impairment, and an insert explaining the exclusion of patients from Study 1160.53 who had moderate or severe hepatic impairment at baseline.

The key PK findings for DE use in adult patients with VTE are:

- Plasma trough concentrations of dabigatran are stable over a time period extending from Day 30 to Day 180, but exhibit high inter individual variability
- Subjects with renal impairment (CrCl < 50 mL/min) have significantly higher trough total dabigatran concentrations indicating a higher drug exposure
- Trough dabigatran concentrations at 30 days are higher in females compared to men, and in older subjects (aged > 75 years) versus younger patients (< 40 years of age)
- Plasma trough levels of dabigatran are higher with the concomitant use of verapamil (P-gp inhibitor) and DE; and
- Overall there is some limited PK data to support a relationship between higher dabigatran plasma concentrations and bleeding events; however a potential relationship between lower dabigatran concentrations and recurrent VTE is not established.

Pharmacodynamics

Studies providing pharmacodynamic data

In support of this application, one of the pivotal studies (Study 1160.53) collected a limited quantity of PD data in the target patient population.

Evaluator's conclusions on pharmacodynamics

In this submission, the sponsor has provided a limited quantity of new PD data (aPTT and ECT results collected at Days 30 and 180 of treatment; as well at unscheduled times for those with specified clinical events) in the target patient population. The newly presented PD data does not demonstrate any new or unexpected PD findings or associations that have not been previously presented. The geometric mean (gMean) trough aPTT and ECT values are stable over an extended treatment period of 30 to 180 days, and exhibit moderate inter subject variability. Differences in the gMean trough aPTT and ECT are consistent with the differences observed for plasma concentration of total dabigatran in the investigated patient subgroups. There is some PD data to suggest a possible relationship between higher aPTT and ECT results and bleeding events but it remains unclear whether or not low aPTT and ECT values are associated with recurrent VTE (that is therapeutic failure). The sponsor does not propose any changes to the current PD section of the PI.

Dosage selection for the pivotal studies

No specific dose finding studies have been performed for patients with VTE. The dose and administration frequency of DE used in the 4 pivotal VTE studies, and proposed by the

sponsor for licensing, has been extrapolated from the posology approved for use to reduce the risk of stroke and systemic embolism in adult patients with atrial fibrillation. The sponsor asserts that the totality of the clinical efficacy and safety data collected in those preceding trials (and approved in previous submissions), supplemented with PK and anticoagulation biomarker data, provides a clear justification for examining the dose selected for the VTE indication (DE 150 mg, given twice daily (BD)). Dose selection for the first pivotal trial in this submission (Study 1160.53) was additionally supported by two dose finding studies performed in patients with atrial fibrillation. One of these dose finding trials (PETRO) was completed before the trial protocol for Study 1160.53 was written, and the other dose finding trial (PETRO-EX) was ongoing at the time of writing. The sponsor also states that the target population in the additional VTE indications have similar demographic and disease characteristics to those with atrial fibrillation. Furthermore, DE 150 mg BD is now approved in > 70 countries for the treatment of atrial fibrillation. Overall, the posology of DE used in the 4 pivotal studies contained in this submission has been reasonably justified by extrapolation.

In three of the four pivotal studies in this submission (Studies 1160.53, 1160.46 and 1160.47), warfarin with a target INR range of 2.0 to 3.0 was the active comparator treatment. This is consistent with contemporary clinical practice in Australia. One of those 3 trials (Study 1160.47) focussed on the secondary prevention of VTE in patients at high risk of recurrence. In the fourth trial in this submission (Study 1160.63), there was no active comparator. This trial was a superiority study examining the efficacy and safety of DE versus placebo over the long term (up to 18 months) in the secondary prevention of recurrent VTE in patients at high risk of relapse. This is an appropriate inclusion as part of the overall study program in VTE. Although several well designed studies have shown that follow up oral anticoagulation therapy with vitamin K antagonists (like warfarin) reduce the risk of recurrent VTE for the duration of therapy, there is a lack of scientific clarity on the optimal duration of secondary prevention and the overall benefit-risk assessment of treatment over extended time frames. The use of a placebo comparator was considered justified given the uncertain scientific evidence for management in this clinical scenario at the time of protocol development and patient recruitment.

Efficacy

Studies providing efficacy data

The submission contains two pivotal controlled trials (Studies 1160.53 and 1160.46) supporting the requested indication for the treatment of VTE. Study 1160.46 was designed to replicate Study 1160.53 (Table 2). In addition, there are two pivotal studies (Studies 1160.47 and 1160.63) supporting the requested indication of prevention of recurrent VTE. One of the VTE prevention trials (Study 1160.63) included an observational follow up period for 12 months. The final clinical study reports for all 4 pivotal studies were provided in this submission.

Table 2. Overview of the 4 pivotal studies for VTE treatment and secondary prevention contained in this submission.

Study	Population	Treatment duration	Treatment groups	Number of patients randomized	Number of patients treated[1]
aVTEt[2]					
1160.53 RE-COVER	Acute symptomatic VTE, eligible for ≥6 months of anticoagulation	6 months	150 mg bid DE Warfarin (target INR 2.0-3.0)	1281 DE) 1283 (W)	1274 (DE) 1265 (W)
1160.46 RE-COVER II	Acute symptomatic VTE, eligible for ≥6 months of anticoagulation	6 months	150 mg bid DE Warfarin (target INR 2.0-3.0)	1293 (DE) 1296 (W)	1279 (DE) 1289 (W)
sVTEp					
1160.47 RE-MEDY	Symptomatic VTE, 3-12 months of prior anticoagulation, at increased risk of recurrent VTE	6 to 36 months (cohort I: 18 months, cohort II: 18-36 months, cohort III: 6-18 months)	150 mg bid DE Warfarin (target INR 2.0-3.0)	1435 (DE) 1431 (W)	1430 (DE) 1426 (W)
1160.63 RE-SONATE	Symptomatic VTE, 6-18 months of prior anti-coagulation, no requirement for further anticoagulation	6 months[3]	150 mg bid DE Placebo	685 (DE) 668 (P)	681 (DE) 662 (P)

DE = dabigatran etexilate, W = warfarin, P = placebo

1 Number of patients who took at least 1 dose of any study medication (i.e., patients in the full analysis set [FAS])

2 Treatment during the aVTEt studies comprised a single-dummy period and a oral only period (double-dummy period). During the former, patients received open-label parenteral anticoagulation and in parallel W or W-matching placebo. During the oral only period (double-dummy period), patients additionally received DE or DE-matching placebo (parenteral anticoagulants were to be stopped at the end of the single-dummy period).

3 The treatment duration was 3 months for those patients who had not yet completed the 3-month visit when the required number of primary efficacy endpoint events was reached and the Steering Committee initiated the study close-out.

The evaluation of clinical efficacy was performed in two parts, each assessing the efficacy relevant to the indication requested, namely:

- Indication 1: *Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of related death.*
- Indication 2: *Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and related death.*

For full details of the designs and results of the studies and the pooled analyses please see Attachment 2.

Evaluator's conclusions on clinical efficacy for indication 1: Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of related death

The sponsor has provided the efficacy data from two replicate, pivotal, randomised, multi-centre, double blind trials (Studies 1160.53 and 1160.46) to support the efficacy of DE in treating adult patients with acute symptomatic VTE and to prevent its associated mortality.

The primary efficacy outcome in the two pivotal Phase III studies was the proportion of subjects who experienced the composite of recurrent symptomatic VTE and VTE related death (centrally adjudicated by an independent committee). The use of this primary

endpoint is consistent with the appropriate regulatory guideline[2] for determining the utility of a therapy in treating acute symptomatic VTE. There were also several secondary efficacy endpoints in both studies (individual components of the primary outcome, as well as all deaths) which are appropriate supporting measures.

In general, the trials were of adequate design to evaluate the proposed indication, and they had a clear and appropriate plan of analysis. In both of the trials, the primary statistical plan was a test for the non inferiority of DE versus warfarin, and if non inferiority was confirmed then the superiority of DE versus warfarin for the primary efficacy outcome was to be assessed. Two non inferiority margins were pre-specified: 2.75 for the HR, and 3.6% for the risk difference at 6 months. The choice of the non inferiority margins was based on the data available at the time of protocol development, and is consistent with the relevant regulatory guideline.[3]

Active comparator therapy with INR adjusted warfarin (target INR 2.0 to 3.0) was used in both studies and this choice is consistent with contemporary practice and literature, including international treatment guidelines. The quality of the warfarin control as measured by various analyses of INR adequacy suggested that warfarin control may have been sub optimal, but overall was consistent with real life clinical practice. Good quality warfarin control is defined as time in the therapeutic range of > 70%. In both of trials, this level of INR control in the warfarin treatment groups was not achieved. Up to 20% of all patients were taking various concomitant treatments such as non-steroidal anti-inflammatory drugs (NSAIDs), low dose aspirin, and P-gp substrates that may be expected in the target population.

In Study 1160.53, a total of 2,564 subjects were randomised to either DE (n = 1,273) or warfarin (n = 1,266) for 180 days of active treatment, and post treatment follow up of an additional 30 days (that is 210 days in total). In Study 1160.46, a total of 2,589 patients were randomised to receive either DE (n = 1,294) or warfarin (n = 1,295) for 6 months of treatment plus another 30 days of follow up. The majority of patients (approximately 85%) in both treatment groups completed the recommended follow up period in both pivotal studies. A relatively low proportion (< 5%) of major protocol violations that may have affected efficacy assessments occurred in both pivotal Phase III studies, with equal incidence among the treatment groups.

The populations examined in the Phase III studies are similar in demographics to patients that would be treated in Australian clinical practice. The trials mainly recruited patients from Western and Central Europe. The majority of recruited subjects were middle aged (younger than expected) and had normal baseline renal function (CrCl ≥ 80 mL/min). Preceding parenteral anticoagulation treatment (rates, as well agents used) is consistent with Australian treated patients. For the majority of patients (68%) the index VTE event was DVT, but PE was appropriately represented in the patient cohorts (> 20%). Nearly 10% of all subjects presented with both symptomatic DVT and PE. In addition to the index VTE episode, almost one third of DVT patients had an asymptomatic PE identified on objective testing. The above is consistent with expectations in the target population and reflects the extensive burden of clot in patients with symptomatic VTE. Moreover, the volume of data is sufficient to make an assessment of the comparative efficacy of DE in patients presenting with DVT, PE, or both manifestations of the same pathological process. More than 60% of all subjects had at least 1 identifiable risk factor for recurrent VTE, and in general the patient cohorts were at high risk for recurrent VTE events.

In general, the incidence and pattern of co-morbid illness was lower than expected. The 2008 Access Economics report estimated that, in Australia, the incidence of VTE was

[2] CPMP/EWP/563/98: Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Venous Thromboembolic Disease. Effective: 25 January 2001.
[3] EMEA/CPMP/EWP/2158/9: Guideline on the choice of the non-inferiority margin. Effective: 27 July 2005.

highest in those aged > 70 years, whereas the average age of patients in both study cohorts was < 60 years with less than one third of all treated patients being aged > 65 years.[1] As such, the generalisability of the study's results to a broader population in Australia has limitations. Moreover, patients at a high risk of bleeding were excluded.

The primary efficacy endpoint analysis in both pivotal Phase III trials demonstrated that DE was non inferior to warfarin for the composite outcome of centrally confirmed recurrent symptomatic VTE and VTE related death. Superiority could not be demonstrated. Furthermore, in both trials pre-defined sensitivity analyses of the primary endpoint using the Per Protocol Set (PPS) (rather than full analysis set (FAS)), and an on-treatment analysis were consistent with the primary analysis. The results for the secondary efficacy endpoints consistently supported the primary analysis demonstrating that in both pivotal Phase III studies DE is non-inferior to warfarin for recurrent symptomatic DVT, PE and death (VTE related and all-cause mortality). The cumulative risk of the primary efficacy endpoint was higher in patients with an initial symptomatic PE (compared to subjects who presented without PE) in Study 1160.53 but this observation was not replicated in the follow up Study 1160.46. In both trials, patients with active cancer had a higher cumulative risk for the primary endpoint. Expectedly, the highest risk of recurrent VTE or VTE related death is recognised to occur in patients with active cancer and/or symptomatic PE at baseline, regardless of treatment option (DE or warfarin). Nonetheless, the current dataset robustly supports that DE is non inferior to warfarin in treating both clinical manifestations of VTE (that is both DVT and PE).

In summary, the data in this submission supports that DE is non inferior to INR adjusted warfarin (at an acceptable level of quality control) in treating adult patients with acute symptomatic VTE, reducing both the risk of recurrent symptomatic VTE as well as VTE related mortality. The two pivotal Phase III studies have assessed the efficacy of DE over an appropriate time frame of follow up (180 days of treatment with an additional 30 days of post treatment follow up) and compared the relative effect of DE to the main alternative treatment approach.

Evaluator's conclusions on clinical efficacy for Indication 2: Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and related death

The sponsor has provided the efficacy data from two pivotal, randomised, multicentre, double blind trials (Studies 1160.63 and 1160.47) to support the efficacy of DE in the secondary prevention of recurrent VTE, and to prevent its associated mortality. Study 1160.47 used an active controlled comparator (warfarin with an INR target of 2.0 to 3.0) and had planned treatment duration of 6 to 36 months (in 3 patient cohorts). Study 1160.63 was a placebo controlled trial with a planned treatment period of 6 months for the majority of recruited subjects. This study included an observational follow up period of up to 12 months after the cessation of study treatment.

The primary efficacy outcome in Study 1160.47 was identical to that evaluated in the two acute VTE treatment trials (Studies 1160.53 and 1160.46). This endpoint was the proportion of subjects in each treatment group who experienced the composite of recurrent symptomatic VTE and VTE related death (centrally adjudicated by an independent committee). The placebo controlled trial (Study 1160.63) had a slightly different primary endpoint, which was the incidence of recurrent symptomatic VTE during the intended treatment period. There were several secondary efficacy endpoints in both studies (individual components of the primary outcome, as well as all deaths) which are appropriate supporting measures for determining the utility of a therapy in the secondary prevention of recurrent symptomatic VTE.

In general, the trials were of adequate design to evaluate the proposed indication, and both studies had a clear and appropriate plan of analysis. In Study 1160.47, the primary

statistical plan was a test for the non inferiority of DE versus warfarin, and if non inferiority was confirmed then the superiority of DE versus warfarin for the primary efficacy outcome was to be assessed. Two non inferiority margins were pre-specified: 2.85 for the HR, and 2.8% for the risk difference at 18 months. The choice of the non inferiority margins was based on the data available at the time of protocol development, and is consistent with the relevant regulatory guideline.[3]

Active comparator therapy with INR adjusted warfarin (target INR 2.0 to 3.0) was used in Study 1160.47. This choice is appropriate. The quality of the warfarin control as measured by various analyses of INR adequacy suggested that warfarin control may have been sub optimal, but overall was consistent with real life clinical practice. Good quality warfarin control is defined as time in the therapeutic range of > 70%. In both of trials, this level of INR control in the warfarin treatment groups was not achieved. In addition, up to a quarter of all patients were taking various concomitant treatments (such as non-steroidal anti-inflammatory drug (NSAID), low dose aspirin, and P-gp substrates) that may be expected in the target population.

In Study 1160.47, a total of 2,866 subjects were randomised: 1,435 to DE and 1,431 to warfarin. The overall median treatment duration was 534 days in both groups, and the overall median observation time was just over 18 months in both treatment groups (567 days in the DE group, and 566 days in the warfarin arm). About 2% of all patients had protocol deviations that may have affected the efficacy evaluation.

In Study 1160.63, a total of 1,343 randomised patients received at least 1 dose of study drug: 681 in the DE group, and 662 subjects in the warfarin arm. Most patients received treatment for the planned 6 months. The majority of patients (> 90%) in both treatment groups completed the recommended 6 month follow up in Study 1160.63. Just over 10% of all subjects were documented to have a major protocol violation that may have affected their efficacy assessment. This occurred at a slightly higher incidence in the DE group (11.5%) compared to the control arm (9.5%).

The populations examined in the two Phase III studies are similar in demographics to patients that would be treated in Australian clinical practice. The trials mainly recruited patients from Europe. The majority of recruited subjects were middle aged (younger than expected) and had normal baseline renal function (CrCl ≥ 80 mL/min). For the majority of patients (65%) the index VTE event was DVT, but PE was appropriately represented in the patient cohorts (approximately 25%). Nearly 10% of all subjects presented with both symptomatic DVT and PE. The volume of patient data is sufficient to make an assessment of the comparative efficacy of DE in patients presenting with DVT, PE, or both manifestations of the same pathological process. More than 60% of all subjects had at least 1 identifiable risk factor for recurrent VTE and in general the patient cohorts were at high risk for recurrent VTE events.

In general, the incidence and pattern of co-morbid illness was lower than expected. The 2008 Access Economics report estimated that in Australia, the incidence of VTE was highest in those aged > 70 years,[1] whereas the average age of patients in both study cohorts was < 60 years, with less than one third of all treated patients being aged > 65 years. As such, the generalisability of the results of the studies to a broader population in Australia has limitations. Moreover, patients at a high risk of bleeding were excluded.

The primary efficacy endpoint analysis in Study 1160.47 demonstrated that DE was non-inferior to warfarin for the composite outcome of centrally confirmed recurrent symptomatic VTE and VTE related death. Superiority could not be demonstrated. Sensitivity analyses of the primary endpoint using the PPS (rather than FAS), an on treatment analysis, and an analysis for the observation period were consistent with the primary analysis. The results for the secondary efficacy endpoints consistently supported

the primary analysis demonstrating that DE is non-inferior to warfarin for recurrent symptomatic DVT, PE and VTE related death.

The primary efficacy endpoint analysis in Study 1160.63 demonstrated that DE was superior to placebo for the composite outcome of centrally confirmed recurrent symptomatic VTE, including unexplained death during the intended treatment period. Sensitivity analyses of the primary endpoint (such as analysis using the PPS) confirmed the robustness of the primary analysis, with confidence intervals (Cis) either the same or very similar to the primary analysis. The results for the secondary efficacy endpoints supported the primary analysis in demonstrating that DE is superior to placebo for preventing recurrent symptomatic VTE, however no fatal PEs were recorded in the trial to examine the claim of preventing VTE related mortality. Two unexplained deaths were observed in the placebo group but this data is insufficiently robust to support the claim of preventing VTE related mortality when DE is used as a secondary prevention approach in those with a previous VTE episode.

In summary, the data in this submission supports that DE is non inferior to INR adjusted warfarin (at an acceptable level of quality control) in preventing recurrent symptomatic VTE, but there is insufficient data to justify the claim that DE is effective in reducing the risk of VTE related mortality. The two pivotal Phase III studies have assessed the efficacy of DE over an appropriate time frame of follow up, comparing the relative effect of DE to both active treatment (warfarin) and placebo.

Safety

Studies providing safety data

There were no pivotal studies in this submission that assessed safety as the primary outcome.

Pivotal efficacy studies

In the four pivotal efficacy studies (Studies 1160.53, 1160.46, 1160.47 and 1160.63) the following safety data was collected:

- General adverse events (AEs) were assessed by face to face questioning, which took place at inclusion, and every scheduled study visit (every 30 days). Telephone interviews for AE reporting were also available at certain pre-specified study visits, including the last follow up visit in each study. AEs were coded according to the Medical Dictionary for Drug Regulatory Activities (MedDRA) code list.
- AEs of particular interest included bleeding events and Acute Coronary Syndrome (ACS) events. These were assessed and reported by site investigators in a standardised manner on the case report forms and then all relevant information was forwarded to a blinded central committee for adjudication (further detail below).
- Laboratory tests including haematology and biochemistry (renal and hepatic function, as well as clinical chemistry) were performed at screening and every 30 days thereafter during the active treatment periods. Abnormalities of liver function tests (particularly, elevations in serum transaminases and/or total serum bilirubin) were a pre-specified laboratory parameter of interest. For 3 of the 4 pivotal studies (excluding Study 1160.46, which was the last pivotal study to be conducted) an independent hepatic review panel monitored liver safety as a standard safety measure. The panel reviewed all liver function data in a treatment blinded fashion from all patients with > x 3 upper limit of normal (ULN) elevations of serum transaminases (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]).

- Pregnancy tests (in young women) and 12 lead electrocardiogram (ECG) were performed at baseline and at the last study visit.
- Vital signs (body weight, blood pressure, heart rate) were assessed at baseline and at each scheduled face to face study visit thereafter (usually every 30 days while on active treatment).

Bleeding events

Bleeding events were an AE of special interest, and were classified as major or minor according to the outcome, extent of blood loss, severity and rate of bleeding. Minor bleeding events were further subdivided into clinically relevant bleeding events (CRBEs) and nuisance bleeds. The definition of major bleeding event (MBE) followed the recommendations of the International Society on Thrombosis and Haemostasis (see Attachment 2).

Acute coronary syndrome

All suspected ACS events occurring in all four pivotal VTE treatment trials with DE were to be recorded, and a blinded central adjudication committee reviewed all suspected ACS events.

Patient exposure

All safety analyses were performed on the treated set (TS), which includes all patients who were documented to have taken at least 1 dose of study drug. The safety data for these patients were analysed according to the treatment they actually received. In case a patient received more than 1 treatment in a study, the first medication kit used by the patient determined the treatment group assignment.

The number of randomised patients was similar in the three active controlled Studies 1160.53, 1160.46, and 1160.47. The placebo controlled Study 1160.63 included about half as many patients as in each of the other studies. Most (> 95%) randomised patients were treated with study drug. A total of 66 DE randomised patients did not receive active study drug across the 4 pivotal studies: 22 withdrew consent, 31 were non-compliant with entry criteria or the study protocol, 3 had an AE prohibiting treatment, and 10 had no specific reason recorded.

For further details regarding exposure to the study drug please see Attachment 2.

Treatment related adverse events (adverse drug reactions)

For details of the treatment related adverse events for each of the studies, please see Attachment 2.

Deaths and other serious adverse events

For details of deaths and other serious adverse events, please see Attachment 2.

Safety issues with the potential for major regulatory impact

Liver toxicity

Abnormalities of liver function tests are of special interest for DE as a preceding direct thrombin inhibitor (ximelagatrin) was known to cause abnormalities of liver function tests (markedly raised serum transaminases with or without increases in serum total bilirubin). In the 4 pivotal studies included in this submission, no important differences in the frequency and severity of liver function test abnormalities were observed in the active controlled studies (DE compared with warfarin). In the placebo controlled trial (Study

1160.63) the frequency of patients with elevations of liver function values of possible clinical significance was similar between the DE and control arms. Further details on the potential for hepatotoxicity have been discussed in Attachment 2. Nonetheless this issue will require ongoing pharmacovigilance in the requested target population if approval is granted.

Bleeding events

DE is associated with an increased risk of bleeding (major, clinically relevant and overall) compared to placebo (known effect plus the results of Study 1160.63 in this submission). However when DE is compared to INR adjusted warfarin for the acute treatment and secondary prevention of VTE the frequency of major and/or clinically relevant bleeding is similar and the incidence of any bleeding is lower. The location of MBE is similar between DE and warfarin, but for all bleeding events tended to be higher in the warfarin treated subjects from the urogenital and nasal tracts, and numerically greater in the DE subjects from the gastrointestinal tract.

Cardiovascular safety

In three of the 4 pivotal studies (all of the active controlled trials) in this submission, myocardial infarctions were numerically greater in the DE treated patients groups (compared to warfarin). In Study 1160.47 a statistically higher incidence of centrally adjudicated definite or likely ACS events was observed in the DE treatment group (0.9%; 13 out of 1,430) than the warfarin arm (0.2%; 3 out of 1,426; p = 0.02). In both of the acute treatment studies (1160.53 and 1160.46) there was a slightly increased absolute risk of ACS events in the DE treatment group compared to the warfarin arm in the order of magnitude of 0.3%. In both of the acute VTE treatment studies, the result was not statistically significant. In the placebo controlled RE-SONATE trial (Study 1160.63) only 1 confirmed myocardial infarction was recorded in each of the treatment groups. A recent meta-analysis by Uchino et al.[4] has hypothesised that the data indicates DE may be less protective of ACS compared to warfarin in subjects at risk of coronary occlusion, but that DE itself does not directly precipitate ACS events (as seen in the placebo controlled trial). Nonetheless, the potential for an increased risk of cardiovascular morbidity and mortality with DE cannot be excluded. This important safety issue will require ongoing pharmacovigilance in the requested target population.

Post marketing data

As DE has not been approved anywhere in the world at present for the indications of treatment and secondary prevention of VTE, there is no post marketing experience specific to the requested target populations in this submission. The sponsor has provided an updated report (data collected up to 18 September 2012) regarding its experience in patients taking DE for thrombo prophylaxis in non-valvular atrial fibrillation and following major orthopaedic surgery. The most recent update does not indicate any newly identified or potential safety concerns with DE.

Other safety issues

Safety in special populations

The current PI provides specific advice about the use of DE in patients with moderate or severe renal impairment. It also warns that patients with moderate renal impairment (CrCl 30 to 50 mL/min) receiving treatment with DE have a 'potentially higher risk' of major bleeding. This submission confirms that patients with significantly impaired renal

[4] Uchino K and Hernandez AV. Dabigatran association with higher risk of acute coronary syndrome: meta-analysis of non-inferiority randomised controlled trials. *Arch Intern Med* 2012; 172: 397-402.

function have an increased risk of AEs, which is comparable between the active treatment strategies of DE and warfarin.

The current submission also indicates that older patients (> 65 years of age) have an increased frequency of AEs compared to younger subjects, but this increased risk is not treatment dependent (that is occurring at the same frequency between DE and warfarin treated subjects).

Safety related to drug-drug interactions

The current PI already contains extensive information about the risk of drug interactions (PK and/or PD related). This submission does not contain any new information on the risk of additional drug interactions or a change in the likelihood of those events occurring.

Evaluator's conclusions on safety

In this submission, the total clinical safety dataset for the use of DE in adult patients with VTE consists of 8,753 patients in 4 pivotal studies: 4,387 of whom received DE at proposed dose of 150 mg BD, 3,707 were treated with INR adjusted warfarin (target 2.0 to 3.0) and 659 subjects took placebo therapy in the secondary prevention trial (Study 1160.63). The overall exposure to DE in the VTE dataset is 3,261 patient-years (and 2,946 patient-years for comparator warfarin). In the 4 pivotal studies, approximately 90% of patients received DE for at least 5 months in total (as part of a first, and then re-treatment period study design). Overall there is sufficient volume of data to make a meaningful assessment of safety over the short and medium term of treatment (that is up to 2 years) in the newly proposed treatment indications of acute treatment of VTE and secondary prevention.

In general, the study populations had baseline characteristics (demographic, disease related and co-morbidity) indicative of the intended target population for the claimed indication. The majority of subjects in the Phase III studies were male, Caucasian and middle aged. In the pivotal Phase III trials, approximately 30% of all recruited patients were aged > 65 years, which is an under representation of older aged subjects compared to Australian community statistics.[1] The pivotal studies excluded patients with a high baseline risk of bleeding. In addition, there is no, or very limited experience in certain patient subgroups of relevance including subjects with renal or hepatic impairment, pregnant or lactating women, and those with a low body weight (< 50 kg).

Bleeding is the most concerning AE associated with any anticoagulant therapy (including DE). MBEs and/or CRBEs occurred at a similar (not statistically different) frequency in DE and warfarin treated patients in all three of the active controlled studies. The overall incidence of any bleeding event was lower in the DE treatment groups than the warfarin arms. The location of MBEs was similar in both the DE and warfarin treatment groups. However, for all bleeding events, warfarin treated subjects tended have a higher bleeding risk from the urogenital and nasal tracts, and for the DE subjects a numerically greater risk of any bleed from the gastrointestinal tract. In the placebo controlled study (Study 1160.63) the incidences of CRBEs and of any bleeding event were significantly higher for patients on DE. Only 2 MBEs occurred during the trial, both affecting DE treated subjects.

The other key safety conclusions identified in the four Phase III trials are as follows:

- The overall incidence of AEs was similar in the DE, warfarin and placebo groups
- However, the incidence of gastrointestinal disorders was higher in patients who received DE compared with placebo, and often higher to that observed in patients receiving warfarin
- Permanent discontinuations from study medication because of AEs were similar in frequency among the active treatment groups, but withdrawal due to gastrointestinal disorders occurred at a higher frequency in those taking DE

- At 6 to 18 months of follow up the overall incidence of serious adverse events (SAEs) was low and similar in frequency between the active treatment groups, with the most frequent type of SAE (excluding recurrent VTE) being pneumonia, dyspnoea and adverse cardiovascular events
- The Phase III studies confirmed that patients with renal impairment and those aged > 65 years are a subset of patients at the highest risk of AEs (regardless of anticoagulant treatment, including DE).

Elevations in hepatic transaminases (AST and ALT) were recorded in approximately 2% of patients treated with DE in the pivotal studies. Abnormalities of liver function tests were observed at a similar frequency with both warfarin and placebo in the 4 clinical trials. The majority of these changes in liver function tests were mild and without associated clinical implications.

In summary, the safety data indicates that DE has an acceptable safety profile compared to the main alternative active therapy (INR adjusted warfarin within the target range of 2.0 to 3.0) in the treatment of adult patients with symptomatic VTE (Studies 1160.53 and 1160.46). Similarly, when DE is used in the secondary prevention of recurrent VTE in patients at high risk, the safety profile is acceptable compared to other active treatment (warfarin) but clearly there is a higher incidence of bleeding with any anticoagulant treatment (including DE) over placebo. The submitted dataset contains a sufficient volume of short and medium term safety data (up to 2 years) to assess the risk of many types of AEs associated with anticoagulation. Nonetheless, in 3 of the 4 pivotal studies (all of the active controlled trials) in this submission, myocardial infarctions were numerically greater in the DE treated patients groups (compared to warfarin), but the observation was not statistically significant in 2 of the 3 pivotal trials. Therefore the potential for an increased risk of cardiovascular morbidity and mortality with DE cannot be excluded and this important safety issue requires ongoing pharmacovigilance. The major identified safety concern with DE is bleeding (major, clinically relevant and overall). The safety concerns identified in this submission are consistent with known profile of DE in other approved indications, mainly when used for thrombo prophylaxis in patients with atrial fibrillation and at least 1 additional risk factor for stroke. Significant pharmacovigilance would be required if approval is granted for extension of treatment indications. This would include vigilance for bleeding, acute coronary syndrome events and the risk of AEs in patient subgroups (for example those with renal impairment).

First round benefit-risk assessment

First round assessment of benefits

The benefits of DE in the proposed usage are:

- DE is non inferior to warfarin for treating acute symptomatic VTE and its associated mortality
- DE is non inferior to warfarin, and superior to placebo, in the secondary prevention of recurrent VTE (however extended duration treatment beyond 18 months is an area of uncertainty)
- DE provides an alternative to INR adjusted warfarin and other anticoagulation therapies in treating patients with VTE (initial parenteral therapy is still required for acute symptomatic VTE)
- No requirement for routine laboratory monitoring of anticoagulant activity

- DE is an orally administered treatment which provides dosing convenience over parenteral therapies for the majority of target patients.

First round assessment of risks

The risks of DE in the proposed usage are:

- Increased risk of bleeding (major, clinically relevant and overall) which is comparable to alternative active therapies such as warfarin but higher than placebo
- Potential for increased risk of myocardial infarction; numerically higher in the DE treated versus warfarin treated subjects in this submission, but not statistically significant difference in 2 of the 3 pivotal studies
- Safety not established in those with a high risk of bleeding (for example bleeding diathesis) as these patients were excluded from the trial populations (that is some limitations to external validity)
- In general safety data in patients with VTE limited to < 2 years of follow up
- No antidote to the anticoagulant effects of DE is currently available for those with major toxicity (in particular those experiencing major bleeding events or requiring urgent surgery)
- No readily available and validated method of monitoring the anticoagulant effect of DE
- DE is contra indicated in patients with severe renal impairment (CrCl < 30 mL/min), and patients with moderate renal impairment have an increased risk of bleeding
- DE is contra indicated during pregnancy (risk factor for VTE) and lactation
- Potential for drug interactions related to changes in intestinal P-gp activity.

First round assessment of benefit-risk balance

The benefit-risk balance of DE is favourable for the acute treatment of symptomatic VTE, and is similarly favourable for the indication of secondary prevention of VTE for up to 18 months of therapy. However, the risk-balance of DE therapy for secondary prevention of VTE beyond 18 months of treatment is unclear from the current dataset.

This submission contains robust data to support the claim that DE is non inferior to warfarin (INR control of sufficient quality) for treating acute symptomatic VTE and its associated mortality. In addition, DE is non inferior to warfarin, and superior to placebo, in the secondary prevention of recurrent VTE. However, extended duration treatment beyond 18 months is an area of uncertainty. DE provides an alternative to INR adjusted warfarin and other anticoagulation therapies in treating patients with VTE after an initial period of parenteral anticoagulation therapy. DE is non inferior to warfarin in treating patients whose initial clinical presentation is with either DVT or PE. Some patient subgroups (such as those with active cancer) are at a higher risk of VTE recurrence, but that risk is consistent with DE or warfarin. There are 2 major safety concerns in the current dataset that require consideration. There is an increased risk of bleeding (major, clinically relevant and overall) with DE which is comparable to alternative active therapies such as warfarin, but higher than placebo. The 3 active controlled studies showed an increased frequency of myocardial infarction in DE versus warfarin treated subjects, which was statistically significant in 1 of those 3 studies (Study 1160.47).

There are some caveats to the current dataset. The efficacy and safety of DE in patients at a high risk of bleeding is not established. In addition DE treatment is contra indicated in those with severe renal impairment (CrCl < 30 mL/min) and there are several important potential drug interactions with P-gp substrates that require caution or avoidance of

concurrent administration. There is no information for DE on the management of patients with recurrent VTE whilst receiving anticoagulation. In practice many clinicians would recommend an increase in target INR for warfarin treated subjects or a switch to heparin based therapy in the maintenance treatment phase (that is, after an initial period of parenteral anticoagulation).

First round recommendation regarding authorisation

The clinical evaluator recommends acceptance of the sponsor's proposed extension of treatment indications for DE to include the treatment and secondary prevention of VTE. However the proposed wording of treatment extension contains an additional element. The sponsor is also asking for the indication to include '*prevention of related death*' in both clinical scenarios (acute treatment phase, as well as in the extended secondary prevention period).

The current submission provides robust evidence of DE reducing the risk of VTE recurrence when used in both the acute treatment phase and secondary prevention period. There is evidence that DE is comparable to warfarin in reducing the risk of VTE related death when commenced in the acute treatment phase; however there is insufficient evidence for the claim of '*prevention of related death*' in the extended secondary prevention period. At the very least, the clinical evaluator recommends that this phrase be removed from the second newly proposed indication (that is prevention or recurrent VTE). However in the clinical evaluator's opinion an indication listing consistent with the proposed US wording would be most appropriate and easily understood by clinicians if licensing is approved. The clinical evaluator proposes the indication of '*For the acute treatment and reduction of risk of recurrence of deep vein thrombosis and pulmonary embolism*'.

The clinical evaluator would recommend that approval of the sponsor's proposed extension of indication be subject to satisfactory response to the questions raised below (clinical questions) and regular periodic safety update reports.

Clinical questions

Pharmacokinetics

1. The pharmacokinetic data from the Study 1160.53 shows that patients with a CrCl of < 50 mL/min had much higher trough concentrations of total dabigatran (more than a 3 fold increase) compared to subjects with CrCl ≥ 80 mL/min. For the approved indication of thrombo prophylaxis in patients with atrial fibrillation, there is flexibility in the dosing of Pradaxa to consider using the lower dose of 110 mg BD (versus 150 mg BD). In this submission, why has the option of dose reduction in patients with moderate renal impairment (CrCl 30 to 50 mL/min) not been requested in the PI, or examined in the clinical study program. Could the sponsor please comment on this issue?

Pharmacodynamics

2. Thrombin Time (TT) is the most sensitive assay for determining if dabigatran is present in the plasma.[5] In the PD sub study of Study 1160.53, were samples for TT collected and if not, why?

[5] Douxfils J, et al. Impact of dabigatrin on a large panel of routine or specific coagulation assays. Laboratory recommendations for monitoring of dabigatrin etexilate. *Thromb Haemost*. 2012; 107: 985-997.

Efficacy

3. In Studies 1160.53 and 1160.46 it was unclear how the variability in sham INR readings (dabigatran treatment groups) compared to the variability in real INR results (warfarin treatment groups) during the active treatment periods of both trials. There appeared to be a higher incidence of treatment interruptions in the warfarin treatment groups for too high or too low INR results compared to the dabigatran arms. Could the sponsor comment on the degree of INR variability (sham versus real INR results) between the treatment groups in Studies 1160.53 and 1160.46? If there was inequity between the active treatments for this observation, could the sponsor comment on whether or not such an observation may have affected the efficacy results, including the potential for unintentional treatment un-blinding?
4. In Studies 1160.53 and 1160.47 the trial protocol required patients to discontinue study treatment if they developed a verified recurrent VTE event. In the submitted tables summarising patient disposition (that is number of subjects '*discontinuing due to worsening of disease under study'*), number of patients with primary efficacy outcome events and discontinuations there is a discrepancy between the patient numbers for each treatment group. For example, in the dabigatran treated patients in Study 1160.53 the patient disposition table indicates 35 subjects discontinued due to worsening of disease under study, the primary efficacy table reports 30 patients experiencing the primary efficacy outcome up to Day 180 and the discontinuation due to adverse events table shows 31 patients recording PE or DVT. Could the sponsor explain how the discrepancy in reported patient numbers with each table has been derived?
5. For subjects rolling over into the RE-MEDY trial (Study 1160.47) from just completing participation in the RE-COVER Study (Study 1160.53) bridging anticoagulation with LMWH was optional. Could the sponsor comment on whether or not there were an increased number of VTE events in subjects changing from dabigatran to warfarin who did not receive bridging anticoagulation versus those who did, and the timing of VTE events after randomisation (that is reflecting inadequate bridging anticoagulation therapy)?
6. In Studies 1160.53 and 1160.46 the pre-specified non inferiority margin was 2.75, and in Study 1160.47 the pre-specified non inferiority margin was 2.85. These appear to be overly generous. In the EINSTEIN Studies examining the effect of rivaroxaban for the treatment of VTE compared to warfarin, the non inferiority margin was 2.0. Could the sponsor provide a detailed clinical justification for the pre-specified non-inferiority margins used in Studies 1160.53, 1160.46 and 1160.47?

Safety

7. Could the sponsor comment what (if any) effect the temporary treatment interruptions as a result of sham INR readings (too low or too high) may have had on safety outcomes?
8. Could the sponsor comment as to why dabigatran (or dabigatran placebo) capsules were withheld for out of range INR results? Should treatment interruptions for too high or too low INR values have been limited to warfarin or warfarin placebo treatment? What is the rationale for ceasing both treatment arms?

Second round evaluation of clinical data

The sponsor's response addresses 8 questions that were raised in the first round clinical assessment. For details of the evaluator's assessment of the response, please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to the clinical questions, the benefits of DE 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 the clinical questions, the risks of DE in the proposed usage are unchanged from those identified in first round assessment of risks.

Second round assessment of benefit-risk balance

After consideration of the responses to the clinical questions, the benefit-risk balance of DE, given the proposed usage is favourable. There is no change to the opinion expressed in the first round assessment of benefit risk-balance.

Second round recommendation regarding authorisation

The clinical evaluator recommends acceptance of the sponsor's proposed extension of treatment indications for DE to include the treatment and prevention of recurrent VTE. The current submission provides robust evidence that treatment with DE reduces the risk of VTE recurrence when used in both the acute treatment and secondary prevention phase and the current submission has demonstrated that DE is comparable to warfarin in reducing the risk of VTE related death when commenced in the acute treatment phase. However the clinical evaluator does not recommend acceptance of the proposed treatment extension wording '*prevention of related death*' in both clinical scenarios (acute treatment phase, as well as in the extended secondary prevention period). There is insufficient evidence for the claim of '*prevention of related death*' in the extended secondary prevention period.

The clinical evaluator would recommend that approval of the sponsor's proposed extension of indication be subject to regular periodic safety update reports and the provision by the sponsor to the TGA of the final clinical study reports for the proposed post marketing studies (as outlined in the updated RMP).

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP); Pradaxa EU-RMP version 26 dated 25 April 2013 (data lock point 18 September 2012) and an Australian Specific Annex (ASA) version to EU-RMP version which was reviewed by the RMP evaluator.

Safety specification

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

Table 3. Ongoing safety concerns.

Important identified risks	Haemorrhage
	Gastrointestinal disorders
	Hypersensitivity
Important potential risks	Hepatotoxicity
	Myocardial infarction
	Pulmonary embolism
	Off-label use in patients with prosthetic heart valves
Important missing information	Patients with renal impairment (creatinine clearance ≤ 30 mL/min)
	Patients with liver impairment (lever enzymes > 2x upper limit of normal)
	Pregnant and lactating women
	Patients under 18 years
	Patients with low bodyweight

Pharmacovigilance plan

Table 4 is a summary of the proposed pharmacovigilance activities in the EU-RMP.

Table 4. Summary of proposed pharmacovigilance activities.

Risk/missing information	Pharmacovigilance activities
Important identified risks	
Haemorrhage	Routine pharmacovigilance activities Additional pharmacovigilance: Studies 1160.84, 1160.86, 1160.71, 1160.130, 1160.136, 1160.157, 1160.162 and 1160.171
Gastrointestinal disorders	Routine pharmacovigilance activities Additional pharmacovigilance: Study 1160.128
Hypersensitivity	Routine pharmacovigilance activities
Important potential risks	
Hepatotoxicity	Routine pharmacovigilance activities Additional pharmacovigilance: Study 1160.71

Risk/missing information	Pharmacovigilance activities
Myocardial infarction	Routine pharmacovigilance activities Additional pharmacovigilance: Studies 1160.71 and 1160.136
Pulmonary embolism	Routine pharmacovigilance activities Additional pharmacovigilance: Studies 1160.71 and 1160.136
Off-label use in patients with prosthetic heart valves	Routine pharmacovigilance activities
Important missing information	
Patients with renal impairment ((creatinine clearance ≤30 mL/min)	Routine pharmacovigilance activities Additional pharmacovigilance: Study 1160.173
Patients with liver impairment (liver enzymes > 2x upper limit of normal)	Routine pharmacovigilance activities
Pregnant and lactating women	Routine pharmacovigilance activities
Patients under 18 years	Routine pharmacovigilance activities
Patients with low body weight	Routine pharmacovigilance activities

The following is a list of planned studies in the pharmacovigilance plan in the EU-RMP:

- Study 1160.144 is an observational EU cross-sectional database study of new users of dabigatran that will characterise on and off label use status and other medical characteristics at the time of the first prescription. 5000 patients are expected to be recruited in each country with the final report is expected in early 2015.
- Study 1160.162 is an observational study assessing the management of gastrointestinal and urogenital bleeding events in patients with atrial fibrillation (AF) treated with dabigatran. The study is planned in the USA and Canada on 400 patients in total. The final report is expected in early 2014.
- Study 1160.173 is a prospective, open label study to evaluate the pharmacokinetics of dabigatran in non-valvular AF patients with severely impaired renal function (CrCl 15 to 30 mL/min) on dabigatran 75mg BD therapy for seven days. The final report is expected in 2014.
- Study 1160.171 (GLORIA-AF) is a global registry on long term (two years for patients initiating dabigatran and three years for all patients irrespective of anticoagulation treatment) oral anti-thrombotic treatment in patients with AF. The final report is expected in 2020.

It is understood that Australia will not be involved in Studies 1160.144 and 1160.162. The sponsor should confirm if Australian patients will be involved in Studies 1160.173 and 1160.171.

It is expected that updates and findings of the ongoing and planned studies will be communicated to the TGA and included in PSURs when available. The sponsor should provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.

Risk minimisation activities

The sponsor refers to routine and additional risk minimisation activities including educational materials and programs for prescribers. The sponsor's approach appears to be consistent with what was evaluated and accepted in the previous review.

Reconciliation of issues outlined in the RMP report

Table 5 summarises the RMP evaluator's first round evaluation of the RMP, the sponsor's responses to issues raised by the RMP evaluator and the evaluation of the sponsor's responses.

Table 5. Reconciliation of issues outlined in the RMP report.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
1. It is understood that Australia will not be involved in study 1160.144 and 1160.162. The sponsor should confirm if Australian patients will be involved in study 1160.173 and 1160.171.	The sponsor confirms that Australian patients will not be involved in studies 1160.173 and 1160.171.	The sponsor's response is acceptable.
2. It is expected that updates and findings of the ongoing and planned studies will be communicated to the TGA and included in PSURs when available.	The sponsor provided an assurance that updates and findings of the ongoing and planned studies that are referenced in the updated version of the ASA to the EU RMP will be communicated to the TGA. All data will be included in PSURs when available.	The sponsor's response is satisfactory.
3. The sponsor should provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.	Please refer to the updated version of the ASA to the EU RMP provided.	The sponsor's response is satisfactory.
4. The sponsor should provide a table summarising the safety specification, pharmacovigilance plan and planned risk minimisation	Please refer to the updated version of the ASA to the EU RMP. The ASA includes a table summarising the safety concern (that is safety specification),	The evaluator noted the summary table in the updated ASA version 26.1. The sponsor has not

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
measures in Australian context in the ASA. Wording pertaining to important safety concerns in the proposed Australian PI and CMI should be included in the table.	pharmacovigilance activities (routine and additional) and the risk minimisation activities (routine and additional).	included the safety concerns: 'patients under 18 years of age' and 'patients with low body weight' in the summary table.
5. The sponsor should specify what 'educational programs' are being proposed in Australia. Pending the approval of the current submission, updated written educational materials reflecting the changes of indications should be submitted to the TGA for evaluation before the registration of these written materials.	The sponsor has provided therapeutic area specific educational activities for dabigatran since first registration in Australia. Educational programs are regularly updated based on the dabigatran PI and regular evaluations. The programs are designed to support the safe and effective use of dabigatran across a range of approved indications through the education of prescribers and other health professionals. The programs will be updated to reflect changes including additional indications. These programs cover the following topics: Identification of patients for whom dabigatran is suitable and is not suitable Clinical data for dabigatran Selection of the suitable dose of dabigatran for each indication The importance of renal function assessment (including the Cockcroft-Gault formula) Switching patients to and from dabigatran Management of bleeding Management of elective / emergency procedures,	The sponsor's response is satisfactory. Drafts of the updated printed educational materials that reflect the changes of indications should be submitted to the TGA for review prior to the approval of the extension of indications.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	ischaemic stroke or TIA Correct storage and administration of dabigatran. Educational materials (printed and electronic) have been produced and will be continuously updated to support the above priorities, including practical guidance from Australian medical and pharmacy experts on initiating patients on dabigatran, appropriate dose selection based on the importance of age and renal function. Patient education materials have also been developed to support the appropriate use of Pradaxa. Evaluation of educational activities is undertaken for both online and face to face activities at the time of interaction by assessing changes in comprehension, knowledge and/or confidence to undertake desired safety behaviours about identified risks. For face to face meetings the assessment is through the completion of printed checklists by participants and online assessments follow a similar format. Both forms of assessment are reviewed regularly to update the overall program objectives and to make adjustments to the program as part of continual improvements to the presentation of educational activities. The sponsor continues to	

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	work closely with key Cardiologists, Stroke Physicians, Vascular Physicians, Haematologists, Emergency Physicians, Respiratory Physicians, General Practitioners and Pharmacists across Australia to update or further develop dabigatran educational materials. Where appropriate, educational programs are accredited by medical colleges or other health professional societies that require adherence to professional standards during the development and evaluation of the programs.	
6. The sponsor should specify how it plans to evaluate the effectiveness of educational materials and programs in Australia.	As stated above, evaluation of educational activities is undertaken for both online and face to face activities at the time of interaction by assessing changes in comprehension, knowledge and/or confidence to undertake desired safety behaviours about identified risks. For face to face meetings the assessment is through the completion of printed checklists by participants and online assessments follow a similar format. Both forms of assessment are reviewed regularly to update the overall program objectives and to make adjustments to the program as part of continual improvements to the presentation of educational activities.	The sponsor's response is satisfactory.
7. As the sponsor has stated	Cumulative data from the	Although the

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
in the PI concomitant use with strong P-gp inhibitors (including cyclosporine, itraconazole, tacrolimus) may lead to increased dabigatran plasma level. It is recommended to the Delegate that 'concomitant use with cyclosporine, itraconazole and tacrolimus' be added under 'contraindication' (as currently stated in Summary of Product Characteristics (SmPC) 4.3).	Boehringer Ingelheim (BI) Global Drug Safety Database (GDSD) up to database lock 31 Jan 2014 were searched for Individual Case Safety Reports (ICSRs) from post-marketing sources reporting tacrolimus, itraconazole or cyclosporin as (co-) suspect or concomitant medication. The MedDRA subSMQ 20000039 'Haemorrhage terms (excluding laboratory terms)' was used to determine cases which reported haemorrhagic adverse events. Of a total of 60,619 post-marketing ICSRs associated with Pradaxa in the GDSD, there were 8 cases reporting concomitant use of cyclosporin. Of the 8 cases, 6 reported a haemorrhagic event. Two ICSRs were retrieved which reported concomitant use of itraconazole, both of which reported bleeding events. There are 16 cases of concomitant use of tacrolimus in the GDSD; only 7 of these reported a haemorrhagic event. Of the ICSRs with these three comedications of interest, there were 3 fatal cases due to haemorrhagic events; one with itraconazole and two with tacrolimus. One of the fatal haemorrhagic events with tacrolimus occurred 2 months after discontinuation of radaxa and cannot plausibly be associated with the	number of adverse events found in the GDSD is relatively small, it should be noted that the total number of such use in practice could also be small given that concomitant use with cyclosporine, itraconazole and tacrolimus is already contraindicated according to the SmPC. The reported events included in the sponsor's response show that there is a real risk of bleeding with concomitant use of dabigatran and strong P-gp inhibitors. Therefore, the recommendation regarding PI revisions remain to the Delegate for consideration.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	combination of medicinal products. Almost all of the ICSRs reporting haemorrhages in all three groups had additional risk factors such as relevant concomitant diseases (for example renal transplantation, interstitial pneumonia, and thrombocytopenia) or comedications (for example colchicin, methotrexate, amiodarone). In summary, the number of sontaneous ICSRs received reporting concomitant use of Pradaxa and tacrolimus, itraconazole or cyclosporin are low and haemorrhagic events reported in association with this concomitant use often occur in situations with multiple risk factors, so that no clear conclusions can be drawn from the data. Only internal in vitro data exists for cyclosporin, itraconazole and tacrolimus (high inhibitory potency on dabigatran etexilate efflux with IC50 < 1 µM). In contrast to ketoconazole, no controlled clinical trial has been conducted with either drug and the observational postmarketing data as summarised above are limited, including multi-morbid patients with additional risk factors (co-medications, phenotypic risk factors) such that this data does not allow any clear conclusion.	

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	In light of the lack of available clinical data the sponsor disagrees with the RMP evaluator's recommendation to add concomitant use with cyclosporin, itraconazole and tacrolimus as a Contraindication. The current approved Australian PI includes the following Precautionary information related to cyclosporin, itraconazole and tacrolimus: '*The concomitant use of PRADAXA with the following treatments has not been studied and may increase the risk of bleeding: unfractionated heparins (except at doses necessary to maintain patency of central venous or arterial catheter) and heparin derivatives, LMWHs, fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfinpyrazone, rivaroxaban, prasugrel, vitamin K antagonists, and the P-gp inhibitors itraconazole, tacrolimus, cyclosporin, ritonavir, tipranavir, nelfinavir and saquinavir (see Interactions with other medicines, Anticoagulants and platelet aggregation agents).* *Coadministration of dabigatran etexilate with strong P-gp inhibitors (amiodarone, clarithromycin, nelfinavir, ritonavir, saquinavir, and verapamil) should be used with caution and close clinical surveillance*	

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	(looking for signs of active bleeding or anaemia) is required, due to a potential risk of higher plasma levels of dabigatran and consequent potentially exaggerated pharmacodynamic effect of dabigatran etexilate (notably bleeding risk) (see Precautions, Interactions with other medicines). The concomitant use of dabigatran etexilate with cyclosporin, tacrolimus or itraconazole is not recommended.'	

An additional round of review of the RMP occurred to resolve outstanding issues from the table above.

Issue relating to recommendation 4

The sponsor should include the safety concerns 'patients under 18 years of age' and 'patients with low body weight' in the summary Table 2 in '5.2 Addendum to Part VI summary of the RMP PVI.' of the ASA.

Sponsor's response

The sponsor agrees to include 'patients under 18 years of age' and 'patients with low body weight' in the ASA to the EU RMP as important missing information.

RMP evaluator's comment

The sponsor's response is satisfactory.

Issue relating to recommendation 5

The drafts of updated printed educational materials that reflect the changes of indications should be submitted to the TGA for review prior to the approval for the extension of indications.

Sponsors response

Since the application is still ongoing the sponsor has not yet updated the Pradaxa educational materials. The sponsor continuously updates all educational materials to appropriately reflect both the current therapeutic area and products related information. As such the sponsor provides a commitment to update the Pradaxa educational materials to reflect the updated indications and to provide these to the TGA when available.

RNP evaluator's comment.

The sponsor's response is satisfactory.

Issue relating to recommendation 7

As the sponsor has stated in the PI, concomitant use with strong P-gp inhibitors (including cyclosporine, itraconazole, tacrolimus) may lead to increased dabigatran plasma level. It is

recommended to the Delegate that 'concomitant use with cyclosporine, itraconazole and tacrolimus' must be added under 'contraindication' (as currently stated in SmPC 4.3).

Sponsor's response

The sponsor agrees with the TGA recommendation to include cyclosporin and itraconazole to the list of Contraindications as follows:

- Concomitant treatment with systemic ketoconazole, cyclosporin, itraconazole or dronedarone (see Precautions).

However, the sponsor disagrees with the recommendation to include tacrolimus to the list of Contraindications. The current Australian PI is aligned with the current EU SmPC that is '*The concomitant use of dabigatran etexilate with … tacrolimus … is not recommended*'.

RMP Evaluator's comment

The recommendation made regarding the PI, remains for consideration by the Delegate.

Summary of recommendations

The recommendation on the revision to the draft PI remains, awaiting consideration by the Delegate.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

In addition to the information presented, the ACSOM referred to papers by Takano et al.,[6] Moore et al.[7] and Reilly et al.[8] during its consideration.

The committee provided advice on specific questions asked by the TGA relating to a RMP.

1. *The sponsor has provided a list of important safety concerns for dabigatran. Can the committee advise whether there are additional safety risks related to the use of dabigatran for the revised indications and dosage proposals?*

The ACSOM noted the list of important safety concerns (identified risks, potential risks and missing information) that were provided by the sponsor. In considering whether there are additional risks related to the use of dabigatran for the revised indications and dosage proposals, the committee advised that the following should be added to the Summary of safety concerns:

- Use in elderly (as use of dabigatran generally appears less favourable compared to warfarin in this age group versus others);
- Patients requiring rapid reversal of effect (for example semi-urgent surgery), especially in patients with compromised renal function; and
- Extensive drug-drug and food-drug interactions (known and unknown).

2. *In its response to the clinical evaluator's questions the sponsor provided justification for not conducting routine, initial or intermittent laboratory monitoring for the proposed indications. Can the committee advise whether there is evidence to support laboratory monitoring for the proposed indications?*

The ACSOM noted the sponsor's tabulation of steady state total dabigatran trough concentrations in both the proposed indications and in AF patients (the current, approved indication) treated with 150 mg BD, showing at least a doubling in exposure in the oldest

[6] Takano, M et al. Expression and function of efflux drug transporters in the intestine *Pharmacology & Therapeutics* 2006; 109: 137-161.
[7] Moore TJ, et al. Dabigatran, bleeding, and the regulators. *BMJ* 2014; 349: 4517.
[8] Reilly PA, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients. *J Am Coll Cardiol* 2014; 63: 321-328.

cohort of patients and a trebling in exposure in patients with the lowest renal function. The sponsor's data also showed an increase in major and clinically relevant bleeding events with age in the pivotal studies for the proposed indication. In particular, there was a three-fold increase in bleeding events between patients aged under 65 years versus those over 80 years.

The ACSOM concluded that for the proposed indication, as for the approved AF indication, there were a priori reasons to consider that safety monitoring of dabigatran may be appropriate.

The therapeutic range has been modelled in relation to optimising the therapeutic plasma concentration for AF patients. However, for the proposed indications there were no data on: the therapeutic range; whether monitoring would help in the clinical management of patients (that is, extent of dosage adjustment required following determination of a patient's plasma level); or the plasma levels associated with serious adverse events. Further, there was no direct evidence provided to the committee which clarified the choice between one-off testing and regular ongoing monitoring.

A therapeutic concentration range has been modelled in an attempt to optimise safety and efficacy for AF patients. There is insufficient data to allow a similar modelling of therapeutic concentration range relevant to the new indication of venous thromboembolic event (VTE) or direct data on whether intervention would help. In principle, being able to assign an individual's likelihood of a major bleeding event based on plasma levels appeared to be good clinical practice. Monitoring of the therapeutic range could lead to a decrease in adverse events without compromise of efficacy.

The ACSOM also advised that there appeared to be gaps in the data provided by the sponsor to allow determination of a plasma concentration range. Areas where the sponsor could be asked to provide additional information include information from both published and unpublished trials, and post-marketing reports:

- individual patient information for patients who experienced adverse bleeding events and adverse clotting events;
- pharmacokinetic/pharmacodynamic data on these patients, preferably taken at the time of hospitalisation after the event; that is, dabigatran levels, coagulation studies (ECT, diluted Thrombin Time (dTT), activated Partial Thromboplastin Time (aPTT), INR, other relevant tests), ideally including time in relation to the event and also time from last dose and routine doses; and
- any relevant risk factor data on these same patients (age, serum creatinine, estimated glomerular filtration rate (eGFR), weight, antiplatelet treatment, treatment indication and duration of treatment before event).

The ACSOM noted that comparisons with warfarin were (largely) irrelevant to strategies for risk reduction in individuals on dabigatran, and that risk minimisation strategies should focus on maximising the safety of dabigatran per se.

Other

The ACSOM noted the comment in the PI that an increase in bioavailability of dabigatran etexilate may occur if the capsule shells are opened and the capsule content is sprinkled over food or into beverages. This risk of unintentional over dosage, including to toxic levels, was particularly relevant to the elderly including those in residential aged care facilities. The TGA noted this comment and would consider whether further action was required.

The ACSOM noted that the Consumer Medicine Information (CMI) included as a contraindication, 'stomach bleeding in the past year, unless it has been fixed' and drug interactions referring to 'selective serotonin re-uptake inhibitors' and 'selective serotonin

norepinephrine re-uptake inhibitors' without generic or brand name examples of the medicines in these therapeutic classes. The committee advised that this information did not seem helpful to consumers.

Outstanding issues

All outstanding issues raised in the RMP evaluations were resolved after the ACPM.

On 13 July 2015, the sponsor provided an updated EU-RMP version 31.2 dated 29 May 2015 (data lock point 18 March 2015), ASA version to EU-RMP version 31.2 dated 10 July 2015.

Key changes to the updated RMP

Key changes from the version evaluated at the last RMP advice are summarised below in Table 6.

Table 6. Key changes to the updated RMP.

Safety specification	**Important identified risk:** Off-label use in patients with severe renal impairment is added; Off-label use in patients with prosthetic heart valves is upgraded from 'potential' to 'identified' risk. <u>Important missing information:</u> Patients with renal impairment, patients under 18 years, patients with low body weight have been deleted from the list.
Pharmacovigilance activities	Routine and additional pharmacovigilance is consistent with what has been evaluated and agreed previously by the TGA
Risk minimisation activities	Routine and additional risk minimisation activities are largely consistent with what has been evaluated and agreed previously by the TGA. Additional warnings in PI are added against the following: **Important identified risk** – haemorrhage, gastrointestinal disorders, off-label use in patients with severe renal impairment. **Important potential risk** – hepatotoxicity, myocardial infarction, pulmonary embolism, patients with liver impairment. **Missing information** – patients under 18 years of age and patients with low body weight.

RMP evaluator comment

The evaluator had no objections for the content of the key updates.

Recommendation

Implement EU-RMP version 26 dated 25 April 2013 (data lock point 18 September 2012) with ASA 26.1 and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

This submission had several mutually agreed pauses in the evaluation process which were negotiated between the sponsor and TGA. To assist the reader, a timeline is presented here:

- The Delegate's request for ACPM advice issued to the sponsor on 1 July 2014, for the August 2014 ACPM meeting.
- The sponsor requested a pause to allow for additional analyses to be conducted seeking to address the questions raised by the Delegate. Consideration by the ACPM was deferred.
- During this pause publications raised concerns about the monitoring of dabigatran for the currently approved indication of stroke prevention. These publications and the sponsor's response to them along with further information regarding monitoring were reviewed by the TGA and advice was sought from ASCOM (ACSOM Meeting 24 September 2014).
- The Delegate formally requested the sponsor address a number of additional questions (these questions are presented under 'Delegates request for additional information' and the response as 'sponsor's response to Delegates request for additional information'. The consideration by ACPM at this stage was deferred.
- The RMP evaluator sought advice from ACSOM regarding the RMP for the proposed VTE indication (this submission). The advice from ASCOM together with the sponsor's response to ASCOM was provided to the June 2015 ACPM together with an additional request for advice from the ACPM by the Delegate.
- Additional advice was sought from the August 2015 ACPM by the Delegate regarding PI matters.

The submission was summarised in the following Delegate's overview and recommendations provided to the August 2014 ACPM:

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

The clinical dossier included the following data:

- 1 clinical pharmacology sub study that provided pharmacokinetic and pharmacodynamic data.
- 4 pivotal efficacy/safety studies:
  - DVT/PE treatment: RE-COVER (Study 1160.53) and RE-COVER II (Study 1160.46)
  - DVT/PE prevention: RE-SONATE (Study 1160.63) and RE-MEDY (Study 1160.47)
- Pooled efficacy analyses.

Pharmacology

The pharmacology sub study of the DVT/PE treatment study, RE-COVER, noted the following findings:

- Changes in dabigatran concentrations with renal impairment were comparable with the changes observed in the RELY trial for the stroke prevention indication in AF patients. The trough concentrations in patients by renal impairment were as follows:
  - CrCl of ≥ 80 mL/min was 50.5 ng/mL
  - CrCl of 50 to 80 mL/min was 85.8 ng/mL
  - CrCl of 30 to 50 mL/min was 170 ng/mL
  - CrCl of < 30 mL/min was 191 ng/mL (contraindicated group)
- Body weight had a minor influence on trough concentrations.
- Concomitant verapamil results in higher dabigatran trough concentrations.
- There is some data to support a relationship between higher dabigatran plasma concentrations and bleeding events; however a potential relationship between lower dabigatran concentrations and recurrent VTE is not established.
- Trough dabigatran concentrations at 30 days are higher in females (69.6 ng/mL) compared to males (53.8 ng/mL) and in older patients as follows:
  - Age ≥ 75 years was 121 ng/mL
  - Age 65 to 75 years was 70.6 ng/mL.
- There is some pharmacodynamic data to suggest a possible relationship between higher activated partial thromboplastin time (aPTT) and ecarin clotting time (ECT) results and bleeding events but it remains unclear whether or not low aPTT and ECT values are associated with recurrent VTE.

Efficacy

Indication 1: Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of related death

Study RE-COVER (Study 1160.53)

Study design

This was a 6 month, Phase III, randomised, double blind, multicentre, multinational, double dummy, parallel group, active controlled, non inferiority trial of DE 150 mg BD compared with warfarin (target INR 2 to 3, mean 66% of the time in the range at 6 months) in 2,564 patients with acute symptomatic VTE (unilateral or bilateral proximal DVT of the legs and/or symptomatic PE) following initial treatment for 5 to 10 days with an approved parenteral anticoagulant. The trial had two phases: an initial open label parenteral therapy with warfarin or placebo (sham INR) and then a double dummy period of blinded oral therapy with DE plus warfarin-like placebo or active warfarin and DE-like placebo. After 6 months, patients could continue standard oral anticoagulation or switch to one of two DE prevention studies. DVT was detected by ultrasonography or venography and PE by ventilation perfusion lung scan, pulmonary angiography or spiral helical computerised tomography (CT) scan. Patients were stratified by active cancer and symptomatic PE status. Exclusion criteria included: VTE for longer than 2 weeks, PE with haemodynamic instability, another indication for anticoagulation, excessive risk of bleeding, hepatic dysfunction and need for moderate to strong P-gp inhibitors.

Treatment completion was 84 to 86%. Baseline subject and disease characteristics were similar between the groups: 58% male, mean 55 years, 31% ≥ 65 years, mean body mass index (BMI) 28.6 kg/m^2, 72% CrCl ≥ 80 mL/min, 22% CrCl 50 to 79mL/min, 36% hypertension, 6.5% coronary artery disease, 69% symptomatic DVT alone, 21% symptomatic PE alone, 9.6% both DVT and PE, 69% with risk factors for recurrent VTE

and 15% had prior anticoagulation therapy. Concomitant medications included: 15% to 19% NSAIDs, 8% aspirin, 1.2% verapamil, 1.3 to 2.4% low molecular weight heparin. The study had 90% power to claim non inferiority with a HR of 2.75 (upper bound of 95% CI) for DE versus warfarin and an absolute increase in risk of 3.6%. This estimated that DE preserved at least 57% of the warfarin effect versus placebo with regards to the HR and at least 75% of the warfarin effect versus placebo with regard to the risk difference.

Results

The primary efficacy endpoint of composite recurrent symptomatic VTE or VTE related death (centrally adjudicated) using the full analysis set was 2.67% on DE versus 2.53% on warfarin, (HR 1.05, 95%CI 0.65, 1.70, $p < 0.0001$ for non inferiority, $p = 0.85$ for superiority). Since the upper bound of the 95% CI was less than 2.75, then non inferiority was concluded but superiority was not seen. The majority of events were symptomatic DVT and then symptomatic non-fatal PE with only 4 VTE related deaths (1 on DE and 3 on warfarin). A sensitivity analysis that used the per protocol set confirmed the primary analysis. The cumulative risk difference at Day 180 was 0.4% (95%CI -0.8, 1.5, $p < 0.0001$ for non inferiority, $p = 0.5026$ for superiority). Subgroup analysis was mostly consistent with the primary endpoint except for three groups where VTE frequency was higher on DE: previous VTE, more than one parenteral therapy and concomitant NSAIDs (HR 4.93, 95%CI 1.05, 23.23). The primary endpoint was also higher in patients presenting with symptomatic PE than no PE and active cancer than no active cancer.

Secondary endpoints were mostly supportive:

- Recurrent symptomatic VTE and all cause death: 3.9% on DE versus 3.6% on warfarin
- Symptomatic DVT: 1.3% on DE versus 1.5% on warfarin
- Symptomatic non-fatal PE: 1.1% on DE versus 0.6% on warfarin. It was noted that the risk of recurrent PE was highest in patients on DE who had an initial symptomatic PE and active cancer (5.9% on DE versus zero on warfarin)
- VTE related death: 0.1% on DE versus 0.2% on warfarin
- All deaths: 1.6% on DE versus 1.7% on warfarin.

Study RE-COVER II (Study 1160.46)

Study design

This study was a replicate of the RE-COVER trial with the design difference being initial treatment with a parenteral anticoagulant of at least 5 days compared with 5 to 10 days with RE-COVER. The study was conducted in 2,589 patients for 6 months. Patients on warfarin were in the target INR range less in this study at 58.9% of the time at 6 months. Treatment completion was 85 to 86%. Baseline subject and disease characteristics were similar between the groups: 61% male, mean 55 years, 31% ≥ 65 years, mean BMI 28.4 kg/m^2, 73% CrCl ≥ 80 mL/min, 22% CrCl 50 to 79 mL/min, 35% hypertension, 7.1% coronary artery disease, 68% symptomatic DVT alone, 23% symptomatic PE alone, 8.6% both DVT and PE, 59% with risk factors for recurrent VTE. Concomitant medications included: 22% NSAIDs, 9% aspirin, 0.7% verapamil, 1 to 1.4% LMWH.

Results

The primary efficacy endpoint of composite recurrent symptomatic VTE or VTE related death (centrally adjudicated) using the full analysis set was 2.66% on DE versus 2.33% on warfarin, (HR 1.13, 95%CI 0.69, 1.85, $p = 0.0002$ for non inferiority, $p = 0.62$ for superiority). The results are similar to RE-COVER with the upper bound of the 95% CI being less than 2.75, thus non inferiority was concluded but superiority was not seen. The majority of events were symptomatic DVT and then symptomatic non-fatal PE with only 1 VTE related death (1 on DE and zero on warfarin). The cumulative risk difference at

Day 180 was 0.2% (95%CI -1.0, 1.3, p < 0.0001 for non inferiority, p = 0.7756 for superiority). Subgroup analysis was consistent with the primary endpoint except for current smokers where the incidence was higher on dabigatran (HR 4.1, 95%CI 1.16, 14.54). Secondary endpoints were mostly supportive:

- Recurrent symptomatic VTE and all cause death: 4.0% on DE versus 3.8% on warfarin
- Symptomatic DVT: 2.0% on DE versus 1.3% on warfarin (risk difference -0.6%, 95CI% -0.3, 1.5)
- Symptomatic non-fatal PE: 0.6% on DE versus 1.0% on warfarin
- VTE related death: 0.2% on DE versus zero on warfarin
- All deaths: 2.0% on DE versus 2.0% on warfarin.

Pooled analysis

A pooled analysis of the above studies showed the primary efficacy endpoint occurred in 2.7% for DE and 2.4% for warfarin, HR 1.09 (95%CI 0.77, 1.54), with a non significant p-value for heterogeneity and an overall excess of 0.4 events (VTE and VTE related deaths) in 100 patient years of treatment for patients on dabigatran compared to warfarin.

Indication 2: Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and related death

Study RE-SONATE (Study 1160.63)

Study design

This was a 6 month, Phase III, randomised, double blind, multicentre, multinational, parallel group, placebo controlled trial of DE 150 mg BD compared with placebo in 1,353 patients with confirmed symptomatic PE or proximal DVT of the leg which had been treated for 6 to 18 months with oral vitamin K antagonists (INR 2 to 3) to determine if DE was superior to placebo in the long term prevention of acute symptomatic VTE. Patients from RE-COVER were eligible to enrol (n = 15 for DE and n = 12 for placebo were from RE-COVER). Exclusion criteria included: extended need for anticoagulation, high risk of bleeding, hepatic dysfunction and need for moderate to strong P-gp inhibitors. Treatment completion was 91 to 95%. The mean time between qualifying VTE episode and randomisation was 9.7 months. Baseline subject and disease characteristics were similar between the groups: 56% male, mean 56 years, 21% ≥ 70 years, mean BMI 28.4 kg/m^2, 70% CrCl ≥ 80 mL/min, 25% CrCl 50 to 79 mL/min, 39% hypertension, history of myocardial infarction (2.1% on DE versus 0.8% on placebo), 65% symptomatic DVT alone, 28% symptomatic PE alone, 7.2% both DVT and PE. Concomitant medications included: 11.9% NSAIDs, 7.7% aspirin. The study had 95% power to demonstrate superiority, assuming a 70% reduction in DE treatment group compared to placebo.

Results

The primary efficacy endpoint was the incidence of recurrent symptomatic VTE (DVT, PE and unexplained deaths) which occurred at 0.4% on DE versus 5.6% on placebo (HR 0.08, 95%CI 0.02, 0.25, p < 0.0001) thus showing superiority of DE. Symptomatic VTE events were reduced by at least 75%. Sensitivity analyses confirmed the primary endpoint result and subgroups analyses did not show a significant effect. Components of the primary endpoint were also less on DE than placebo (DVT: 0.3% versus 3.3%, PE: 0.1% versus 2.1%). The secondary endpoint of recurrent symptomatic VTE excluding unexplained deaths showed similar findings to the primary endpoint given there were only two unexplained deaths and both were on placebo. In the extended follow up period when DE was ceased, the rate of VTE events increased to 6.9% on DE versus 10.7% on placebo.

Study RE-MEDY (1160.47)

Study design

This was a 6 to 36 months, Phase III, randomised, double blind, parallel group, active controlled trial of DE 150 mg BD compared with warfarin (target INR 2 to 3, mean 66% of the time in the range at 6 months) in 2,866 patients with confirmed symptomatic PE or proximal DVT of the leg which had been treated for 3 to 12 months with either a vitamin K antagonist (INR 2 to 3) or DE if rolling over from RE-COVER (about 35%) or RE-COVER II (about 5%). Subjects were randomised based on presence or not of cancer and symptomatic PE. Exclusion criteria were similar to RE-COVER. The objective was to compare DE with warfarin for the long term treatment and secondary prevention of symptomatic VTE in patients who had been treated with DE as part of the RE-COVER or RE-COVER II trials or another anticoagulant for 3 to 12 months for confirmed VTE. The study had an initial 85% power to claim non inferiority with a HR of 2.85 (non inferiority margin) and a primary event rate of 2% in both groups and a 2.8% risk difference (second non inferiority margin) in VTE at 18 months. Both non inferiority margins had to be achieved which preserves at least 70% of the warfarin effect versus placebo for the HR and two thirds of the warfarin effect against placebo for the risk difference. During the trial, the total HR was 1.2% over 18 months which reduced the power to 66% to prove non inferiority, therefore to maintain power at 80% at least, the treatment duration of patients was extended to up to 36 months. Treatment completion was 80 to 81% (treatment stopped early mostly due to adverse events). The mean time between qualifying VTE episode and randomisation was 199 days. Baseline subject and disease characteristics were similar between the groups: 61% male, mean 55 years, 30% ≥ 65 years, mean BMI 29.1 kg/m^2, 74% CrCl ≥ 80 mL/min, 22% CrCl 50 to 79 mL/min, 39% hypertension, 7.2% coronary artery disease, 65% symptomatic DVT alone, 23% symptomatic PE alone, 11.7% both DVT and PE. Concomitant medications included: 18% NSAIDs, 6.7% aspirin.

Results

The primary efficacy endpoint of centrally adjudicated recurrent VTE or VTE related death was 1.8% on DE versus 1.3% on warfarin (HR 1.44, 95%CI 0.78, 2.64, p = 0.0137 for non inferiority, p = 0.2424 for superiority). The majority of events were symptomatic DVT and then symptomatic PE with only one death in each group. The upper bound of the 95% CI was less than 2.85, thus non inferiority was concluded but superiority was not seen. The risk difference at 18 months was 1.74% on DE versus 1.38% on warfarin (risk difference 0.38%, 95%CI -0.50, 1.25%, p < 0.0001 for non inferiority, p = 0.4013 for superiority). Sensitivity analyses were consistent with the primary analysis for per-protocol set, on treatment analysis and observation period). The primary endpoint was higher in patients with PE or active cancer as their qualifying event. Subgroup analysis was also consistent with the primary endpoint except for those with a higher BMI (risk difference 3.11%) and CrCl of 50 to 80 mL/min (risk difference of 2.04%). Secondary efficacy endpoints showed:

- Recurrent symptomatic VTE and all cause death: 2.94% on DE versus 2.52% on warfarin
- Symptomatic DVT: 1.2% on DE versus 0.9% on warfarin (CER (Attachment 2) incorrectly states 1.9% for DE)
- Symptomatic non-fatal PE: 0.7% on DE versus 0.35% on warfarin
- VTE related death: 1 person on DE versus 1 person on warfarin
- All deaths: 1.2% on DE versus 1.3% on warfarin.

Safety

A total of 4,387 patients were exposed to DE along with 3,707 to warfarin and 659 to placebo. The mean exposure to DE was 277.6 days with 163 days in the treatment studies and 473 days in the warfarin controlled prevention study and 165 days in the placebo controlled prevention study. The overall incidence of adverse events was similar in the treatment studies between DE and warfarin (RE-COVER: 66% versus 68%, RE-COVER II: 67% versus 71%) with gastrointestinal disorders being most common (RE-COVER: 25% versus 19%, RE-COVER II: 23% versus 23%). This was mainly due to diarrhoea and dyspepsia. Epistaxis, dyspnoea, haematuria and investigation adverse events were higher on warfarin. Hepatobiliary disorders were slightly higher on DE. In the prevention studies, adverse event incidence overall was comparable with warfarin and placebo (RE-SONATE: 51% versus 49%, RE-MEDY: 72% versus 71%). Gastrointestinal AEs were higher on DE than placebo and warfarin which was mostly due to diarrhoea, dyspepsia and rectal haemorrhage (versus placebo). Investigation AEs and epistaxis were higher on warfarin. AEs on DE were higher in those 65 years and older than younger patients, females than males, worsening renal function and those taking P-gp inhibitors. Adverse drug reactions were similar to slightly less on DE than warfarin but higher on DE than placebo.

Bleeding events

Major bleeding events in RE-COVER occurred in a similar number of patients on DE and warfarin (1.6% versus 1.9%) with the cumulative risk of MBEs at 6 months being 1.7% on DE versus 2.0% on warfarin. Bleeding risk was higher in those with active cancer at baseline compared to those with no active cancer, which was higher during the first month. Patients with MBEs and/or CRBEs was slightly less on DE than warfarin (5.6% versus 8.8%) and any bleeding event was also less on DE than warfarin (16.3% versus 22.1%, HR 0.71, 95%CI 0.59, 0.85) indicating significantly less overall bleeding on DE than warfarin. In RE-COVER II, MBEs occurred on DE versus warfarin at 1.2% versus 1.7% with the cumulative risk of MBEs at 6 months being 1.2% on DE versus 1.8% on warfarin. Bleeding risk was higher in those with active cancer at baseline compared to those with no active cancer. Patients with MBEs and/or CRBEs was slightly less on DE than warfarin (5.0% versus 7.9%) and any bleeding event was also less on DE than warfarin (15.6% versus 22.1%, HR 0.67, 95%CI 0.56, 0.81), indicating significantly less overall bleeding on DE than warfarin. Bleeding locations in both trials were urogenital, nasal and gastrointestinal. Similar numbers of patients needed blood transfusions on DE and warfarin.

Bleeding events in the prevention studies were different to the treatment studies. In the placebo controlled trial, RE-SONATE, MBEs occurred in only 2 patients on DE (both gastrointestinal haemorrhage) and none on placebo. CRBEs were significantly higher on DE than placebo (5.3% versus 1.8%, HR 2.92, 95%CI 1.52, 5.6) and any bleeding was also significantly higher on DE than placebo (10.5% versus 5.9%). In the warfarin controlled study, MBEs occurred less on DE than warfarin at 0.9% versus 1.8% as did MBEs and/or CRBEs (5.6% versus 10.2%) and any bleed (19.4% versus 26.2%, HR 0.71, 95%CI 0.61, 0.83). One patient died on warfarin from a cerebral haemorrhage and two non-fatal intracranial bleeds occurred on DE and warfarin. Bleeding locations in this trial were urogenital, nasal and gastrointestinal and about half the number of patients needed a transfusion on DE compared to warfarin.

Acute coronary syndrome

Acute coronary syndrome events that were suspected occurred as follows in the four studies:

- RE-COVER: 0.7% on DE versus 0.4% on warfarin
- RE-COVER-II: 0.9% on DE versus 0.6% on warfarin

- RE-SONATE: 0.4% on DE versus 0.3% on placebo
- RE-MEDY: 2.2% on DE versus 1.4% on warfarin

The analysis of definite or likely ACS events that were centrally confirmed showed a statistically significant higher incidence in the DE group compared to warfarin in the RE-MEDY study (0.9% versus 0.2%).

Deaths and other serious adverse events

Deaths in the studies were similar between DE and warfarin (RE-COVER: 2.1% versus 2.3%, RE-COVER II: 2.4% versus 2.2%, RE-MEDY: 0.8% versus 1.3% during treatment) and in the placebo controlled prevention trial it was one patient on DE and 2 on placebo during the treatment period. Malignancy was the most common cause of death.

Serious adverse events occurred at a similar incidence on DE and warfarin (RE-COVER: 13% versus 11.8%, RE-COVER II: 12.2% versus 11.9%, RE-MEDY: 15.9% versus 15.7%) with recurrent VTE being common. SAEs were less on DE than placebo in RE-SONATE (6.9% versus 9.1%) mainly due to recurrent VTE on placebo. Discontinuations due to AEs were similar or higher on DE than warfarin and mainly due to recurrent VTE for the treatment studies or cardiac disorders in the prevention study. Discontinuations were less on DE than placebo mainly due to recurrent VTE on placebo.

Safety issues with the potential for major regulatory impact

Liver function abnormalities in the treatment studies tended to be similar or slightly higher on warfarin with the mean changes being small and mostly related to ALT or AST. In RE-COVER, there were 6 cases (2 on DE and 4 on warfarin) meeting Hy's law during treatment, of which all were obstruction and 4 had neoplasms. In the prevention study with placebo, liver function test (LFT) abnormalities were similar between DE and placebo with no potential Hy's law cases and in the prevention study with warfarin, LFT abnormalities were also similar between DE and warfarin with 4 potential Hy's law cases (2 on DE and 2 on warfarin) with both DE cases having liver or pancreatic cancer. Kidney function and clinical chemistry abnormalities were low and similar between DE and warfarin. Decreases in haemoglobin were similar on DE and warfarin. No significant treatment related differences were seen in ECG changes or vital signs. Adverse events in older patients were increased compared to younger but tended to be similar between DE and warfarin.

Clinical evaluator's recommendation

The clinical evaluator has recommended approval for dabigatran for the new indications but has not supported the claim of prevention of related death in both indications.

Risk management plan

The RMP evaluator has accepted the EU RMP for Pradaxa (dabigatran), version 26, dated 25 April 2013 (data lock point 18 September 2012), with the ASA, version 26.1.

The following were outstanding matters that were followed up with the RMP evaluator prior to finalisation of this submission and responded to in the Pre-ACPM Response:

- The sponsor should include 'patients under 18 years of age' and 'patients with low body weight' in the RMP since there is missing information in these groups.
- Updated printed educational materials should be provided to TGA (OPR) for review prior to finalisation of this submission that reflects the updated indications.
- Concomitant use with strong P-gp inhibitors may increase the risk of serious bleeding since dabigatran etexilate is a substrate of the efflux transporter P-gp, therefore

co administration with a P-gp inhibitor may increase dabigatran plasma levels. Although there are no drug interaction studies with these medicines, reports of bleeding, including fatal bleeding, have occurred when given concomitantly. Although there may have been other explanations and the number of cases is small, the risk is significant for patients. There have been 6 haemorrhagic events with cyclosporine reported, 2 with itraconazole and 7 with tacrolimus. The PI currently warns that concomitant use with cyclosporine, tacrolimus and itraconazole is not recommended and the EU SmPC includes cyclosporine and itraconazole as contraindications and tacrolimus as not recommended. Dronedarone and ketoconazole are currently contraindicated in the Australian PI, therefore given the adverse events observed, it seems reasonable to also contraindicate cyclosporine, tacrolimus and itraconazole.

Please note that subsequent to the ACPM, the sponsor submitted an amended RMP EU-RMP version 26 dated 25 April 2013 (data lock point 18 September 2012) with ASA 26.1. This was evaluated by the RMP evaluator and all outstanding issues (see above) were resolved.

Risk-benefit analysis

Delegate's considerations

Efficacy: Indication 1

The RE-COVER study showed no statistically significant difference between dabigatran and warfarin on the primary efficacy endpoint for treatment of DVT and/or PE with less DVTs and fatal PEs but more symptomatic PEs on DE than warfarin and the same number of deaths. In RE-COVER II, which was a similar trial to RE-COVER, there was also no statistically significant difference between treatment groups, with the results showing DE was associated with more symptomatic DVTs and fatal PEs than warfarin, but less non-fatal PEs. The pooled analysis showed the primary efficacy endpoint occurred in 2.7% for DE and 2.4% for warfarin, HR 1.09 (95%CI 0.77, 1.54) and an overall excess of 0.4 events (VTE and VTE related deaths) in 100 patient years of treatment for patients on DE versus warfarin. The studies assessed appropriate endpoints, consistent with the EU guidelines and the trials were of adequate design. The pre-specified non inferiority margin was very wide (2.75) and wider than that used in the rivaroxaban trials (2.0), however the actual results showed a confidence interval upper limit that was well within this margin at 1.70 for RECOVER and 1.85 for RECOVER-II thus supporting the validity of the data. Warfarin control in the studies (RECOVER: mean 66% and RECOVER II mean 58.9% in the INR range of 2 to 3, overall median of 60.6%) appeared sub-optimal but was considered to reflect real life practice. In the RELY[9] trial, a median time in the therapeutic range was 67% and in the rivaroxaban trial for the treatment of acute DVT which is approved in Australia, the percentage of time in the therapeutic range was 57.7% overall and 66.4% at month 10). Good warfarin control should be > 70% of the time in the therapeutic range, so these trials were less. Better warfarin control may have provided different results. The populations in the trial differed in some aspects to expected Australian practice in that those at high bleeding risk were excluded, the majority had normal renal function and the incidence of VTE is highest in those > 70 years compared to the mean age of 55 years in the trials. However, almost a third of the patients were over 65 years of age. Therefore there are some limitations in the generalisability of the data.

The dose selected for the pivotal studies was based on the findings from the stroke prevention data that used 150 mg BD and similar patient characteristics with the proposed indication population. Although this is partially reasonable, a 110 mg BD dose is

[9] RELY trial was submitted for a previous application for Pradaxa.

also approved for stroke prevention in AF and therefore this dose should also have been investigated in the proposed VTE indications, especially for patients with moderate renal impairment, age > 75 years and those at higher risk of bleeding.

Efficacy: Indication 2

The RE-SONATE study showed DE was superior to placebo in preventing recurrent VTE during a 6 month period however when DE was ceased in the extended follow up period, the incidence of VTE was similar to the control group indicating there is no preservation of effect following discontinuation. In RE-MEDY, DE was non-inferior to warfarin for the prevention of recurrent symptomatic VTE although the results numerically favoured warfarin (primary endpoint: 1.8% versus 1.3%). The endpoints used in the studies were appropriate for secondary prevention and the studies were of adequate design and duration. Again, the non-inferiority margin was wide (2.85) for the RE-MEDY study as per the RECOVER studies but the upper limit of the confidence interval was closer to the margin this time at 2.64. The sponsor explained that no published data existed at the time for this indication to validate an appropriate margin and therefore such a wide margin retains some concern regarding dabigatran's benefit compared to warfarin but a calculation shows that dabigatran preserves at least 50% of the treatment benefit in this indication. Again the warfarin control appeared suboptimal but similar to the RELY study for stroke prevention. The data had similar generalisability issues as per the RE-COVER trials.

Safety and RMP

The safety data was of a sufficient amount and duration and appeared mostly acceptable and consistent with the previous understanding of dabigatran's profile. Overall adverse event rates were similar on DE compared to warfarin and placebo and bleeding events tended to occur at a similar rate on DE than warfarin for major bleeds, clinically relevant bleeds and any bleed. Bleeding events were however higher on DE than placebo. Deaths and serious adverse events occurred at a similar incidence on DE and warfarin. Liver function abnormalities showed a similar frequency and severity on DE and warfarin. Two major concerns remain: increased risk of bleeding compared to placebo but similar to warfarin and an increased incidence of myocardial infarction compared to warfarin (significant in one of three warfarin controlled studies). Bleeding locations tended to be higher from nasal and urogenital tracts on warfarin and higher from the gastrointestinal tract on DE. Three of the four studies (all warfarin controlled) showed myocardial infarctions were higher on DE than warfarin, which was statistically higher on DE than warfarin in the prevention study RE-MEDY (absolute risk increase of 0.7%). The two treatment studies had an absolute risk increase of about 0.3% which was not statistically significant. It has been suggested that DE does not directly precipitate ACS events but rather warfarin is more protective but this has not been proven and therefore remains an ongoing concern.

On balance, the data are sufficient and supportive of a new indication for dabigatran with efficacy demonstrated to be non inferior to warfarin for DVT/PE treatment and non inferior to warfarin and superior to placebo in prevention of recurrence of DVT/PE. The safety profile is acceptable and similar to warfarin but worse on dabigatran than placebo for bleeding events (major, clinically relevant and overall). Bleeding risk remains a concern and a similar signal of increased risk of myocardial infarction compared to warfarin has again been seen, this time in three studies. Concern remains about whether a lower dose is needed in some populations and the lack of an available antidote and method of monitoring anticoagulation should it be needed.

Dose in special populations

The clinical evaluator has supported the standard 150 mg BD dose for some populations however in the past there has been a lower dose recommended of 110 mg BD. For the

stroke prevention in AF indication, a lower dose of 110 mg BD was recommended or should be considered for those with moderate renal impairment, patients aged 75 years and above and those with higher risk of major bleeding, for example concomitant selected P-gp inhibitors. The data presented in this submission indicated from the pharmacology sub study that changes in dabigatran concentrations with renal impairment were comparable with the changes observed in the RELY trial for the stroke prevention indication in AF patients. However unlike in the RELY trial, there was no investigation of a lower dose of 110 mg BD in the any of the four pivotal studies for DVT/PE treatment and prevention. Therefore, it is not clear that a lower dose would be efficacious should it be used in these patient groups.

The pharmacology sub study from the RE-COVER trial, see Attachment 2 and Table 7 below, showed that patients ≥ 75 years compared to those 65 to 75 years had much higher trough dabigatran concentrations (121 ng/mL versus 70.6 ng/mL) but the range of values was large, for example in those ≥ 75 years, the minimum to maximum range was 11.4 ng/mL to 401 ng/mL. Similarly in those patients with moderate renal impairment, the trough dabigatran concentrations were also much higher than those with mild or normal renal function (170 ng/mL versus 85.8 ng/mL or 50.5 ng/mL); severe renal impairment is a contraindication. However the range is also very wide, for example for moderate renal impairment it is 11.4 ng/mL to 401 ng/mL. Patients who had a major bleeding event also had elevated trough dabigatran concentrations compared to those with no bleeding events (80.1 ng/mL versus 58.5 ng/mL). The use of P-gp inhibitors appeared lower in these trials compared to RELY therefore it is less clear on whether a dose reduction is needed. On a pharmacology basis alone there is some evidence to support a reduced dose in those with moderate renal impairment, age ≥ 75 years and those at high risk of bleeding given their elevated dabigatran concentrations but the range of values is large and there is a lack of efficacy data with a reduced dose to support the pharmacology data. The sponsor provided further data to address this matter in the second round clinical evaluation and showed that for both DE and warfarin the rates of MBEs increased with decreasing renal function and that major bleeding events were higher in moderate renal impairment on DE at 5.7% compared to warfarin at 4.4% but if a CRBE or any bleeds are included then the rates are similar (11.4% versus 10.6% for MBE/CRBE and 19.8% versus 25.4% for any bleeds), thus leading to the evaluator's conclusion that 150 mg BD was an acceptable dose in moderate renal impairment. However, there is still a higher rate of major bleeding events on DE at the 150 mg BD dose in this group.

Table 7. Trough plasma concentrations of total dabigatran at Visit 4 in Study RE-COVER (1160.53) by demographic characteristics.

	Patients with values (n)	$C_{pre,ss}$			
		gMean [ng/mL]	gCV [%]	min-max [ng/mL]	Q1-Q3 [ng/mL]
Sex, n (%)					
Male	506	53.8	79.8	3.58-401	37.0-81.8
Female	344	69.6	80.2	3.15-395	43.5-109
Age categories					
18 to <40 years	167	43.3	60.5	6.58-262	29.2-60.3
40 to <50 years	150	48.2	65.7	9.70-336	33.2-66.7
50 to <65 years	263	58.8	76.8	3.15-392	41.4-86.2
65 to <75 years	186	70.6	83.7	3.58-363	49.5-113
≥75 years	84	121	74.6	11.4-401	81.0-179
Weight					
<50 kg	2	66.6	110	35.5-125	35.5-125
50 to <100 kg	666	62.5	80.0	3.15-401	40.7-98.0
≥100 kg	181	50.2	82.8	3.58-329	33.1-75.0
BMI					
<25 kg/m2	200	55.9	77.1	3.76-395	37.4-80.4
25 to <30 kg/m2	348	61.7	85.0	3.15-401	38.9-101
30 to <35 kg/m2	189	59.2	80.7	6.44-315	38.1-93.1
≥35 kg/m2	112	61.2	78.4	3.58-329	41.7-91.8
Creatinine clearance categories					
<30 mL/min	4	191	32.7	146-298	153-246
30 to <50 mL/min	32	170	83.6	11.4-401	106-306
50 to <80 mL/min	181	85.8	65.2	8.47-297	60.3-133
≥80 mL/min	627	50.5	73.0	3.15-392	35.0-74.7
Active cancer at any time					
No	789	58.7	81.1	3.15-401	38.5-90.5
Yes	61	74.8	82.4	5.08-282	47.4-122
Race					
White	822	59.6	82.1	3.15-401	38.5-94.5
Black	16	62.5	63.4	22.2-208	41.8-91.9
Asian	12	68.6	68.0	25.7-282	47.6-96.7
Geographical region					
Western Europe	136	55.3	69.6	12.2-401	36.8-79.8
Central Europe	248	63.5	74.7	9.70-395	42.2-99.5
North America	304	56.5	94.8	3.15-363	37.8-94.6
Latin America	50	66.7	81.7	12.9-337	45.1-97.5
Asia	8	71.8	79.7	25.7-282	48.7-96.7
Other	104	63.1	72.1	19.1-366	38.2-97.7

$C_{pre,ss}$: trough plasma concentrations of total dabigatran within 10-16 hours after dabigatran dose
Q1, Q3: first and third quartile

Overseas, different approaches have been taken on the dose for patients based on moderate renal impairment, age, bleeding risk and concomitant use with P-gp inhibitors. The USA has not included a dose reduction for those with moderate renal impairment or aged 75 years and above or on P-gp inhibitors alone without renal impairment but their stroke prevention indication also did not propose a dose reduction in moderate renal impairment (excluding concomitant dronedarone and ketoconazole use which are contraindicated here), aged 75 years and above or on P-gp inhibitors alone. The USA PI does advise that patients with moderate renal impairment and on P-gp inhibitors to avoid co-administration which has not been included in the Australian PI.

In Europe, the SmPC advises a dose of either 150 mg or 110 mg BD for moderate renal impairment based on an individual assessment of the thromboembolic risk and risk of bleeding with patients at high risk of bleeding having a 110 mg BD dose considered. For patients 80 years and above, it is recommended to take a 110 mg BD dose and if they are 75 to 80 years then either 150 mg or 110 mg BD dose may be selected based on an individual assessment of the thromboembolic risk and risk of bleeding. For patients at increased risk of bleeding when excessive dabigatran exposure is identified, a dose of 110 mg BD is recommended and also for patients with gastritis, esophagitis or gastroesophageal reflux, there is advice to consider a 110 mg BD dose. A statement has

been included in Europe that dosing advice for the 110 mg BD dose for DVT/PE is based on pharmacology studies only and has not been studied in this clinical setting.

There are clear differences in the dosing advice between US and Europe for special populations and the sponsor has not proposed dose reductions here for the new indications. It is unclear why this has not occurred for moderate renal impairment given the similar trough concentrations seen in this new indication and the stroke prevention indication for renal impairment (see Attachment 2) and the elevated dabigatran concentrations in those with moderate renal impairment, age ≥ 75 years and those who had a major bleeding event. A reduced dose in these groups appears reasonable on a pharmacology basis, but such a dose has not been assessed in the DVT/PE indications from an efficacy and safety perspective and it is unclear if the plasma concentrations of dabigatran differ between stroke prevention and DVT/PE patients either overall or for all these subgroups. The EU SmPC includes some data on plasma concentrations with dabigatran that differ between the stroke prevention and DVT/PE populations overall, making it less clear on the appropriate dose. For example, in the stroke prevention population, the dabigatran geometric mean trough concentration, measured in the morning, at the end of the dosing interval (that is, 12 hours after the 150 mg evening dose) was on average 91 ng/mL whereas in the DVT/PE population it was 59.7 ng/mL. ACPM's advice is requested on this matter. The sponsor should provide a robust analysis and justification for each of the above populations for why a dose reduction has not been proposed and why the dosing advice differs with that for the stroke prevention indication and differs from that in Europe.

Indication

The clinical evaluator recommended the indication be modified to exclude the claim of prevention of related death due to lack of sufficient evidence in extended secondary prevention period. The Delegate supports this amendment to the indication. This is also consistent with the US and European approved indications for Pradaxa. Claims for prevention of related death are too broad, do not define the population as such for treatment and are not based on sufficient data. Information relating to efficacy outcomes of a medicine is more appropriate in the Clinical Trials section of the PI. The US wording includes reference to use after a parenteral anticoagulant for 5 to 10 days for the treatment indications; however, this information is located in the Dosage and Administration section of the Australian PI. The US indication also discusses reducing the risk rather than prevention, however, TGA have previously used the term prevention, as seen in the stroke prevention indication and the rivaroxaban PI for this indication. It is noted that the European indication specifies adults however this has not been proposed here and use is not recommended in paediatrics as discussed in the Precautions section. The rivaroxaban indication for DVT/PE does not include adults either and the Pradaxa PI proposes a similar approach. The evaluator has also recommended that the indication wording be aligned with the originally wording proposed in the US PI, however the final approved wording differed in the US. ACPM's advice on the indication wording is requested. The recommended indication wording is:

> *Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE.*

Data deficiencies

There is a lack of data using a lower dose of dabigatran for special populations such as moderate renal impairment, patients aged 75 years and above and those with a higher risk of major bleeding. There is uncertainty regarding duration of treatment, especially for prevention of recurrence of DVT/PE and a lack of data in clinical scenarios when a comparison with warfarin at a higher INR may be needed. Further data would be helpful on use with P-gp inhibitors to elucidate an appropriate dabigatran dose.

Conditions of registration

The following are proposed as conditions of registration:

The implementation in Australia of the EU RMP for Pradaxa (dabigatran), version 26, dated 25 April 2013 (data lock point 18 September 2012), with the ASA, version 26.1, and the RMP agreements from the pre ACPM Response of (date), included with the submission, and any subsequent revisions, as agreed with the TGA.[10]

Questions for the sponsor

The sponsor is requested to address the following issues in the pre ACPM response:

1. Please provide an update on the sponsor's activities in relation to the availability of a product to reverse the effects of dabigatran in the event of an overdose.
2. Please provide an update on the availability of specific assays to determine the level of anticoagulation of a patient on chronic dabigatran treatment.
3. Are any studies planned in paediatric populations in relation to venous thromboembolism?
4. Are further studies underway or planned to investigate the efficacy and safety of a lower dose of dabigatran at 110 mg BD for special populations such as those with moderate renal impairment, patients aged 75 years and above and those with a higher risk of major bleeding?
5. Please provide any further analyses if available examining the use of a 110 mg BD dose in the above special populations including any analyses presented to the European Medicines Agency.
6. The sponsor is requested to provide a robust justification for each of the special populations (moderate renal impairment, patients aged 75 years and above and those with a higher risk of major bleeding) for why a dose reduction has not been proposed and why therefore the proposed dosing advice differs from that for the stroke prevention indication and differs from that in Europe for this new indication. In the response please include a discussion of the similarities or differences in dabigatran concentrations between stroke prevention in AF patients and the proposed DVT/PE patients for each of the special populations.
7. Please provide a sensitivity analysis summary for the RE-MEDY study for the primary efficacy endpoint and secondary endpoints in relation to patient who were rollover patients from the RE-COVER studies compared with patients who had previously been given a Vitamin K antagonist.
8. Please provide a summary table of gastrointestinal bleeding adverse event rates with hazard ratios and confidence intervals for comparing dabigatran with control from all four studies.
9. It is noted that a Study 1160.88 in adolescents exposed to dabigatran has been included in the EU SmPC. Please advise if this study has been submitted to the TGA or if a submission will be submitted post-finalisation?

Proposed action

The Delegate had no reason to say, at this time, that the application for Pradaxa should not be approved for registration with a modified indication.

[10] Note the proposed conditions of registration were revised after advice from the RMP evaluator which was provided subsequent to the presentation of this application to the ACPM.

The Delegate's suggested indication is as follows:

> *Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE.*

Request for ACPM advice (for meeting of August 2014, meeting 299)

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

10. Should the indication exclude the claim of prevention of related death from both indications and provide a revised single indication? Should adults be specified?
11. Should a reduced dose of dabigatran be considered for patients with moderate renal impairment and if so what would be the most appropriate dose? Pradaxa is contraindicated in patients with severe renal impairment and the sponsor is not proposing a reduced dose for moderate renal impairment.
12. Should a reduced dose of dabigatran be considered in patients aged ≥ 75 years and if so what would be the most appropriate dose? The sponsor is not proposing a dose adjustment for this group.
13. Should a reduced dose of dabigatran be considered for patients with an increased risk of bleeding and if so what would be the most appropriate dose? The sponsor is not proposing a dose adjustment for this group.
14. Should specific mention be made of patients with gastritis, esophagitis or gastroesophageal reflux disease as having an increased risk of gastrointestinal bleeding and that the use of a lower dose of dabigatran should be considered for these patients in the PI? The sponsor is not proposing to specifically mention these groups in the PI.
15. Should the PI recommend against the concomitant use of P-gp inhibitors with dabigatran in those with moderate renal impairment? At present, the sponsor is not proposing to include this statement in the PI.
16. Are the dosing instructions in the PI, stating no dose adjustment is necessary in relation to concomitant use with P-gp inhibitors, appropriate or should information be included that there is limited data and that results may vary depending on the individual P-gp inhibitor?
17. The PI is proposing treatment for up to 6 months and then lifelong for the prevention indication. Are these clinically appropriate or would the statements included in the EU SmPC be more appropriate?

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

Timeline

The above Delegate's Request for ACPM's Advice was issued to the sponsor on 1 July 2014 and was then planned for the August 2014 ACPM meeting. Following the issuance of the Request for ACPM's Advice, the sponsor initially requested a 2 month 'clock stop' to allow for additional analyses to be conducted to address some of the Delegate's questions and to provide that information in the pre ACPM Response. The TGA agreed to this request and the consideration of this item by ACPM was deferred. Below is the response by the sponsor to the issues raised in the Delegate's request for advice from the August 2014 ACPM (meeting 299).

Response from sponsor

Presented here is the sponsor's pre ACPM response to the TGA Delegate's proposed action and request for advice in relation to our application to extend the indications for Pradaxa (dabigatran etexilate) to include two new indications for the treatment and prevention of deep venous thrombosis and pulmonary embolism.

Responses to questions for the sponsor by the delegate from delegate's request for ACPM advice (August 2014 ACPM, Meeting 299)

1. *Please provide an update on the sponsor's activities in relation to the availability of a product to reverse the effects of dabigatran in the event of an overdose.*

Boehringer Ingelheim is currently developing the antidote idarucizumab to provide another treatment option for patient management during rare critical care situations. Idarucizumab is a humanised monoclonal antibody fragment that specifically binds to dabigatran and inhibits its function. Two Phase I trials have been conducted in volunteers. In addition to safety and dose exploration, these two Phase I trials also demonstrated proof of concept, namely reversal of dabigatran anticoagulant effects in subjects pre-treated with dabigatran. A Phase III case series clinical study in patients treated with dabigatran etexilate who have uncontrolled bleeding or require emergency surgery or procedures was initiated in May 2014. The submission for marketing approval is expected in early 2015.

2. *Please provide an update on the availability of specific assays to determine the level of anticoagulation of a patient on chronic dabigatran treatment.*

Pradaxa does not require routine anticoagulant monitoring. However, the measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors, or to assess the level of anticoagulation from dabigatran in situations where immediate surgery is required or a patient has severe bleeding.

The Hemoclot Direct Thrombin Inhibitors (DTI) test is a diluted thrombin time test for the quantitative measurement of plasma dabigatran level. This test is marketed by Hyphen BioMed and received a CE marking in the EU in 2010 and is available in Australia.

The sponsor is currently collaborating with several manufacturers to develop other assays for the measurement of dabigatran plasma concentrations. In June 2014, Technoclone GmbH received a CE declaration of conformity in the EU for the Technoclot DTI test, a dabigatran calibrated laboratory assay based on diluted thrombin time. This test has been available in Australia since June 2014.

It is expected that other tests being developed within the the sponsor collaboration will become available later in 2014/2015.

3. *Are any studies planned in paediatric populations in relation to venous thromboembolism?*

In the EU a Paediatric Investigational Plan (PIP) for dabigatran etexilate in the indication 'treatment of venous thromboembolic events in paediatric patients (secondary venous thrombotic event prevention)' has been in place since 2008. The current status of the paediatric clinical studies with dabigatran etexilate in the VTE indication is provided in Table 8.

Table 8. The current status of paediatric clinical studies with dabigatran etexilate.

Study number and title	Study objective	Study status
1160.87 (PIP measure 2) Relative bioavailability of dabigatran after administration of different application forms of 150 mg dabigatran etexilate q.d. (capsule, powder in solution, pellets in healthy male and female volunteers	To assess relative bioavailability of different paediatric formulations	completed (U09-1839-01)
1160.88 (PIP measure 3) Open-label pharmacokinetic and safety study of dabigatran etexilate given for 3 days at the end of standard anticoagulant therapy in children aged 12 years to less than 18 years	To assess PK and safety	Completed (U12-3378-01)
1160.89 (PIP measure 4) Single dose open-label PK/PD, safety and tolerability study of dabigatran etexilate given at the end of standard anticoagulant therapy in children aged 1 year to less than 12 years	- To assess PK, PD and safety - To assess tolerability of the proposed age-appropriate formulation	ongoing (study completed in age group 2 to < 12 years; as of July 10th, 2014 two patients in age group 1 to < 2 years recruited)
1160.105 (PIP measure 6) Open-label, single-dose, tolerability, PK/PD and safety study of dabigatran etexilate given at the end of standard anticoagulant therapy in children aged less than 1 year.	To confirm the dosing algorithm and to demonstrate comparable PK/PD relationship to older children and adults	In preparation
1160.106 (PIP measure 7) Open-label randomized, parallel-group, active controlled, multi-centre non-inferiority study of dabigatran etexilate versus standard of care in children from birth to less than 18 years.	- To assess the efficacy and safety of dabigatran - To document the appropriateness of the dosing algorithm	ongoing (as of July 10th, 2014 three patients recruited)
1160.108 (PIP measure 8) Open-label, single-arm safety study of dabigatran etexilate for extended secondary prevention of venous thrombosis in children aged 0 years to less than 18 years	To assess long-term safety of dabigatran	In preparation

4. *Are further studies underway or planned to investigate the efficacy and safety of a lower dose of dabigatran at 110 mg BD for special populations such as those with moderate renal impairment, patients aged 75 years and above and those with a higher risk of major bleeding?*

There are currently no further clinical studies planned in special populations of patients with VTE to investigate the lower doses of dabigatran at 110 mg BD for special populations such as those with moderate renal impairment, patients aged 75 years and above and those with a higher risk of major bleeding.

The sponsor considers the clinical data from the 4 pivotal trials with a total of 8,197 randomised patients sufficiently supports the recommended 150 mg BD dosing for all patients in the VTE indication.

The results of the 3 pivotal studies (dabigatran etexilate (DE) versus warfarin (W)) demonstrate that DE given at a dose of 150 mg BD was non inferior to warfarin for the treatment of acute VTE treatment (aVTEt) and for the prevention of recurrent VTE events in a broad spectrum of low to high risk patients. In the 4th pivotal study, DE was superior to placebo in preventing recurrent VTEs in those thought to be at equipoise for the need for continuing anticoagulant therapy. There were no significant interactions between treatment and subgroup results, further supporting the use of DE 150 mg BD dose in all patient subgroups. The incidence of all categories of Major Bleeding Events (MBEs) (MBEs, adjudicated MBEs with a fatal outcome, Thrombolysis in Myocardial Infarction (TIMI) major bleeding, and intracranial MBEs) as well as life-threatening bleeding events, any bleeding events (including MBEs, CRBEs, and nuisance/trivial bleeding), and discontinuation of study drug due to bleeding was consistently lower in DE patients compared to warfarin for studies of short (6 months in the aVTEt studies) and longer duration (up to 36 months in secondary VTE prevention (sVTEp) Study 1160.47). Fewer DE patients than warfarin patients discontinued study drug due to all severities of

bleeding. In the overall results, and in most of the subgroup analyses, including patients with moderate renal impairment and patients aged 75 years, the incidence of centrally adjudicated MBEs, MBE/CRBEs, and any bleeding events was lower in DE treated patients compared with warfarin treated patients.

However, the sponsor acknowledges that in certain subgroups the number of events is small and a firm conclusion cannot be made. Therefore the sponsor agrees to harmonise the recommended dosage for the VTE indication and the stoke prevention in atrial fibrillation (SPAF) indication.

The PK/PD analyses of both the RE-LY and RE-COVER studies show that the PD response (that is anticoagulation) as well as therapeutic response (that is bleeding and antithrombotic efficiency) are closely related to dabigatran exposure. Furthermore, consistency was demonstrated in the PK (see Table 10) PK/PD and the relation between the exposure and the clinical safety (MBEs) between the non valvular atrial fibrillation (NVAF) and VTE patient population, although no dedicated exposure efficacy relationship could be demonstrated for the VTE patient population.

Table 9 displays the steady state total dabigatran trough concentrations (geometric Mean and geometric CV) in VTE (Study 1160.53, RE-COVER) and AF patients (Study 1160.26, RE-LY (from an earlier submission)) treated with 150 mg BD by age, renal function (CrCl) and verapamil co medication. For Study RE-COVER, both measurements at Visit 4 (1) and Visit 9 (2) are presented. The age category in RECOVER was 50 to < 65 years while in RE-LY, the equivalent category was < 65 years.

Table 9. Steady state dabigatran trough concentrations in VTE and AF patients for RECOVER and RE-LY studies.

	RE-COVER		RE-LY	
	N	Dabigatran trough conc. (ng/mL)	N	Dabigatran trough conc. (ng/mL)
AGE (years)		gMean (gCV%)		gMean (gCV%)
≥75	84[1] 66[2]	121 (74.6) 139 (88.4)	1616	114 (76.9)
≥65-<75	186 159	70.6 (83.7) 77.0 (69.4)	1860	84.6 (73.9)
<65			746	67.1 (90.6)
50-<65	263 230	58.8 (76.8) 56.9 (81.2)		
CRCL (mL/min)	N	gMean (gCV%)	N	gMean (gCV%)
30-<50	32 23	170 (83.6) 185 (61.3)	761	144 (80.6)
50-<80	181 170	85.8 (65.2) 91.7 (84.8)	1969	95.2 (73.0)
≥80	627 544	50.5 (73.0) 49.4 (77.6)	1347	64.8 (71.6)
Verapamil Co-med	N	gMean (gCV%)	N	gMean (gCV%)
+Verapamil	14 11	82.4 (170) 97.3 (107)	322	110 (79.3)
-Verapamil	836 735	59.4 (80.1) 59.1 (89.3)	5940	90.6 (82.3)

Source: RECOVER, 1160.53 (U09-1400-01) and RE-LY, 1160.26 (U09-3249-02)
[1] and [2] trough concentration at visit 4 and 9, respectively

Therefore, in the sub populations defined by the current NVAF PI, exposure with 110 mg BD is expected to stay within or even above the average exposure in the majority

of VTE patients receiving 150 mg BD Hence, it can be assumed that most of the anticoagulation efficacy will be preserved when this VTE population with a higher risk of bleeding is treated with DE 110 mg BD.

In conclusion, the sponsor considers the existing data on the 110 mg BD dose from RE-LY together with the high consistency between the patient populations in terms of the PK, PK/PD and exposure-response results seen in the RE-LY and RE-COVER studies, as sufficient evidence to consider the 110 mg BD dose for the same sub-populations in VTE as in NVAF, without further need of a dedicated clinical study. However, the sponsor will continue to perform PK analyses in the ongoing and upcoming clinical trials where relevant, to check the consistency of the results between studies on the correlation of PK data to MBE events and ischaemic events and provide the results of these analyses within the upcoming PSURs.

5. *Please provide any further analyses if available examining the use of a 110mg BD dose in the above special populations including any analyses presented to the European Medicines Agency.*

Only the DE 150 mg BD dose was used in the four pivotal VTE trials (RE-COVER, RE-COVER II, RE-MEDY, RE-SONATE). Therefore, the sponsor cannot provide further analysis in subgroups using the DE 110 mg BD dose. Please also refer to the sponsor's response to Question 4 above.

6. *The sponsor is requested to provide a robust justification for each of the special populations (moderate renal impairment, patients aged 75 years and above and those with a higher risk of major bleeding) for why a dose reduction has not been proposed and why therefore the proposed dosing advice differs from that for the stroke prevention indication and differs from that in Europe for this new indication. In the response please include a discussion of the similarities or differences in dabigatran concentrations between stroke prevention in AF patients and the proposed DVT /PE patients for each of the special populations.*

There has been a consistent relationship observed between DEs PK and PD in all populations studied, in human volunteers and in patients with different disease entities. Additionally, there has been a consistent relationship between dabigatran plasma levels (exposure and/or PK) and the occurrence of centrally adjudicated and investigator reported clinical safety (bleeding) and efficacy (strokes and systemic embolic events). The probability of bleeding events increases with increasing dabigatran plasma levels, while the occurrence of efficacy events decreases with increasing dabigatran plasma levels. Thus, as with all anticoagulants, improved efficacy can be obtained at the cost of increased bleeding risk. It is important to note that the consequences of bleeding and the occurrence and sequelae of PEs and/or VTEs differ among patients with different characteristics (age, renal function, concomitant illnesses, frailty, and so on). In general, patients with NVAF have more concomitant medical illnesses and take more drugs with an impact on bleeding (for example acetylsalicylic acid, anti-platelet agents, NSAIDs, verapamil, amiodarone, dronedarone, etcetera) than those treated for VTEs and/or their prevention. As such, NVAF patients have worse outcomes when bleeding occurs.

Given these known differences between NVAF and VTE patients, subgroup analyses of multiple factors known to impact clinical outcomes were conducted in the VTE populations studied in this development program. Factors analysed included renal impairment, age, previous gastrointestinal bleeds, and intake of aspirin, NSAIDs, P-gp inhibitors or SSRIs. Each factor was analysed as a single risk factor and selected combinations of key risk factors, specifically renal impairment and old age, where sample sizes were of potentially acceptable size were also analysed. Since there were relatively few MBEs on dabigatran, the safety profile assessment in the VTE indications primarily utilised the pool of all bleeding categories (MBEs, MBE/CRBEs, and any bleeds).

Overall, and in most subgroups, the incidence of centrally adjudicated MBEs, MBE/CRBEs, and any bleeding events was lower in DE treated patients compared with warfarin treated patients. In cases where bleeding was not lower on DE than warfarin, there were either very few patients in that subgroup, or the number of events differing between the groups was too small to make valid conclusions regarding potential differences.

The data from this VTE development program supports the recommendations made by the sponsor for the use of the 150 mg BD regimen for the overall population and for subgroups of patients with each of the individually analysed risk factors. Therefore, these data support a recommendation of no dose adjustment for any subgroup of patients with single risk factor receiving DE for acute VTE treatment or secondary prevention of recurrent VTE.

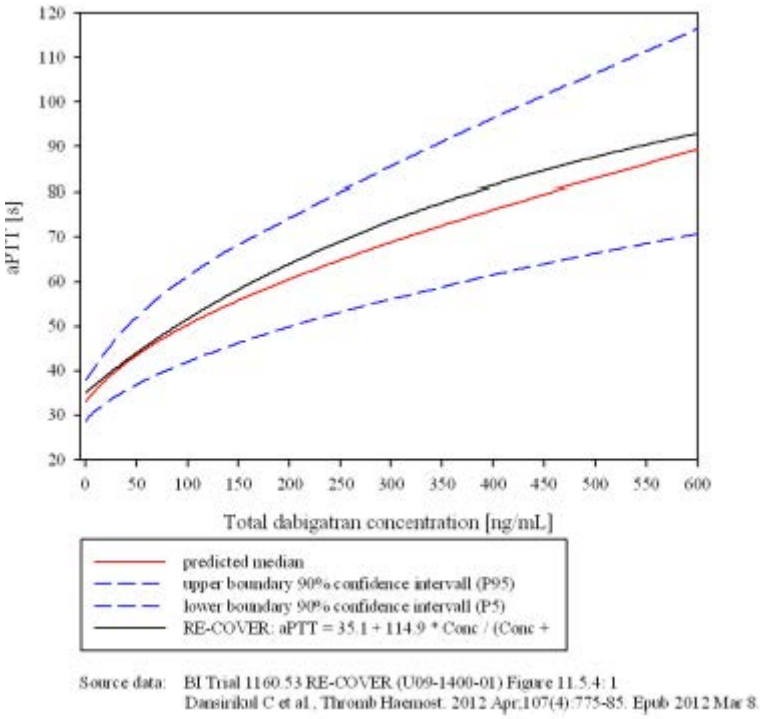
Data for patients with renal impairment, using various age categorisations and for the combination of varying degrees of renal impairment combined with age categorisations are provided below.

However, the sponsor acknowledges that in certain subgroups the number of events is small and a firm conclusion cannot be made. Therefore the sponsor agrees to harmonise the recommended dosage for the VTE indication and the SPAF indication. Please note, that the arguments and the data presented by the sponsor are identical to what has been submitted to EMA.

PK/PD data

As depicted in Figure 1, the relationship between total dabigatran concentration and the PD marker aPTT was highly comparable between data derived from Study 1160.53 (RE-COVER) with an analysis using pooled data from atrial fibrillation patients (Study 1160.20 PETRO), orthopedic surgery patients (Study 1160.11, BISTRO I) and healthy volunteers (Study 1160.61).

Figure 1. PK/PD (aPTT) relationship comparing data from Study 1160.53 (RE-COVER) with pooled data from studies in patients with atrial fibrillation, orthopaedic surgery (Studies 1160.20 and 1160.11) and healthy volunteers (Study 1160.61).



Source data: BI Trial 1160.53 RE-COVER (U09-1400-01) Figure 11.5.4: 1
Dansirikul C et al., Thromb Haemost. 2012 Apr;107(4):775-85. Epub 2012 Mar 8.

The red and black lines show the predicted median dabigatran concentration - aPTT relationship for patients with atrial fibrillation (from PETRO, 1160.20) and VTE (from RECOVER, 1160.53), respectively. The blue hatched line shows the 95% confidence interval from the pooled analysis.

The dose of 150 mg BD was, therefore, consistently chosen for both clinical development programs, VTE and SPAF, as this dose was expected to provide the optimum risk/benefit profile.

With respect to subpopulations at a potentially higher risk of bleeding, the database in VTE patients is generally substantially smaller than the NVAF (RE-LY) database. This is especially true for PK datasets since, in the whole VTE program, trough plasma concentrations were only measured in Study 1160.53 (RE-COVER). However, the PK effects of age and renal impairment were very consistent across patient groups (see Table 10 above) especially when the absolute values in the age subgroups of ≥ 75 or 65 to < 75 and CrCl 30 to < 50 are compared across populations.

According to the recent exposure-response (MBE) analyses of Study 1160.53 (RE-COVER) data in VTE patients, the PK effect by age would theoretically result in a probability of MBE of 1.91% for age ≥ 80. This would still be below the overall average MBE frequency of 2.0% observed in Study 1160.53 (RE-COVER) for warfarin treated patients.

In the case of moderate renal impaired patients (CrCl 30 to < 50 mL/min), in the worst case (trough concentration = 185 ng/mL) the predicted probability of MBE would be 2.29%.

For patients ≥ 80 years or patients with moderate renal impairment, it is unclear how much of the beneficial clinical effect could be preserved with a dose of 110 mg as no clear exposure efficacy relationship could be established for VTE patients.

With respect to MBE, reduction of the dose from 150 to 110 mg BD assuming dose proportionality and applying the exposure MBE model would lead to a reduction in the probability of MBE from 2.29% to 1.73% and 1.91% to 1.45% for patients with CrCl 30 to < 50 mL/min and patients aged ≥ 80 years, respectively.

Clinical outcome data

Efficacy

The analyses of efficacy in subgroups were performed for the primary endpoint VTE and VTE related deaths and for the secondary endpoint of PE. Subgroups were analysed based on categories of age; gender; race; ethnicity; geographical region; BMI; smoking history; creatinine clearance; active cancer at any time; prior VTE (before the index event); thrombophilia; idiopathic VTE; history of bleeding; history of venous insufficiency; history of coronary artery disease; history of myocardial infarction; history of diabetes mellitus; use of concomitant ASA, P-gp inhibitors, NSAIDS, or anticoagulants; asymptomatic PE at baseline; symptomatic PE as index event; open label parenteral therapy for index event; and time since index event. No clinically important subgroup-by-treatment interactions were detected. Data on patients with renal impairment and age are included in the text.

Safety (bleeding)

Subgroup of patients with impaired renal function

Table 10 shows data from patients with normal and impaired renal function for both treatment groups from pooled aVTEt Studies 1160.53/1160.46 and Study 1160.47. Of note, patients with renal function less than 30 mL/min were to be excluded from participation in these VTE trials as for all other DE studies. Administration of DE to patients with CrCl < 30mL/min is contraindicated. In both the DE and warfarin treatment groups, the rates of MBE, MBE/CRBE and any bleeds increased with declining renal function. In almost all comparisons across bleeding categories (MBE, MBE/CRBE and any

bleeds) and declining renal function of DE treated patient versus vitamin K antagonist (VKA) treated patients, there were less bleeds within the DE treatment group. The only exception is the MBE rate of DE patients with 30 to < 50mL/min being slightly higher (5.7%) compared with VKA patients (4.4%) but for MBE/CRBE or any bleeds the rates with DE were similar or less (11.3%/19.8%) compared with VKA (10.5%/25.4%), respectively.

Table 10. Summary of bleeding events (MBEs, MBEs/CRBEs, and any bleeding) by creatinine clearance category in the pivotal aVTEt and sVTEp studies; treated set.

Creatinine clearance categories, n/N (%)*	Treatment No. events/no. of patients (%)		DE/W Hazard Ratio (95% CI)
MBEs			
Pooled aVTEt studies	**DE**	**W**	
Pooled aVTEt studies from start of any treatment			
<30 mL/min	1/12 (8.3)	0/11 (0)	NC
30 to <50 mL/min	6/114 (5.3)	5/123 (4.1)	1.31 (0.40, 4.31)
50 to <80 mL/min	14/538 (2.6)	23/562 (4.1)	0.63 (0.33, 1.23)
≥80 mL/min	16/1861 (0.9)	23/1837 (1.3)	0.69 (0.36, 1.30)
Pooled aVTEt studies from start of double-dummy treatment			
<30 mL/min	0/8 (0)	0/10 (0)	NC
30 to <50 mL/min	6/106 (5.7)	5/114 (4.4)	1.32 (0.40, 4.31)
50 to <80 mL/min	9/504 (1.8)	16/536 (3.0)	0.58 (0.26, 1.31)
≥80 mL/min	9/1811 (0.5)	19/1783 (1.1)	0.47 (0.21, 1.03)
sVTEp Study 1160.47	**DE**	**W**	
<30 mL/min	0/0	0/4 (0)	--
30 to <50 mL/min	2/59 (3.4)	3/45 (6.7)	0.51 (0.09, 3.09)
50 to <80 mL/min	3/328 (0.9)	8/289 (2.8)	0.32 (0.09, 1.21)
≥80 mL/min	8/1031 (0.8)	14/1072 (1.3)	0.60 (0.25, 1.42)
MBEs/CRBEs			
Pooled aVTEt studies	DE	W	
Pooled aVTEt studies from start of any treatment			
<30 mL/min	2/12 (16.7)	1/11 (9.1)	1.99 (0.17, 23.58)
30 to <50 mL/min	13/114 (11.4)	13/123(10.6)	1.11 (0.52, 2.40)
50 to <80 mL/min	49/538 (9.1)	79/562 (14.1)	0.63 (0.44, 0.90)
≥80 mL/min	71/1861 (3.8)	123/1837(6.7)	0.56 (0.42, 0.75)
Pooled aVTEt studies from start of double dummy treatment			
<30 mL/min	1/8 (12.5)	0/10 (0)	NC
30 to <50 mL/min	12/106 (11.3)	12/114 (10.5)	1.10 (0.49, 2.45)
50 to <80 mL/min	36/504 (7.1)	66/536 (12.3)	0.55 (0.36, 0.82)
≥80 mL/min	59/1811 (3.3)	110/1783 (6.2)	0.52 (0.38, 0.71)
sVTEp Study 1160.47	DE	W	
<30 mL/min	0/0 (0.0)	0/4 (0.0)	NC-
30 to <50 mL/min	3/59 (5.1)	5/45 (11.1)	0.46 (1.11, 1.91)
50 to <80 mL/min	23/328 (7.0)	33/289 (11.4)	0.60 (0.35, 1.02)
≥80 mL/min	54/1031 (5.2)	107/1072 (10.0)	0.52 (0.37, 0.72)
Any bleeding			
Pooled aVTEt studies	DE	W	
Pooled aVTEt studies from start of any treatment			
<30 mL/min	3/12 (25.0)	3/11 (27.3)	1.07 (0.21, 5.50)
30 to <50 mL/min	25/114 (21.9)	34/123(27.6)	0.79 (0.47, 1.32)
50 to <80 mL/min	114/538 (21.2)	145/562 (25.8)	0.80 (0.62, 1.02)
≥80 mL/min	266/1861 (14.3)	380/1837 (20.7)	0.66 (0.57, 0.77)
Pooled aVTEt studies from start of double-dummy treatment			
<30 mL/min	2/8 (25.0)	2/10 (20.0)	1.47 (0.21, 10.47)
30 to <50 mL/min	21/106 (19.8)	29/114 (25.4)	0.79 (0.45, 1.38)
50 to <80 mL/min	97/504 (19.2)	125/536 (23.3)	0.78 (0.60, 1.02)
≥80 mL/min	231/1811 (12.8)	342/1783 (19.2)	0.64 (0.54, 0.75)
sVTEp Study 1160.47	DE	W	
<30 mL/min	0/0 (0)	1/4 (25.0)	--
30 to <50 mL/min	16/59 (27.1)	15/45 (33.3)	0.87 (0.43, 1.78)
50 to <80 mL/min	67/328 (20.4)	79/289 (27.3)	0.70 (0.51, 0.97)
≥80 mL/min	194/1031 (18.8)	275/1072 (25.7)	0.70 (0.58, 0.84)

* In the VTE studies, patients with CrCl < 30 mL/min were not enrolled.

The efficacy of DE 150 mg BD appeared favourable in this population, with no endpoint event in 114 patients, while in warfarin treated patients with moderate renal impairment,

5/123 (41%) had VTE or VTE related death. The incidence in DE patients with CrCl ≥ 80 mL/min was 58/1,860 (3.1%).

Subgroup of elderly patients

Table 11 shows data from patients stratified by age for both treatment groups from pooled aVTEt Studies 1160.53/1160.46 and Study 1160.47. For both treatment groups, the bleeding rates in all bleeding categories generally increased with increasing age. Bleeding rates in the DE group were consistently lower across age groups and bleeding categories compared to VKA patients. The only exceptions with the aVTEt studies with groups of patients > 75 years of age with similar MBE bleeding rates (DE: 3.5%/VKA :3.8%) and patients > 80 years with one major bleed in excess in the DE group (DE3.3% versus VKA 2.5%); and in study 1160.47 the patient group of 65 to 75 years with more MBEs or MBE/CRBE with DE (2.7%, 10%) compared with VKA (1.0%, 7,6%), respectively.

Table 11. Bleeding events (MBEs, MBEs/CRBEs and any bleeding) by age categories in the pivotal aVTEt and sVTEp studies; treated set.

Age categories, n/N (%)	Treatment No. events/no. of patients (%)		DE/W Hazard Ratio (95% CI)
MBEs			
Pooled aVTEt studies	**DE**	**W**	
Pooled aVTEt studies, from start of any treatment			
<65 years	14/1771 (0.8)	24/1746 (1.4)	0.57 (0.30, 1.11)
65 to 75 years	12/529 (2.3)	15/532 (2.8)	0.76 (0.36, 1.64)
>75 years	11/253 (4.3)	12/276 (4.3)	1.03 (0.45, 2.33)
≥80 years	6/135 (4.4)	3/125 (2.4)	1.99 (0.50, 7.95)

Age categories, n/N (%)	Treatment No. events/no. of patients (%)		DE/W Hazard Ratio (95% CI)
Pooled aVTEt studies, from start of double-dummy treatment			
<65 years	11/1722 (0.6)	19/1685 (1.1)	0.57 (0.27, 1.20)
65 to 75 years	5/503 (1.0)	11/515 (2.1)	0.43 (0.15, 1.24)
>75 years	8/231 (3.5)	10/262 (3.8)	0.90 (0.35, 2.28)
≥80 years	4/122 (3.3)	3/121 (2.5)	1.31 (0.29, 5.86)
sVTEp Study 1160.47	**DE**	**W**	
<65 years	3/987 (0.3)	14/1019 (1.4)	0.22 (0.06, 0.78)
65 to 75 years	9/329 (2.7)	3/307 (1.0)	2.70 (0.73, 9.96)
>75 years	1/114 (0.9)	8/100 (8.0)	0.10 (0.01, 0.82)
≥80 years	0/52 (0)	4/47 (8.5)	--
MBEs/CRBEs			
Pooled aVTEt studies, from start of any treatment			
<65 years	65/1771 (3.7)	117/1746 (6.7)	0.54 (0.40, 0.73)
65 to 75 years	42/529 (7.9)	63/532 (11.8)	0.66 (0.44, 0.97
>75 years	29/253 (11.5)	37/276 (13.4)	0.88 (0.54, 1.43)
≥80 years	16/135 (11.9)	17/125 (13.6)	0.95 (0.48, 1.88)
Pooled aVTEt studies, from start of double-dummy treatment			
<65 years	58/1722 (3.4)	102/1685 (6.1)	0.55 (0.40, 0.76)
65 to 75 years	29/503 (5.8)	54/515 (10.5)	0.52 (0.33, 0.82)
>75 years	22/231 (9.5)	33/262 (12.6)	0.74 (0.43, 1.26)
≥80 years	11/122 (9.0)	16/121 (13.2)	0.69 (0.32, 1.48)
sVTEp Study 1160.47	DE	W	
<65 years	40/987 (4.1)	101/1019 (9.9)	0.40 (0.28, 0.58)
65 to 75 years	33/329 (10.0)	23/307 (7.5)	1.35 (0.79, 2.30)
>75 years	7/114 (6.1)	21/100 (21.0)	0.28 (0.12, 0.65)
≥80 years	4/52 (7.7)	10/47 (21.3)	0.39 (0.12, 1.27)
Any bleeding			
Pooled aVTEt studies, from start of any treatment			
<65 years	256/1771 (14.5)	363/1746 (20.8)	0.66 (0.56, 0.78)
65 to 75 years	100/529 (18.9)	133/532 (25.0)	0.73 (0.56, 0.95)
>75 years	55/253 (21.7)	71/276 (25.7)	0.87 (0.61, 1.24)
≥80 years	33/135 (24.4)	33/125 (26.4)	0.99 (0.61, 1.60)
Pooled aVTEt studies, from start of double-dummy treatment			
<65 years	229/1722 (13.3)	324/1685 (19.2)	0.66 (0.56, 0.78)
65 to 75 years	81/503 (16.1)	115/515 (22.3)	0.68 (0.51, 0.91)
>75 years	44/231 (19.0)	64/262 (24.4)	0.76 (0.52, 1.12)
≥80 years	25/122 (20.5)	31/121 (25.6)	0.79 (0.47, 1.34)
sVTEp Study 1160.47	**DE**	**W**	
<65 years	176/987 (17.8)	261/1019 (25.6)	0.67 (0.55, 0.81)
65 to 75 years	70/329 (21.3)	75/307 (24.4)	0.84 (0.60, 1.16)
>75 years	32/114 (28.1)	37/100 (37.0)	0.74 (0.46, 1.19)
≥80 years	13/52 (25.0)	18/47 (38.3)	0.66 (0.32, 1.35)

In contrast, DE at a dose of 150 mg BD demonstrated favourable efficacy in this patient population. For the primary endpoint VTE and VTE related death the frequency was 0.7%, 4.0% and 2.8% in DE patients ≥ 80 years and DE patients < 80 years, respectively.

Combination of risk factors

The only meaningful subgroup of patients with more than one risk factor constitutes a group of patients ≥ 75 years of age combined with moderately reduced renal function (n = 76 patients on DE and n = 83 patients on warfarin). A new analysis for bleeding is shown in Table 12. Numerically more bleeds were recorded in DE treated patients for MBE and MBE/CRBE but less any bleeds compared to VKA treated patients. The results should be interpreted with caution as the sample size in this group is too small to form conclusions.

Table 12. Analysis of bleeding events in elderly patients with moderately reduced renal function.

Table 9.3.1.1 Frequency of centrally adjudicated MBE by age >=75 yrs and moderate renal impairment for acute VTE treatment studies - treated set

Age >=75 yrs and moderate renal impairment		DE	W
No	Patients [N (%)]	2380 (100.0)	2379 (100.0)
	MBE [n (%)]	20 (0.8)	37 (1.6)
Yes	Patients [N (%)]	76 (100.0)	83 (100.0)
	MBE [n (%)]	4 (5.3)	3 (3.6)

Table 9.3.3.1 Frequency of centrally adjudicated MBE or CRBE by age >=75 yrs and moderate renal impairment for acute VTE treatment studies - treated set

Age >=75 yrs and moderate renal impairment		DE	W
No	Patients [N (%)]	2380 (100.0)	2379 (100.0)
	MBE or CRBE [n (%)]	100 (4.2)	181 (7.6)
Yes	Patients [N (%)]	76 (100.0)	83 (100.0)
	MBE or CRBE [n (%)]	9 (11.8)	8 (9.6)

Table 9.3.2.1 Frequency of centrally adjudicated any bleeding by age >=75 yrs and moderate renal impairment for acute VTE treatment studies - treated set

Age >=75 yrs and moderate renal impairment		DE	W
No	Patients [N (%)]	2380 (100.0)	2379 (100.0)
	Any bleeding [n (%)]	339 (14.2)	482 (20.3)
Yes	Patients [N (%)]	76 (100.0)	83 (100.0)
	Any bleeding [n (%)]	15 (19.7)	21 (25.3)

Data have been presented evaluating the primary efficacy and multiple bleeding outcomes, including the primary bleeding outcome, for multiple subgroups of interest. Data demonstrating a consistent relationship for VTE patients between DE PK and PD was also presented. Data for age and renal impairment have been included in the text. In general, no risk factor identified a subgroup for which DE had neither any substantial increase in bleeding when compared to warfarin nor any loss of efficacy. For the subgroup combining older age and renal impairment the findings were similar. The risk of bleeding and its consequences was less severe in patients included in the VTE clinical development program compared to the NVAF development program, as there were very few bleeding events on DE and warfarin in the VTE development program. The totality of these data, support in general a recommendation to utilise only one dosing regimen, 150 mg BD for all patient subgroups for this treatment indication.

However as stated above, the sponsor acknowledges that in certain subgroups the number of events is small and a firm conclusion cannot be made. Therefore, the sponsor agrees to harmonise the recommended dosage for the VTE indication and the SPAF indication.

7. *Please provide a sensitivity analysis summary for the RE-MEDY study for the primary efficacy endpoint and secondary endpoints in relation to patient who were rollover patients from the RE-COVER studies compared with patients who had previously been given a vitamin K antagonist.*

Table 13 shows the requested analysis of the RE-MEDY study for the primary efficacy endpoint and secondary endpoints stratified for patients who rolled over from the RE-COVER studies compared with patients who had previously been treated with a vitamin K antagonist outside of clinical controlled study. Patients who rolled over are displayed in column DE and warfarin whereas patients who had previously been treated with vitamin K antagonist outside of clinical controlled study are shown as NA.

No meaningful between treatment differences in the frequencies of the primary endpoint were observed when comparing roll over patients (those re allocated to a different study drug or continuing the same study drug). The event rates of patients who had previously been treated with vitamin K antagonist outside of a clinical controlled study (NA) were lower compared with the event rate seen in patients who rolled over (DE or warfarin). Patients from outside a clinical controlled study (NA) who continued with warfarin had a lower event rate compared with DE patients. However, the difference between DE and warfarin in terms of absolute risk is considered low.

Table 13. Summary of centrally adjusdicated primary and secondary efficacy endpoints until the end of planned treatment period, by roll over status for study 1160.47 (RE-MEDY) – FAS (roll over VKA).

	Treatment in VTE treatment study					
	DE		W		NA#	
	Treatment in study 1160.47		Treatment in study 1160.47		Treatment in study 1160.47	
	DE N (%)	W N (%)	DE N (%)	W N (%)	DE N (%)	W N (%)
Number of patients	266 (100.0)	266 (100.0)	303 (100.0)	262 (100.0)	807 (100.0)	853 (100.0)
Primary endpoint						
VTE and VTE related death	6 (2.3)	6 (2.3)	6 (2.0)	5 (1.9)	11 (1.4)	6 (0.7)
Secondary endpoints						
VTE and all death	7 (2.6)	11 (4.1)	14 (4.6)	10 (3.8)	17 (2.1)	13 (1.5)
Symptomatic DVT	5 (1.9)	3 (1.1)	4 (1.3)	3 (1.1)	6 (0.7)	6 (0.7)
Symptomatic PE	1 (0.4)	3 (1.1)	3 (1.0)	2 (0.8)	5 (0.6)	0 (0.0)
Death related to VTE	0 (0.0)	1 (0.4)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
All death	1 (0.4)	6 (2.3)	9 (3.0)	5 (1.9)	6 (0.7)	7 (0.8)

8. Please provide a summary table of gastrointestinal bleeding adverse event rates with hazard ratios and confidence intervals for comparing dabigatran with control from all four studies.

The following Tables 14 to 19 display the hazard ratios for gastrointestinal MBE for RE-COVER/ RE-COVER pooled (Table 14), RE-MEDY (Table 15) and the placebo controlled RE-SONATE study (Table 16). Tables 17, 18 and 19 show the hazard ratios for any gastrointestinal bleeds as reported in the RE-COVER/RE-COVER pooled, RE-MEDY and RE-SONATE study respectively. There were numerically less gastrointestinal MBE in DE treated patients compared with warfarin patients but more gastrointestinal bleeds with DE than with warfarin patients. Compared with placebo the rate of gastrointestinal MBE and any gastrointestinal bleeds was higher in patients treated with DE. None of these comparisons were statistically significant.

Table 14. Hazard ratio for gastrointestinal MBE until the end of treatment for acute VTE treatment studies – treated set.

	DE	W
Number of patients	2456	2554
Gastrointestinal MBE [N(%)] *	10 (0.4)	14 (0.5)
Model 1 #		
Hazard Ratio vs. warfarin		
Estimate (95% CI)	0.73 (0.32, 1.64)	

Table 15. Hazard ratio for gastrointestinal MBE until end of treatment for Study 1160.47 (RE-MEDY) – treated set.

	DE	W
Patients [N(%)]	1430	1426
Gastrointestinal MBE *	4 (0.3)	8 (0.6)
Hazard Ratio vs. Warfarin		
Estimate (95% CI) #	- (-, -)	
p-value for superiority	-	

Table 16. Hazard ratio for gastrointestinal MBE until end of treatment for Study 1160.63 (RE-SONATE) – treated set.

	DE	P
Patients [N(%)]	684	659
Gastrointestinal MBE *	2 (0.3)	0
Hazard Ratio vs. placebo		
Estimate (95% CI) #	- (-, -)	
p-value for superiority	0.9964	

Table 17. Hazard ratio for gastrointestinal bleedings until end of treatment for acute VTE treatment studies – treated set

	DE	W
Number of patients	2456	2554
Gastrointestinal BE [N(%)] *	70 (2.9)	62 (2.4)
Model 1 #		
Hazard Ratio vs. warfarin		
Estimate (95% CI)	1.16 (0.82, 1.63)	

Table 18. Hazard ratio for gastrointestinal bleedings until end of treatment for study 1160.47 (RE-MEDY) – treated set

	DE	W
Patients [N(%)]	1430	1426
Gastrointestinal BE *	45 (3.1)	32 (2.2)
Hazard Ratio vs. Warfarin		
Estimate (95% CI) #	1.39 (0.87, 2.20)	
p-value for superiority	0.1645	

Table 19. Hazard ratio for gastrointestinal bleedings until end of treatment for study 1160.63 (RE-SONATE) – treated set

	DE	P
Patients [N(%)]	684	659
Gastrointestinal BE *	5 (0.7)	2 (0.3)
Hazard Ratio vs. placebo		
Estimate (95% CI) #	2.38 (0.46, 12.27)	
p-value for superiority	0.3000	

9. *It is noted that a Study 1160.88 in adolescents exposed to dabigatran has been included in the EU SmPC. Please advise if this study has been submitted to the TGA or if a submission will be submitted post-finalisation?*

Study 1160.88 has not been submitted to TGA for evaluation. The results of this study will be submitted to the TGA post finalisation, that is, after completion of the ongoing VTEt/sVTEp application.

Sponsor's response to issues raised by the Delegate for advice from ACPM (August 2014 meeting 299).

10. Should the indication exclude the claim of prevention of related death from both indications and provide a revised single indication? Should adults be specified?

Sponsor's response:

The sponsor agrees to exclude the claim prevention of related death from both indications and proposes the following revised indications:

> *Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in adults.*
>
> *Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in adults.*

11. Should a reduced dose of dabigatran be considered for patients with moderate renal impairment and if so what would be the most appropriate dose? Pradaxa is contraindicated in patients with severe renal impairment and the sponsor is not proposing a reduced dose for moderate renal impairment?

Please refer to the sponsor's detailed response regarding dosing in subgroups provided above to questions 6 and 4 (above). The sponsor considers the 150 mg BD dose of dabigatran etexilate appropriate for all subgroups analysed in patients with VTE. However, the interpretation of the data might be limited by the small number of events in some subgroups. Therefore the sponsor agrees to the harmonisation of the dosage for VTE and SPAF indications with respect to patients with moderate renal impairment.

12. Should a reduced dose of dabigatran be considered in patients aged ≥ 75 years and if so what would be the most appropriate dose? The sponsor is not proposing a dose adjustment for this group.

Please refer to the sponsor's responses to question 11 and to questions 6 and 4.

13. Should a reduced dose of dabigatran be considered for patients with an increased risk of bleeding and if so what would be the most appropriate dose? The sponsor is not proposing a dose adjustment for this group.

Please refer to the sponsor's responses to question 11 and to questions 6 and 4.

14. Should specific mention be made of patients with gastritis, esophagitis or gastro oesophageal reflux disease as having an increased risk of gastrointestinal bleeding and that the use of a lower dose of dabigatran should be considered for these patients in the PI? The sponsor is not proposing to specifically mention these groups in the PI.

Please refer to the sponsor's response to question 4 above. It is the sponsor's opinion that the 150 mg BD dose is the appropriate dose for all patients including all subgroups investigated. However, the sponsor has agreed to harmonise the dosage information between SPAF and the VTE indication. Therefore, in line with the current Pradaxa SPAF PI, the sponsor does not agree that a lower dose for patients with gastritis, esophagitis or gastro oesophageal reflux disease should be included in the PI.

15. Should the PI recommend against the concomitant use of P-gp inhibitors with dabigatran in those with moderate renal impairment? At present, the sponsor is not proposing to include this statement in the PI.

Please refer to the sponsor's detailed response regarding dosing in subgroups provided above to questions 6 and 4. The sponsor considers the 150 mg BD dose of dabigatran etexilate appropriate for all subgroups analysed in patients with VTE.

The only meaningful subgroup of patients with more than one risk factor constitutes a group of patients older than 75 years of age combined with moderately reduced renal

function (n = 76 patients who were treated with DE). Only a few patients had P-gp inhibitors as concomitant medication in the four pivotal trials (1.7% to 2.7 %). Due to the small sample size no subgroup analysis was done with these combined risk factors. The current PI states '*Specifically, with concomitant intake of antiplatelets or strong P-gp inhibitors in patients aged ≥ 75 years, the risk of major bleeding, including gastrointestinal bleeding, increases.*' The main evidence for this statement is the RE-LY trial which appears to be transferable for the VTE population as well. The sponsor considers that this statement is also appropriate for patients with DVT and/or PE.

16. *Are the dosing instructions in the PI, stating no dose adjustment is necessary in relation to concomitant use with P-gp inhibitors, appropriate or should information be included that there is limited data and that results may vary depending on the individual P-gp inhibitor?*

Limited data are available in VTE patients with concomitant intake of P-gp inhibitors. Only 1.7% to 2.7% of all patients in the four pivotal studies took P-gp inhibitors concomitantly. However, there is a comprehensive data set of P-gp inhibitor intake from the RE-LY trial that appears to be transferable for the VTE population as well.

In the 'Precautions', 'Haemorrhagic risk' and 'Interactions with other medicines' sections of the PI, overview of the interactions with P-gp inhibitors which is applicable for all indications that is not limited to a single indication, is provided. The sponsor considers the current information comprehensive and that no additional information is required.

17. *The PI is proposing treatment for up to 6 months and then lifelong for the prevention indication. Are these clinically appropriate or would the statements included in the EU SmPC be more appropriate?*

The sponsor proposes to add the following statement into the 'Dosage and administration section':

'*The recommended daily dose of Pradaxa is 300 mg taken as one 150 mg capsule BD following treatment with a parenteral anticoagulant for at least 5 days. The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (for example recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.*'

Timeline

Prior to the August 2014 ACPM meeting, the sponsor requested a 2 month 'clock stop' to allow for additional analyses to be conducted to address some of the Delegate's questions and to provide that information in the Pre ACPM Response. The TGA agreed to this request and the consideration of this item by ACPM was deferred.

During this time, however, publications in the British Medical Journal raised concerns about the monitoring of dabigatran for the currently approved indication of stroke prevention in patients with NVAF. The publications also raised concerns about the differences in approach between regulators, mainly the EMA and FDA, and the alleged withholding of information to regulators regarding analyses of dabigatran in relation to monitoring that could improve the medicine's safety. These publications and the sponsor's response to them along with further information regarding monitoring provided by the sponsor were reviewed by the Post Market Surveillance Branch (PMSB) (formerly Office of Product Review (OPR)) for the currently approved uses of dabigatran. PMSB also sought advice from ACSOM regarding monitoring of dabigatran for the NVAF indication. PMSB has completed their review and has made the following recommendations:

'*There is currently no evidence to support a recommendation regarding the utility of routine new oral anticoagulant (NOAC) plasma concentration monitoring.*

The proposal by the sponsor to update the Pradaxa PI to include information regarding the measurement of dabigatran related anticoagulation in specific situations such as overdose and urgent surgery is acceptable, provided that the data can be validated. Inclusion of such data would bring the Australian PI more in line with international product monographs.'

The sponsor has been requested to validate the data.

Timeline

For the current submission for the proposed VTE indication, the Delegate requested the sponsor address a number of additional questions in relation to the monitoring of dabigatran. These questions were formally sent to the sponsor (under Section 31 of the *Therapeutic Goods Act*) and their response is reviewed below. Due to these additional questions from the Delegate and the safety review being conducted by PMSB, consideration of this application by ACPM was deferred.

Questions raised by the delegate under section 31

The sponsor was requested to respond to the following questions in relation to the VTE indications requested in this submission. A summary of their response and then commentary is provided with each question. PMSB sent similar questions to the sponsor in relation to the NVAF indication which they have reviewed.

Question 1

1. *Please explain why dabigatran should not undergo routine, initial or intermittent laboratory monitoring either by plasma concentration monitoring or by using anticoagulation assays such as Ecarin Clotting Time, Thrombin Time or diluted Thrombin Time for the proposed indications or populations.*
    a. *Discuss if there are any special circumstances/populations where laboratory monitoring could be beneficial, e.g. the elderly, those with renal impairment, those with a higher risk of bleeding, etc.*
    b. *Discuss whether new patients or patients switching to dabigatran could benefit from laboratory monitoring.*
    c. *Discuss whether any changes to the Product Information are proposed as a result of the above?*

Sponsor's response summarised

Based on the totality of the data across the indications for dabigatran, the sponsor states that neither routine, initial or intermittent monitoring is needed for the safe use of dabigatran. This is based on nine Phase III trials across indications with the most data coming from the RE-LY trial in the NVAF population. The sponsor states that dabigatran does not require monitoring in the elderly, those with renal impairment, those with a higher risk of bleeding, for new patients or for patients switching from another oral anticoagulant. The sponsor does not propose to change the PI in relation to this matter. The sponsor has indicated that they have not performed any study in NVAF patients in which cohorts were dose adjusted to achieve different exposures to dabigatran in different predefined concentration ranges, thus there is no primary data correlating exposure with outcomes. The Reilly et al. paper[8] examined the relationship between dabigatran concentrations and clinical outcomes in patients receiving a single fixed dose throughout the study. Analyses showed a relationship between plasma concentrations and risks of ischemic stroke and major bleeding but the sponsor contends that the strongest predictor of clinical events was demographic factors and not plasma concentrations as shown from the c-statistic results. Figure 2 from Reilly et al. shows that at a higher concentration there is an increase in the risk of bleeding but the sponsor's internal simulations could not find

any dose adjustment where an improvement in safety was not counterbalanced by a loss of efficacy or vice versa. The sponsor noted difficulties with defining a therapeutic range and addressing the variability in plasma concentrations within a patient.

Delegate's evaluation of sponsor's response

The sponsor has provided a rationale for why there should not be monitoring of dabigatran, based on a number of clinical trials, with the most data coming from the RE-LY trial. There are no studies in which patients were dosed based on plasma concentrations and no studies comparing regularly monitored dabigatran with unmonitored dabigatran or monitored warfarin for the VTE indications proposed. The sponsor's response mainly discusses the issues with the NVAF population where analyses have been conducted by the sponsor examining the relationship between plasma concentrations and clinical outcomes. This information was reviewed by PMSB for the current indications. There was no further data provided in relation to the currently proposed indications.

A therapeutic range has not been defined and it may vary for each indication. Pradaxa is available in three strengths of 75 mg, 110 mg and 150 mg and being capsules cannot be divided to provide other doses. It should be noted that bioavailability significantly increases if the capsule is opened and sprinkled onto food (1.8 fold).

The Delegate remains concerned at the lack of data in the VTE indications to explore whether monitoring could be beneficial, especially for the more at risk populations, the lack of studies using doses other than 150 mg BD, especially for patients at higher risk of bleeding, and the lack of a therapeutic range being defined. Given the association between plasma concentrations and risk of bleeding, then knowing an approximate upper limit on the plasma concentration of dabigatran, where the risk of bleeding would be significant, might be helpful to prescribers to manage patients who could have an excessive exposure due to risk factors. However, it is unclear for when and how often to monitor patients. The sponsor should continue to analyse and study these issues.

Question 2

2. *Has there been any modelling or analysis of dabigatran plasma concentrations or anticoagulation assay results in the proposed indications or populations to:*
    a. *Investigate the potential role for any laboratory monitoring?*
    b. *Investigate a potentially improved efficacy and/or safety profile for dabigatran?*
    c. *Investigate dose adjustment?*
    d. *If there has been any modelling or analysis undertaken for the above questions, please submit the reports to the TGA.*

Sponsor's response summarised

One study in this submission, RE-COVER, assessed PK and PD aspects that assessed steady state dabigatran at Days 30 and 180. The analysis provided evidence of consistency with the RE-LY data. Due to the low number of ischaemic events, no assessment of efficacy related to exposure could be performed. Only a limited exposure response analysis on major bleeding could be performed. The sponsor concluded that the analysis did not allow any conclusion on the value of any laboratory monitoring for the newly proposed indications nor could it be used for any investigation on a potentially improved efficacy or safety profile or dose adjustment by means of laboratory monitoring.

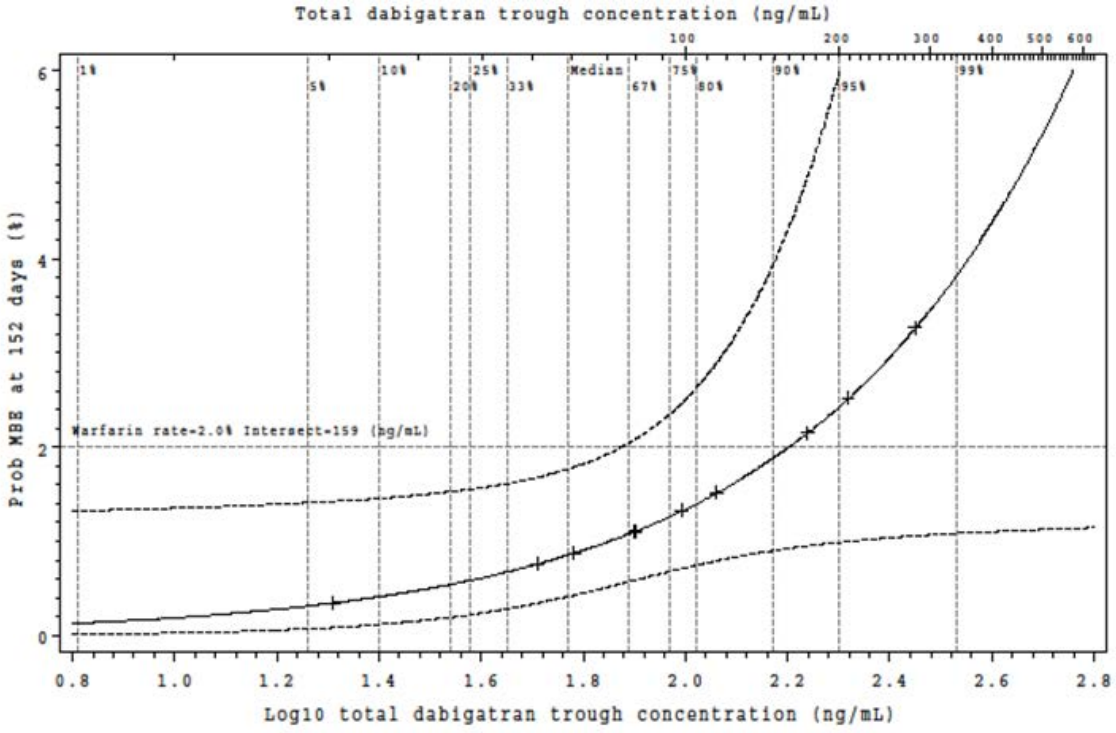
Delegate's evaluation of sponsor's response

The sponsor conducted a limited exposure response analysis for major bleeding and VTE related deaths. A summary is provided below.

The sponsor conducted an exposure response analysis (U12-3388) between bleeding and total dabigatran trough concentrations (TDTC) and between VTE or VTE related death and TDTC. This was based on data from patients treated for acute onset VTE with 150 mg BD DE for 6 months. The analysis was based on a Cox regression time to event model and included the $\log_{10}$ TDTC. PK samples were collected at Day 30 and Day 180 along with unscheduled samples from patients who had a DVT, PE, major bleed or acute renal failure. Samples from Day 30 were primarily used unless not available. Of the 1,273 patients treated with dabigatran, there were 997 samples available. There were some small differences between these two groups in demographics. The data were $\log_{10}$ transformed to make it more normally distributed. The TDTC values on the original scale ranged from 1.9 to 891 ng/mL and the median was 58.9 ng/mL. The 10th, 25th, 75th, and 90th percentiles were 25.2, 38.3, 94.2, and 149.0 ng/mL, respectively. Of the 1,273 patients exposed to dabigatran 17 had major bleeding events. Of this group only 10 patients had PK samples, thus the sample size is very small. Of these 10 major bleeding patients, 5 occurred within the first 30 days of treatment. Two occurred at both extremes of the TDTC (1 between the 5th and 10th percentile, and 1 just above the 95th percentile), and the other 3 occurred within close proximity to the median. The other 5 events all occurred after 2 months of active treatment (between 70 and 152 days post first medication), and at higher trough concentrations (between the 67th and 99th percentiles). A clear relationship was apparent between TDTC and time to first major bleed (p-value for slope = 0.0494, HR=7.2).

Figure 2 presents the predicted model based risk of an MBE event at 6 months (using the latest time point of an event carried forward from Day 152). The 95% confidence intervals are also presented graphically and the x-axis range of 0.8 to 2.8 included the range of the 1st and 99th percentiles of the observed total dabigatran trough concentrations in study 1160.53 (RE-COVER). Vertical lines corresponded to various $\log_{10}$ TDTC percentiles and the horizontal line of 2% referred to the warfarin reference rate described above.

Figure 2. Probability of an MBE occurring up to end of treatment period versus $\log_{10}$ TDTC.



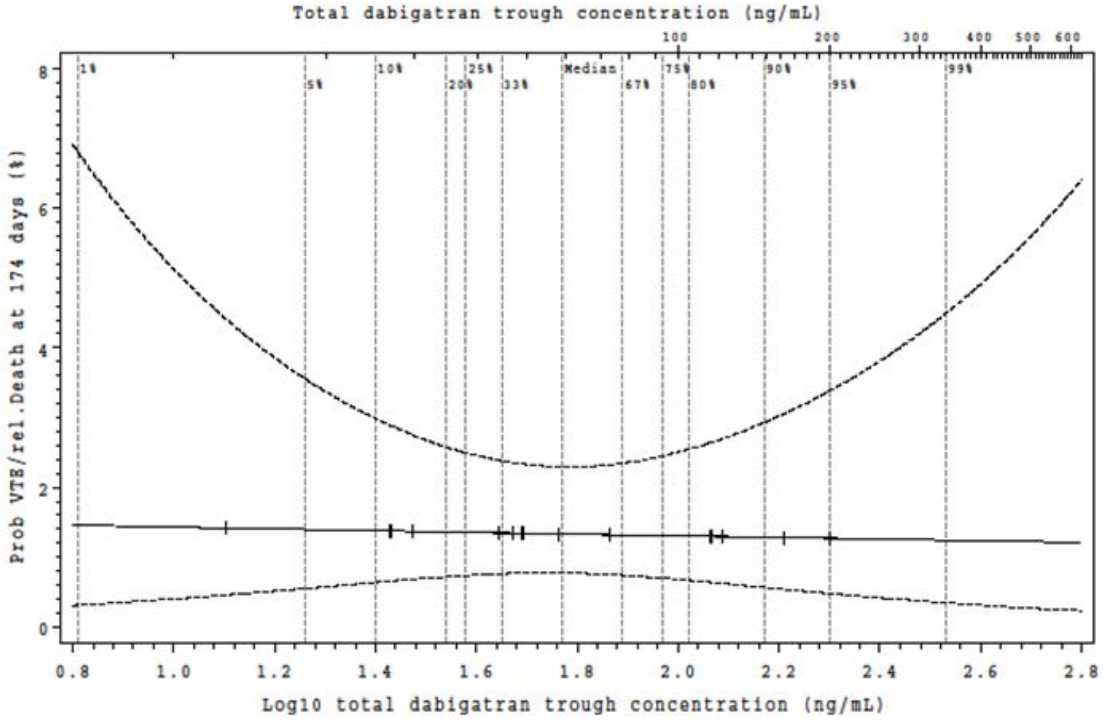
The sponsor states that since the lower bound of the 95% confidence interval for the estimate of the probability of an MBE within 6 months never crosses the designated warfarin MBE rate (2.0% within 6 months), it cannot be concluded that there was more

bleeding with DE than warfarin at any plasma level within this data set. However, although the figure may appear to support this, the dataset is too small to draw this conclusion and the true value could be anywhere between the confidence intervals. Going from the 10th to the 90th percentile (25 to 148 ng/mL), the probability of a major bleed increases from 0.4% to 1.9%, however the results should be interpreted with caution given the low sample size and widening confidence intervals.

Of the 1,273 patients exposed to dabigatran, 34 had VTE related death. Of this group, only 16 patients had PK samples, thus the sample is again very small. The 16 events appeared to be evenly distributed across time and across TDTC. There appeared to be no relationship between TDTC and time to first VTE related death (p = 0.9056).

Figure 3 presents the predicted model based risk of a VTE/related death event at Day 174, the latest time point of an event up to 6 months. The 95% CIs are also presented. Vertical lines corresponded to various log_{10} TDTC.

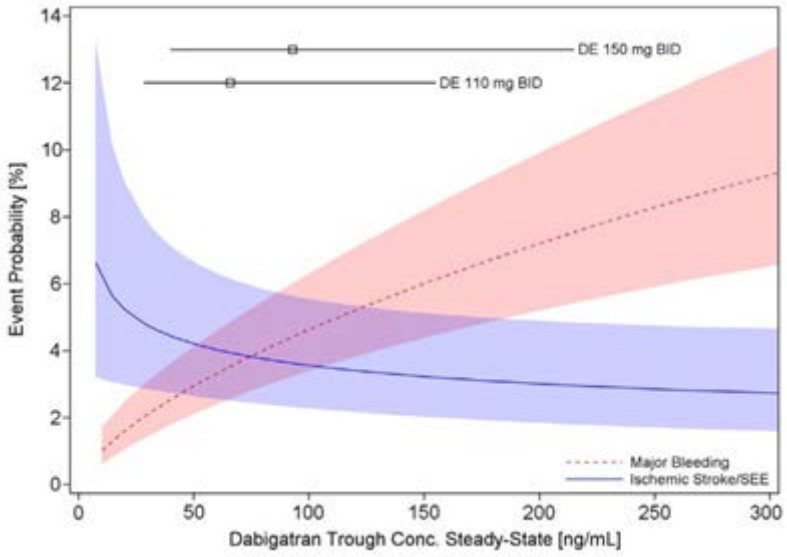
Figure 3. Probability of VTE related death occurring up to end of treatment versus log_{10} TDTC.



Given the small amount of data from the single VTE study, then further information on the exposure response relationship seen in the RE-LY trial between dabigatran plasma concentrations and the probability of bleeding or stroke was considered. This relationship has been explored in the Reilly et al. paper[8] which has been reviewed by PMSB. In brief, the Reilly et al paper examined the effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischaemic stroke and major bleeding in atrial fibrillation patients using data from the RE-LY trial. The RE-LY trial randomised 18,113 patients with atrial fibrillation to either 110 mg or 150 mg BD doses of dabigatran or dose adjusted warfarin (INR 2 to 3) in a non inferiority design. Plasma samples from the RE-LY trial were collected once at one month post randomisation in all DE patients who gave consent, without regard to when the patient had a stroke or bleeding event. About 12% of samples were excluded from the analysis and additional samples were included from 2,143 patients who had samples taken at 3, 6 and 12 Months. About 70% of randomised patients provided trough dabigatran levels and 76% provided peak levels. The mean trough concentrations were 64.7 and 91.0 ng/mL for the 110 and 150 mg doses. The 10th

and 90th percentiles were 28.2 to 155 ng/mL for the 110 mg dose and 39.8 to 215 ng/mL for the 150 mg dose, indicating a range of over 5 fold in concentrations. Renal function was important in determining concentrations (mild impairment had 47% increase in trough concentrations and moderate impairment had a 2.29 fold increase in trough concentrations compared with normal renal function (CrCl ≥ 80 mL/min)). Increasing age, females and low body weight patients also had higher concentrations. Patients with a major bleeding event had a median trough concentration on average 55% higher than those without a major bleeding event. Median and 10th to 90th percentiles for the 323 patients with a major bleed were 116 (46.7 to 269)ng/mL compared with 75.3 (30.7 to 175) ng/mL for the 5,899 patients without a major bleed. Using the logistic regression curves for stroke and major bleeding, a comparison was made for a 72 year old male with previous stroke and diabetes and the predicted 10th to 90th percentiles for the 110 and 150 mg doses as shown in the Reilly et al paper and reproduced below. This paper suggested that some patients may benefit from having their dose adjusted if their dabigatran concentration was at the high end or the low end, although there is a lack of supporting clinical data for this hypothesis, amongst other limitations (for example most concentrations were assessed at one month into the study, 30% of patients did not provide trough levels, lack of temporal proximity to the event).

Figure 4. Probability of a major bleeding event and ischaemic stroke/SEE versus trough dabigatran plasma concentration (from Reilly et al.[8]).



Calculated for an atrial fibrillation patient with prior stroke and diabetes. Lines and boxes at the top of the panel indicate median dabigatran concentrations in the RE-LY trial with 10th and 90th percentiles. Conc. ¼ concentration; DE ¼ dabigatran etexilate; SEE ¼ systemic embolic event(s).

Figures 5 and 6 show the probability of a major bleed or stroke from RE-LY.

Figure 5. Probability of major bleeds vs. trough plasma concentration of total dabigatran in AF patients receiving either 110 or 150 mg DE BD.

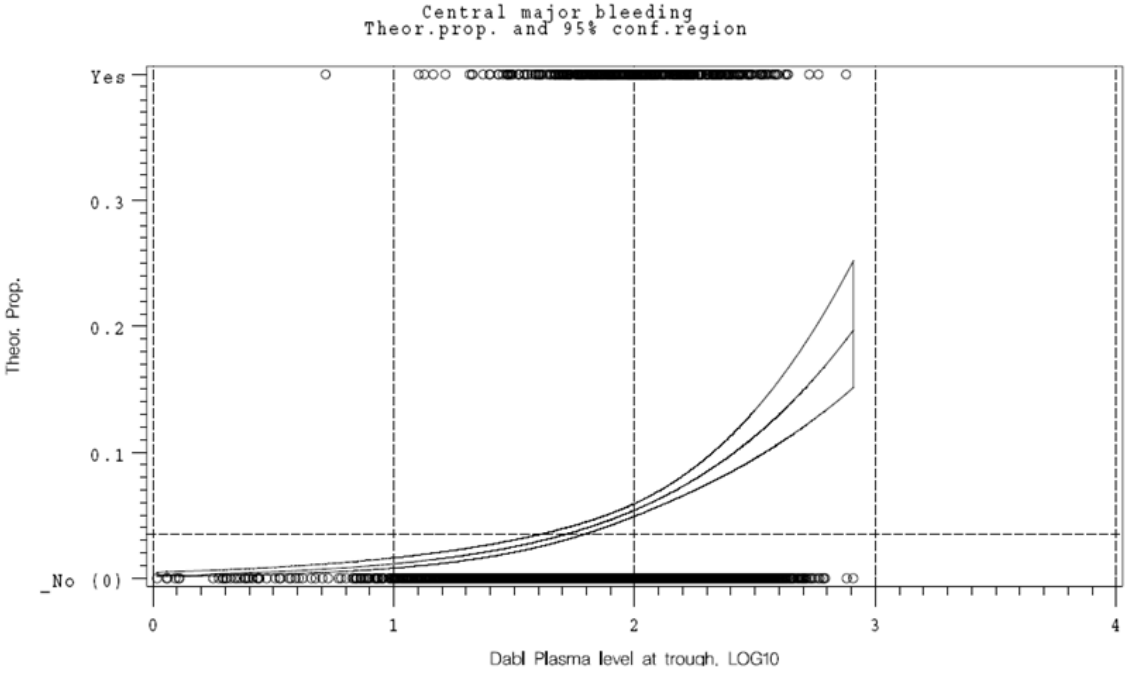
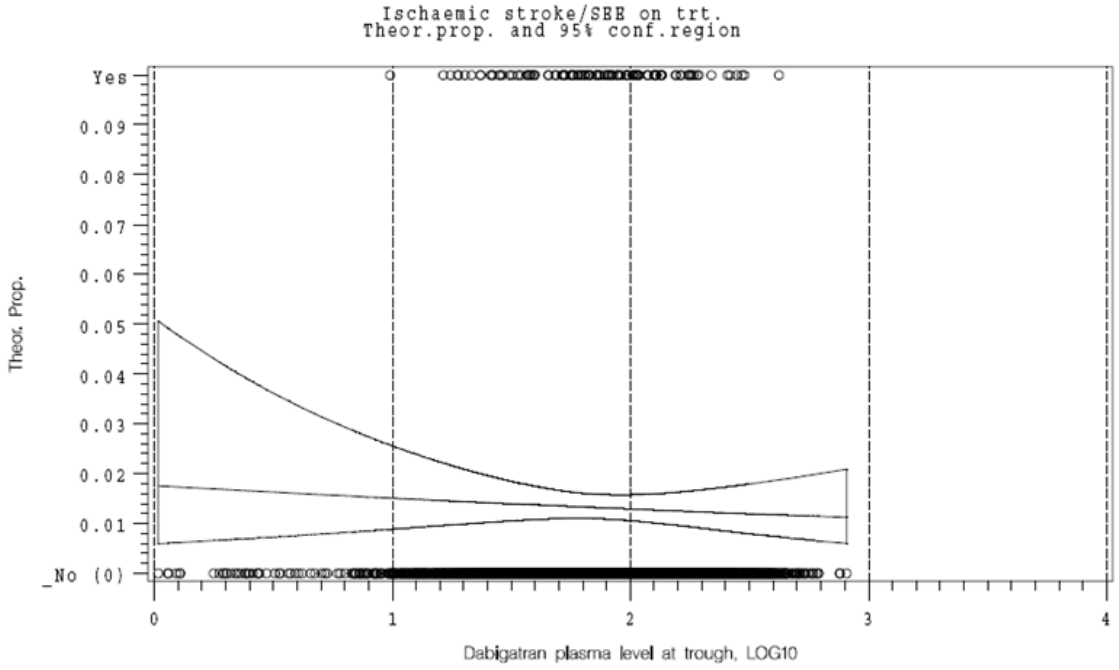


Figure 6. Probability of ischaemic stroke and systemic embolic events versus. log_{10} trough plasma concentration of total dabigatran (Dabi) in AF patients receiving either 110 or 150 mg DE BD.



The conclusion from the VTE exposure response analysis was that the sample size determining the predicted models was small with wide confidence intervals thus making definitive conclusions difficult. Whilst no clear relationship was seen between dabigatran concentrations and VTE/related death, there appeared to be a relationship between dabigatran concentrations and major bleeding which is consistent with the RE-LY data.

Question 3

3. Please confirm whether all data, including modelling, in relation to dabigatran and the proposed indications or populations have been submitted to the TGA.

Sponsor's response summarised

For the new indications, the sponsor has provided the exposure response analyses above and additional sub group analyses.

Delegate's evaluation of sponsor's response

The sponsor has confirmed that all analyses have been provided.

Question 4

4. Please discuss if there is a therapeutic range for dabigatran that could be defined for the proposed indications or populations?

Sponsor's response summarised

PK and PD data are only available from the RE-COVER study and not from the VTE prevention studies. The small amount of data from this study and the use of only one dose, that is 150 mg BD, are substantial limitations. RE-COVER showed some difference in dabigatran trough levels in patients with and without symptomatic DVT (50.1 versus 59.8 ng/mL) but no difference in PK for PE, VTE or all death. Therefore the lack of a clear exposure response relationship was missing information for a therapeutic range to be defined. The exposure to major bleed analysis indicated that going from the 10th to the 90th percentile (25 to 148 ng/mL) the probability of a major bleed increases from 0.4% to 1.9% and that above a concentration of 125 ng/mL, the confidence intervals became very wide. The analysis was not stratified by age and therefore the higher percentage of bleeding at the higher concentration was biased by the greater presence of elderly patients (who have a higher risk of bleeding irrespective of dabigatran exposure). Thus the data do not allow a therapeutic range to be defined at present.

Delegate's evaluation of sponsor's response

The sponsor was unable to define a therapeutic range from a single VTE treatment study (no VTE prevention data) given the small sample size on which the analysis is based, wide confidence intervals, lack of stratification by other factors such as age and lack of clinical data examining dose adjustment based on plasma concentrations. However it does display consistency with the RE-LY data for the exposure bleeding relationship. It may be that the therapeutic range is different for each indication, given the plasma concentrations were on average lower in the RE-COVER study than the RE-LY study. Further data should be obtained by the sponsor to examine this matter. It is noted that half the patients (n = 5) who had a major bleed did so after 2 months on treatment and their concentrations were between the 67th and 99th percentiles, indicating that major bleeds can occur later on treatment.

Question 5

5. The clinical evaluation report, noted that bleeding tended to increase with plasma concentrations. Please explain why a dose adjustment or laboratory monitoring of patients would not be beneficial to reduce the risk of bleeding. Are any changes to the PI proposed based on the pharmacokinetic results?

Sponsor's response summarised

The sponsor acknowledges that there is a an increase in bleeding with increasing plasma concentrations but notes that the rate of major bleeding in the pooled RE-COVER and RE-MEDY trials was less than warfarin. The sponsor's view is that at present there is inadequate data to support an exposure measurement/dose adjustment scheme aimed at

improving dabigatran's overall risk-benefit profile and therefore no changes to the PI are proposed.

Delegate's evaluation of sponsor's response

The Delegate acknowledges the limitations of the data, but of the data that is available, it appears that increasing concentrations of dabigatran are associated with an increased risk of bleeding. Major bleeding events by CrCl tended to be similar on DE and warfarin, although the numbers are sometimes too small to be clear. Major bleeding events by age showed an increasing hazard ratio with age for patients on DE compared to warfarin (Table 20), especially for those ≥ 80 years. When clinically relevant bleeding events were considered with major bleeding events or any bleeding, then this trend was less clear. Although the event rate was low, there were twice as many major bleeding events in people aged ≥ 80 years on DE than warfarin for the VTE treatment study. The PI should include this information.

Table 20. Bleeding events (MBEs, MBEs/CRBEs and any bleeding) by age categories in the pivotal aVTEt and sVTEp studies – treated set.

Age categories, n/N (%)	Treatment No. events/no. of patients (%)		DE/W Hazard Ratio (95% CI)
MBEs			
Pooled aVTEt studies	**DE**	**W**	
Pooled aVTEt studies, from start of any treatment			
<65 years	14/1771 (0.8)	24/1746 (1.4)	0.57 (0.30, 1.11)
65 to 75 years	12/529 (2.3)	15/532 (2.8)	0.76 (0.36, 1.64)
>75 years	11/253 (4.3)	12/276 (4.3)	1.03 (0.45, 2.33)
≥80 years	6/135 (4.4)	3/125 (2.4)	1.99 (0.50, 7.95)

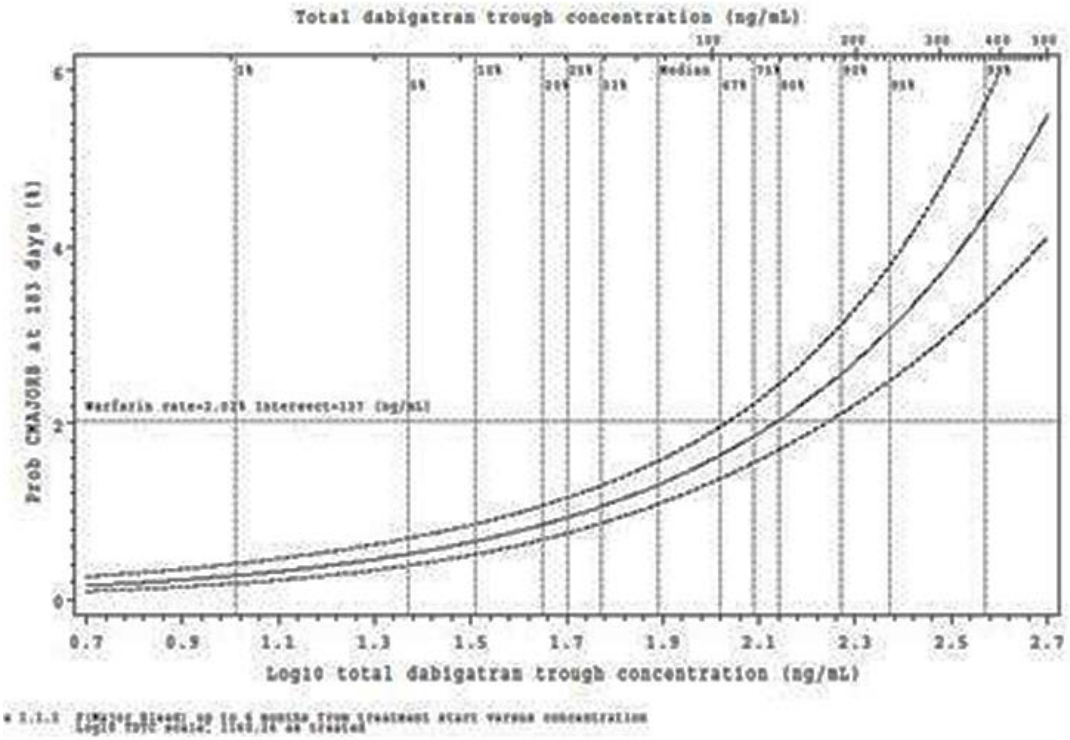
6. *Please submit details regarding any discussions with the FDA, EMA or Health Canada regarding laboratory monitoring of dabigatran in relation to the new indications proposed.*

Sponsor's response summarised

During the review for the new indications, there were no discussions with the US FDA or Health Canada regarding laboratory monitoring of dabigatran. The EMA did raise a question that the sponsor should further assess the correlation between dabigatran exposure in VTE patients and clinical events in order to be able to define the target range of PK values where it is necessary to perform drug monitoring (in a bleeding or emergency setting for example). The sponsor responded that the RE-COVER study was the only study in the current submission that assessed PK, as discussed above, and although the correlation is weaker in this study than RE-LY (see below), the data clearly confirm a relationship between exposure and bleeding.

Figure 7 represents total dabigatran trough concentration to major bleeding (MBE) relationship for RE-LY (at Day 183). Vertical lines represent percentiles from 1 to 99 percentile. The trough total dabigatran concentration corresponding to 2% MBE risk probability was 159 ng/mL and 137 ng/mL for RE-COVER and RE-LY patients, respectively.

Figure 7. Total dabigatran trough concentrations – major bleeding relationship for RE-LY.



The sponsor also noted a high consistency between RE-COVER and RE-LY patients when comparing trough dabigatran concentrations from patients stratified by age, renal function or verapamil co-medication (see below).

Table 21. RE-COVER and RE-LY comparing trough dabigatran concentrations from patients stratified by age, renal function or verapamil co-medication.

	RE-COVER		RE-LY	
	N	Dabigatran trough conc. (ng/mL)	N	Dabigatran trough conc. (ng/mL)
AGE (years)		gMean (gCV%)		gMean (gCV%)
≥ 75	841	121 (74.6)	1616	114 (76.9)
	662	139 (88.4)		
≥ 65 to < 75	186	70.6 (83.7)	1860	84.6 (73.9)
	159	77.0 (69.4)		

	RE-COVER		RE-LY	
< 65			746	67.1 (90.6)
50 to < 65	263	58.8 (76.8)		
	230	56.9 (81.2)		
CrCl (mL/min)	N	gMean (gCV%)	N	gMean (gCV%)
30 to < 50	32	170 (83.6)	761	144 (80.6)
	23	185 (61.3)		
50 to < 80	181	85.8 (65.2)	1969	95.2 (73.0)
	170	91.7 (84.8)		
≥ 80	627	50.5 (73.0)	1347	64.8 (71.6)
	544	49.4 (77.6)		
Verapamil Co- med	N	gMean (gCV%)	N	gMean (gCV%)
+Verapamil	14	82.4 (170)	322	110 (79.3)
	11	97.3 (107)		
-Verapamil	836	59.4 (80.1)	5940	90.6 (82.3)
	735	59.1 (89.3)		

[1] and [2] trough concentration at visit 4 and 9, respectively.

A trough dabigatran concentration exceeding 200 ng/mL which is exceeding the 90th percentile in RE-LY, may be associated with a presumably increased risk of bleeding for VTE patients also if the co-morbidities and co-medications are similar.

The EU SmPC includes a table that contains this information and was updated to add VTE patients as having the same thresholds of increased risk of bleeding. The sponsor says that the EMA accepted their argument that monitoring is not justified and that the sponsor is required to conduct further analyses in ongoing and upcoming clinical trials to check for consistency of the results between studies on the correlation of PK data to major bleeding events and ischaemic events and provide these results in the upcoming PSURs.

Delegate's evaluation of sponsor's response

It is recommended that the Australian PI should be updated to include further information on coagulation assay results which indicate an increased risk of bleeding and the requirement for further analyses by the EMA should be a condition of registration here.

Question 7

7. *Are there any clinical trials completed, underway or being proposed or discussed for dabigatran that includes laboratory monitoring as part of the study design? Are there any clinical trials that compare routine, initial or intermittent monitoring of dabigatran with unmonitored dabigatran or with warfarin?*

Sponsor's response summarised

The sponsor does not intend to further explore the relationship between dabigatran exposure levels and outcome events for the current indications. They do not plan to compare monitored and non-monitored dabigatran to each other or to warfarin. Routine anticoagulation testing was not utilised in any of the clinical trials for dabigatran; therefore there is no clinical trial evidence to support regular anticoagulation testing for the proposed indication or current indications. The RE-LY trial for NVAF demonstrated dabigatran to be safe and effective using fixed doses. An upcoming trial in secondary stroke prevention will assess PK sampling at one sample per patient. There are two other studies in which PK sampling has been done in patients with severe renal disease to verify the PK model used in the USA for the 75 mg BD dose which is approved for patients in the US with severe renal impairment for the NVAF indication (this group is contraindicated in Australia). Two other studies have investigated plasma levels of dabigatran in a paediatric program that is ongoing and the trial in artificial heart valves which was terminated due to thromboembolic and bleeding imbalance.

The sponsor comments on the difference between dabigatran and warfarin including: dabigatran works on thrombin compared to warfarin on multiple coagulation factors, T_{max} is 1 to 2 hours compared to days for warfarin, mean terminal half-life in elderly volunteers was 12 to 14 hours compared to days for warfarin, faster onset of action and offset, linear pharmacokinetics compared to variable PK for warfarin, renal excretion is the dominant elimination route, advancing age affects exposure, wider therapeutic margin than warfarin, dose titration is not needed. The sponsor notes that although dabigatran plasma levels are approximately 40% higher in females than males, the efficacy and bleeding profile between females and males is comparable. Age and renal function are the two main factors that impact bleeding risk.

Delegate's evaluation of sponsor's response

The sponsor's response is noted however the sponsor is still encouraged to further investigate the pharmacokinetics of dabigatran to determine if laboratory monitoring could provide a further improved safety profile, especially in certain high risk patient groups such as the elderly and those with renal impairment.

Question 8

8. *Is the sponsor proposing to include further information in the PI for dabigatran regarding plasma concentrations or anticoagulant activity that may be associated with an increased risk of bleeding or regarding a therapeutic range or any form of laboratory monitoring in relation to the proposed indications?*

Sponsor's response summarised

The sponsor acknowledges that the EU SmPC includes information on dabigatran plasma levels that might be associated with an increased risk of bleeding which was included at the request of the EMA but is not part of the sponsor's Company Core Data Sheet for Pradaxa. The sponsor acknowledges that the TGA and healthcare providers in Australia might find it desirable to include this information. The sponsor notes that the FDA advisory committee meeting in 2010 did not believe that monitoring was necessary.

Delegate's evaluation of sponsor's response

The sponsor should include further information in the PI on dabigatran plasma levels associated with an increased risk of bleeding.

Question 9

9. Does the sponsor intend to undertake any post-marketing studies with dabigatran such as a patient registry or surveillance of the product's safety in the populations proposed for registration?

Sponsor's response summarised

The sponsor is planning a worldwide post-market observational study in 6,000 patients with acute DVT and/or PE to compare the rate of major bleeding and clinically relevant non-major bleeding in patients treated with DE versus warfarin on a background of a LMWH, amongst other endpoints.

Delegate's evaluation of sponsor's response

The sponsor should submit this information to the TGA for evaluation once the study is complete.

Question 10

10. Is the sponsor intending to undertake a product familiarisation programme with regards to the new indications proposed?

Sponsor's response summarised

The sponsor is not intending to conduct a product familiarisation programme for the new indications proposed.

Delegate's evaluation of sponsor's response

The sponsor's response is noted.

Delegate's conclusion

The Delegate has provided comments on the sponsor's response to each of the questions above which has led to some further questions for ACPM, along with PI changes and questions for the sponsor below. Additional conditions of registration have also been proposed. Based on the limited PK data, the data suggest that increased concentrations of dabigatran are associated with an increased risk of bleeding for the VTE indication; however, it is unclear what the therapeutic range should be at present. The sponsor has indicated that a trough concentration exceeding 200 ng/mL, which is exceeding the 90th percentile in RE-LY, may also be associated with an increased risk of bleeding for VTE patients if the co-morbidities and co-medications are similar. Whilst this approach is noted, patients may not necessarily have the same medications or co-morbidities. ACSOM and the RMP evaluator have provided advice in relation to monitoring.

Delegate's comments on the interim pre ACPM response from the sponsor

The sponsor provided an interim pre ACPM Response with the Section 31 response that includes information covered above along with responses to some other questions.

The sponsor lodged a submission in early 2015 for an antidote to dabigatran called idarucizumab following a Phase III case series study that was commenced in May 2014. The availability of specific assays for dabigatran includes the Hemoclot direct thrombin inhibitor test which is a diluted Thrombin Time test that is available in Australia and another assay called the Technoclot DTI assay based on dTT which has been available since June 2014. The sponsor is expecting other assays will become available later in 2014/15. The sponsor also has a paediatric investigational plan in Europe for dabigatran that includes six studies that are completed, ongoing or planned.

Dosing in subgroups

One of the concerns of the Delegate raised is the lack of clinical data examining the safety and efficacy of DE at a dose of 110 mg BD for the proposed VTE indications for patients with moderate renal impairment, aged ≥ 75 years or for patients at increased risk of bleeding. The sponsor has responded to this concern to indicate that no further studies are planned to investigate whether a lower dose of 110 mg BD is safe and efficacious in the VTE indications, unlike that for the NVAF indication. The sponsor considers that the four pivotal studies in VTE support the 150 mg BD dose given the non inferiority demonstrated to warfarin and the lack of significant interactions between treatments and subgroups. However, the sponsor acknowledges that in certain subgroups, the number of events was small and a firm conclusion cannot be made. Therefore the sponsor is proposing to harmonise the recommended dosage for the VTE indication subgroups with the NVAF indication. The sponsor states, '*Therefore, in the sub populations defined by the current NVAF PI, exposure with 110 mg BD is expected to stay within or even above the average exposure in the majority of VTE patients receiving 150 mg BD. Hence, it can be assumed that most of the anticoagulation efficacy will be preserved when this VTE population with a higher risk of bleeding is treated with DE 110 mg BD.*' The sponsor is requested to fully explain the logic and predicted dabigatran exposure levels in these patients exposed to 110 mg BD compared with patients exposed to 150 mg BD.

RE-MEDY sensitivity analysis

The sponsor provided a sensitivity analysis of patients who were rollover patients from the RECOVER studies compared with patients who were previously given a Vitamin K antagonist. The analysis indicated no significant difference in the primary efficacy endpoint frequency between patients previously treated with DE who then went on to DE or warfarin or patients previously treated with warfarin who then went on to DE or warfarin. However patients previously treated with a vitamin K antagonist outside of a controlled clinical study who then went on to DE or warfarin showed that those who stayed on warfarin had a lower event rate than those who went on to DE.

Gastrointestinal bleeding

The sponsor provided data from the four pivotal studies on gastrointestinal bleeding which showed that for any GI bleeding events, the frequency was higher on DE compared with warfarin but for major bleeding events, the frequencies were about the same. The comparisons did not show statistically significant results. Compared to placebo, any or major GI bleeds were higher on DE.

Dosage in severe renal impairment

The sponsor provided a paper by Liesenfeld et al.[11] which was a population pharmacokinetic analysis of dabigatran in patients with non-valvular atrial fibrillation from the RE-LY trial. The simulations in this analysis suggested that a dose of 75 mg BD would provide similar exposure in patients with severe renal impairment (CrCl 15 to 30ml/min) and normal renal function patients on 150 mg BD. In the US, a 75 mg BD dose is approved for patients with severe renal impairment with atrial fibrillation but for patients with DVT/PE a dose recommendation could not be made. In Australia, Canada and Europe, severe renal impairment is a contraindication for all indications.

[11] Liesenfeld KH et al. Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial. *Journal of Thrombosis and Haemostasis* 2011; 9: 2168-2175.

Additional publication

The sponsor provided a publication by Wan et al.[12] that was a systematic review of anticoagulation control and prediction of adverse events in patients with atrial fibrillation that concluded that time in the therapeutic range and percentage of INRs in the range effectively predict INR control.

Comments by the sponsor on the delegate's questions to ACPM

The sponsor has agreed to delete the indication claim of prevention of related death from the indications and has specified adults in both indications. The sponsor has now proposed to reduce the dose in patients with moderate renal impairment, age ≥ 75 years and for patients at increased risk of bleeding. The sponsor does not propose to reduce the dose in patients with gastritis, esophagitis or gastroesophageal reflux disease since they are aligning the dose with the NVAF indication. However in the EU, it is noted that for patients with NVAF or DVT/PE, it is recommended that a dose of 110 mg BD be considered due to the elevated risk of major GI bleeding. The sponsor is also not proposing against the use of concomitant P-gp inhibitors with dabigatran in patients with moderate renal impairment, given the low use in the VTE studies (1.7 to 2.7%) and therefore no subgroup analysis was done due to the small sample size.

RMP

The sponsor has agreed to include patients under 18 years and patients with low body weight in the ASA to the RMP as important missing information and has agreed to update the educational materials to reflect the new indications and provide these to the TGA. The RMP evaluator has reviewed the ACSOM advice and response by the sponsor and has advised that the sponsor's response is acceptable. The same RMP condition of registration is proposed. The following matters should be addressed by the sponsor with PMSB and responded to in the pre ACPM response:

1. The risk of unintentional over dosage resulting from capsule content being opened and sprinkled over food or into beverages is communicated adequately in the educational material and CMI.
2. The CMI comments from ACSOM are considered so that the information is understood by consumers.
3. Updated printed educational materials should be provided to TGA (PMSB) for review prior to finalisation of this submission that reflects the updated indications.
4. The recommendation regarding concomitant use with strong P-gp inhibitors remains as per the original discussion in the request for ACPM advice.

Questions for sponsor

The sponsor is requested to address the following questions in their Pre-ACPM Response in addition to those identified in the original Request for ACPM's Advice:

5. Please summarise any commitments or conditions made by the sponsor with the FDA or EMA in relation to this submission and further studies or analyses.
6. The sponsor is requested to fully explain the rationale and predicted dabigatran concentrations in each of the patient subgroups who are proposed for the 110 mg BD dose compared with patients exposed to 150 mg BD for the VTE indications, given the lack of clinical data at the 110 mg BD dose from the submitted studies.

[12] Wan Y et al. Anticoagulation Control and Prediction of Adverse Events in Patients With Atrial Fibrillation : A Systematic Review. *Circulation Cardiovascular Quality and Outcomes* 2008; 1: 84-91.

7. For dosing in the elderly, if a reduced dose of 110 mg BD is proposed for the VTE indications, please explain the rationale supporting the age cut-off of ≥ 75 vs ≥ 80 years. Are there further analyses or simulations to support either age cut-off?

Conditions of registration

The following are proposed as conditions of registration and the ACPM and sponsor are invited to comment:

8. The implementation in Australia of the EU RMP for Pradaxa (dabigatran), version 26, dated 25 April 2013 (data lock point 18 September 2012), with the ASA, version 26.1, and the RMP agreements from the pre ACPM response, included with the submission, and any subsequent revisions, as agreed with the TGA.
9. The sponsor is to continue to perform pharmacokinetic analyses in the ongoing and upcoming clinical trials, to check the consistency of the results between studies on the correlation of PK data to major bleeding events and ischaemic events and provide the results of these analyses within the upcoming PSURs.
10. The sponsor is to further investigate/analyse the pharmacokinetics of dabigatran to determine if laboratory monitoring could provide an improved safety and efficacy profile.
11. The final study reports for the following studies must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission or submissions:
    a. The worldwide post-market observational study in 6000 patients with acute DVT and/or PE to compare the rate of major bleeding and clinically relevant non-major bleeding in patients treated with dabigatran versus warfarin on a background of a low molecular weight heparin.
    b. Study 1160.88 in adolescents.

Additional advice requested from ACPM

ACPM's advice is requested on the following questions in addition to those put forward for the request for advice from the August 2014 ACPM.

12. Does ACPM have any comments on the advice in the PI that dabigatran does not require routine laboratory anticoagulant monitoring? It is noted that the EU SmPC, Canadian PI and the US PI all include similar statements.
13. In addition to the advice from ACSOM on laboratory monitoring, does ACPM have any further comments on the utility of laboratory monitoring for the VTE indications, including for special populations who may be at increased risk of bleeding, and if so what is the evidence to support such a recommendation?
14. Should the PI include additional information on coagulation test thresholds that may be associated with an increased risk of bleeding, such as the information in the EU SmPC? If so, should the threshold for the VTE indications be the same as for the NVAF indication?
15. In relation to ACPM questions 11, 12 and 13[13] in the original Request for ACPM's Advice, the sponsor proposes to align the dosing instructions for VTE subgroups at increased risk of bleeding with the dosing for the NVAF subgroups at increased risk of bleeding. In addition to these questions, if dosing in the elderly is lowered, should the age cut-off be ≥ 75 or ≥ 80 years?

[13] In this document, the numbers of the questions have been changed for ease of reference; in the original document, these were questions 2, 3 and 4 respectively.

Sponsors response to Delegate's overview for ACPM meeting of June 2015

Sponsor's response to comments on RMP

1. *The risk of unintentional over-dosage resulting from capsule content being opened and sprinkled over food or into beverages is communicated adequately in the educational material and in the CMI.*

Sponsor's response

The sponsor provided a revised CMI. The information pertaining to the correct usage of the drug has been strengthened and made more prominent by the use of capitals. In addition, new educational materials will address this topic.

2. *The CMI comments from ACSOM are considered so that the information is understood by consumers*

Sponsor's response

The sponsor provided a revised CMI. The contraindication '*…stomach bleeding in the past year, unless it has been fixed*' has been expanded to '*…stomach bleeding in the past year, unless the cause has been permanently eliminated e.g. by surgery*'. The drug interactions referring to '*selective serotonin re-uptake inhibitors*' and '*selective serotonin norepinephrine re-uptake inhibitors*' have been expanded to include generic examples of the medicines – SSRIs citalopram, escitalopram, fluoxetine; SNRIs duloxetine, venlafaxine, desvenlafaxine.

3. *Updated printed educational materials should be provided to TGA (PMSB) for review prior to finalisation of this submission that reflect the updated indications.*

Sponsor's response

The sponsor has provided a commitment to provide the PMSB with updated printed educational materials for review that reflect the updated indications.

4. *The recommendation regarding concomitant use with strong P-gp inhibitors remains as per the original discussion in the Request for ACPM Advice.*

Sponsor's response

The sponsor agrees with the TGA recommendation to include cyclosporin and itraconazole to the list of contraindications as follows:

- Concomitant treatment with systemic ketoconazole, cyclosporin, itraconazole or dronedarone (see Precautions).

However, the sponsor disagrees with the recommendation to include tacrolimus to the list of Contraindications. The current Australian PI is aligned with the current EU SmPC that is; '*The concomitant use of dabigatran etexilate with … tacrolimus … is not recommended*'.

Sponsor's response to questions for the sponsor raised by the TGA Delegate

5. *Please summarise any commitments or conditions made by the sponsor with the FDA or EMA in relation to this submission and further studies or analyses.*

Sponsor's response

The following commitments are made with the FDA and EMA in relation to the DVT/PE submission:

EMA:

> '*It was agreed that the Applicant should continue to perform PK analyses in the ongoing and upcoming clinical trials, to check the consistency of the results between studies on the correlation of PK data to MBE events and ischaemic events and provide the results of these analyses within the upcoming PSURs.*'

FDA:

Post marketing requirements to conduct paediatric studies in the VTE indication is shown in Table 22.

Table 22. FDA post marketing requirements to conduct paediatric studies in the VTE indication.

PMR 2139-1	Conduct an open label, single dose, single arm, tolerability, PK/PD and safety study of dabigatran etexilate given at the end of standard anticoagulant therapy in children aged less than 1 year old.
PMR 2139-2	Conduct an open label, randomised, parallel group, active controlled, multi-centre, non-inferiority efficacy study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than. 18 years of age. Include PK/PD (sparse sampling) in all patients. The anticipated enrolment is 240 evaluable patients for the efficacy analysis. Enrol adequate numbers of patients in 3 age groups, from 12 to < 18 years of age, from 2 to < 12 years of age, from birth to < 2 year of age. Submit the clinical study report with datasets. Patients from birth to < 2 year of age may be enrolled only after data from a planned interim analysis have shown efficacy and safety of dabigatran in the older paediatric age groups.
PMR 2139-3	Conduct an open label, single arm trial to evaluate safety of dabigatran etexilate for secondary prevention of venous thromboembolism in children aged 0 to less than 18 years. The anticipated enrolment is 100 patients. Submit the clinical study report with datasets.

The above mentioned clinical studies are already reflected in the Paediatric Committee (PDCO), EMA.

6. *The sponsor is requested to fully explain the rationale and predicted dabigatran concentrations in each of the patient subgroups who are proposed for the 110 mg BD dose compared with patients exposed to 150 mg BD for the VTE indications, given the lack of clinical data at the 110 mg BD dose from the submitted studies.*

Sponsor's response

The sponsor considers the clinical data from the 4 pivotal trials with a total of 8,197 randomised patients sufficiently supportive for the recommendation that the 150 mg BD dosing is suitable for all patients in the VTE indication. However, the sponsor acknowledges that in certain subgroups, the number of events is small and a firm conclusion cannot be made, and therefore has agreed to harmonise the posology for the VTE indication and the SPAF indication based on the following argumentation.

The results of the 3 pivotal studies (DE versus. warfarin) demonstrate that DE given at a dose of 150 mg BD was non inferior to warfarin for the treatment of aVTEt and for the prevention of recurrent VTE events in a broad spectrum of low to high risk patients. In the fourth pivotal study, DE was superior to placebo in preventing recurrent VTEs in those thought to be at equipoise for the need for continuing anticoagulant therapy. There were no significant interactions between treatment and subgroup results, further supporting the use of 150 mg BD dose of DE in all patient subgroups.

The incidence of all categories of MBEs (MBEs, adjudicated MBEs with a fatal outcome, Thrombolysis in Myocardial Infarction (TIMI) major bleeding, and intracranial MBEs) as well as life threatening bleeding events, any bleeding events (including MBEs, CRBEs, and nuisance/trivial bleeding), and discontinuation of study drug due to bleeding was consistently lower in DE 150 mg BD patients compared to warfarin for studies of short (6 months in the aVTEt studies) and longer duration (up to 36 months in sVTEp Study 1160.47). Fewer DE patients than warfarin patients discontinued study drug due to all severities of bleeding. In the overall results, and in most of the subgroups analyses including patients with moderate renal impairment and patients aged 75 years, the incidence of centrally adjudicated MBEs, MBE/CRBEs, and any bleeding events was lower in DE treated patients compared with warfarin treated patients.

From the PK/PD analyses of both RE-LY and RE-COVER studies, the pharmacodynamic response (anticoagulation), as well as therapeutic response (bleeding and antithrombotic efficiency), are closely related to dabigatran exposure. Furthermore, consistency could be demonstrated in the PK (Table 23), PK/PD and the relationship between exposure and clinical safety (major bleeding events) between the NVAF and VTE patient population, although no dedicated exposure to efficacy relationship could be demonstrated for the VTE patient population.

Table 23. Steady state total dabigatran trough concentrations (geometric Mean and geometric CV) in VTE (1160.53, RE-COVER) and AF patients (1160.26, RE-LY) treated with 150 mg BD by age, renal function (CrCl) and verapamil co-medication. For Study 1160.53, both measurements at visit 4 (1) and visit 9 (2) are presented. The age category in 1160.53/RECOVER was 50 to < 65 while in RE-LY, the equivalent category was < 65.

	RE-COVER		RE-LY	
	N	Dabigatran trough conc. (ng/mL)	N	Dabigatran trough conc. (ng/mL)
AGE (years)		gMean (gCV%)		gMean (gCV%)
≥75	84[1] 66[2]	121 (74.6) 139 (88.4)	1616	114 (76.9)
≥65-<75	186 159	70.6 (83.7) 77.0 (69.4)	1860	84.6 (73.9)
<65			746	67.1 (90.6)
50-<65	263 230	58.8 (76.8) 56.9 (81.2)		
CRCL (mL/min)	N	gMean (gCV%)	N	gMean (gCV%)
30-<50	32 23	170 (83.6) 185 (61.3)	761	144 (80.6)
50-<80	181 170	85.8 (65.2) 91.7 (84.8)	1969	95.2 (73.0)
≥80	627 544	50.5 (73.0) 49.4 (77.6)	1347	64.8 (71.6)
Verapamil Co-med	N	gMean (gCV%)	N	gMean (gCV%)
+Verapamil	14 11	82.4 (170) 97.3 (107)	322	110 (79.3)
-Verapamil	836 735	59.4 (80.1) 59.1 (89.3)	5940	90.6 (82.3)

[1] and [2] trough concentration at visit 4 and 9, respectively.

Therefore, in the subpopulations defined by the current NVAF label, exposure with 110 mg BD is expected to stay within or even above the average exposure in the majority

of VTE patients receiving 150 mg BD. Hence, it can be assumed that most of the anticoagulation efficacy will be preserved with this VTE population with a higher risk of bleeding is treated with DE 110 mg BD.

In conclusion, the sponsor considers the existing data on the 110 mg BD dose from RE-LY together with the high consistency between the patient populations in terms of the PK, PK/PD and exposure-response results seen in the TR-LY and RE-COVER studies, as sufficient evidence to consider the 110 mg BD dose for the same sub-populations in VTE as in NVAF. However, the sponsor will continue to perform PK analysis in the ongoing and upcoming clinical trials where relevant, to check the consistency of the results between studies on the correlation of PK data to MBE events and ischaemic events and provide the results of these analyses within the upcoming PSURs.

7. *For dosing in the elderly, if a reduced dose of 110 mg BD is proposed for the VTE indications, please explain the rationale supporting the age cut-off of ≥ 75 versus ≥ 80 years. Are there further analyses or simulations to support either age cut-off?*

Sponsor's response

Please see also the response to question 6 above with detailed information about dabigatran plasma concentration across different patient population stratified by age, renal function and intake of P-gp inhibitors. The sponsor agrees to the proposal by TGA to align the dosages between the VTE indication and SPAF. This clearly has the advantage that a dosing error in the VTE indication and SPAF can be prevented. An evaluation with an age cut-off ≥ 80 years has the limitation of a small sample size in this age group which does not allow for firm conclusions with n = 122 patients in the DE group and n = 121 patients in the warfarin group. Table 24 and 25 display the frequencies of MBE stratified by < or ≥ 75 years and < or ≥ 80 years. The MBE frequencies in the DE groups appear to be consistent if < 75 years (0.7%) is compared with < 80 years (0.9%) and ≥ 75 (3.0%) is compared with ≥ 80 years (3.3%). When the latter groups are compared with the warfarin groups a small numerical but not statistical difference in favour of warfarin can be seen.

Table 24. Frequency of centrally adjudicated MBE by age group (< 75, ≥ 75 years) for acute VTE treatment studies – treated set.

Age		DE	W
<75 years	Patients [N (%)]	2191 (100.0)	2165 (100.0)
	MBE [n (%)]	16 (0.7)	29 (1.3)
>=75 years	Patients [N (%)]	265 (100.0)	297 (100.0)
	MBE [n (%)]	8 (3.0)	11 (3.7)

Table 4.13.5.1.3.1.1 Frequency of centrally adjudicated MBE by age group (< 80, >=80 years) for acute VTE treatment studies - treated set

Table 25. Frequency of centrally adjudicated MBE by age group (<80, ≥80 years) for acute VTE treatment studies - treated set.

Age		DE	W
<80 years	Patients [N (%)]	2334 (100.0)	2341 (100.0)
	MBE [n (%)]	20 (0.9)	37 (1.6)
>=80 years	Patients [N (%)]	122 (100.0)	121 (100.0)
	MBE [n (%)]	4 (3.3)	3 (2.5)

Sponsor's response to conditions of registration

8. *The Implementation in Australia of the EU Risk Management Plan for Pradaxa (dabigatran), version 26, dated 25 April 2013 (data lock point 18 September 2012), with the Australian Specific Annex (ASA), version 26.1, and the RMP agreements from the Pre-ACPM Response of (date) included with the submission PM-2103-02038-1-3, and any subsequent revisions, as agreed with the TGA.*

Sponsor's response

An updated EU RMP for Pradaxa version 30.1, dated 15 December 2014 (DLP 18 Mar 2013) and updated ASA will be submitted to the PMSB before the end of May 2015.

9. *The sponsor is to continue to perform pharmacokinetic analyses in the ongoing and upcoming clinical trials, to check the consistency of the results between studies on the correlation of PK data to major bleeding events and ischaemic events and provide the results of these analyses within the upcoming PSURs.*

Sponsor's response

The sponsor commits to perform PK sampling and descriptive analyses for a new target indication (efficacy and safety of 150 mg BD, adjusted to 110 mg BD DE in specific subgroups versus 100 mg Acetylsalicylic acid in patients for secondary stroke prevention who had an embolic stoke of undetermined source (ESUS), 1160.189 Phase III study RESPECT-ESUS trial).

Several PK/PK and Exposure/Response analyses have already been conducted throughout the clinical development for the approved indications. A therapeutic range applicable to all patients within the respective indications is not definable as clinical characteristics of patients such as age, renal function and specific co-medications as described in the PI determine primarily the exposure level. The sponsor does not intend to further explore the relationship between dabigatran exposure levels and outcome events in the licensed adult indications (SPAF, pVTEp, and DVT/PE) for the following reasons:

- Routine anticoagulation testing was not utilised in any of the clinical trials in any indication for the NOACs, therefore there is no clinical trial evidence to support regular anticoagulation testing.
- Fixed doses of DE in Phase III clinical trials were demonstrated to be effective and safe, and provided a positive net clinical benefit in the absence of anticoagulant testing.
- The properties of dabigatran are very different to warfarin (the anticoagulation effect of dabigatran is predictable, time to C_{max} for dabigatran is 1 to 2 hours, T½ for dabigatran is 12 to 14 hours, dabigatran has fast onset and offset of action, dabigatran has predictable linear pharmacokinetics, plasma levels of dabigatran are unaffected by body weight, gender, ethnicity or hepatic function, dabigatran is not considered a narrow therapeutic index drug, in clinical trials no monitoring and dose titration were needed for dabigatran, key variables for dabigatran's fixed dose profile are age and renal impairment, dabigatran has limited and clearly defined drug/drug interactions and no drug food interactions).
- Plasma concentrations of dabigatran alone are not be predictive of bleeding events and stroke occurrences.
- Age and renal function had been demonstrated across various trials and patient populations as decisive factors for PK and PD including the stroke and bleeding risk of patients treated with dabigatran. It seems highly unlikely that any new trial will provide new information in this regard.
- The European Society of Cardiology Guidelines[14] agree that '*the NOACs do not require dose adjustment on the basis of a specific coagulation test*'.
- In certain situations such as suspected overdose, emergency situation, in the perioperative setting, in the event of bleeding due to potential excessive dabigatran exposure, anticoagulant testing may be indicated. In these situations, the Hemoclot thrombin inhibitor assay may be used to determine whether the cause of bleeding is

[14] The European Society of Cardiology Guidelines. *European Heart Journal* 2013; 33: 2719-2747.

dabigatran or whether the patient may be at an increased risk (perioperative setting) related to dabigatran A value of 200 ng/mL may be associated with a higher risk of bleeding.

- The approved PI for Pradaxa provides adequate guidance on dosing reflecting the important patient characteristics like age, renal function, and co-medication for the three approved Pradaxa indications. Furthermore, the warning and precaution section points out the need for close monitoring of signs of bleeding throughout dabigatran treatment.

10. The sponsor is to further investigate / analyse the pharmacokinetics of dabigatran to determine if laboratory monitoring could provide an improved safety and efficacy profile

Please refer to the sponsor's response to Question 9 above.

11. The final study reports for the following studies must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission or submissions:

a. The worldwide post-market observational study in 6000 patients with acute DVT and/or PE to compare the rate of major bleeding and clinically relevant non-major bleeding in patients treated with dabigatran versus warfarin on a background of a low molecular weight heparin.

b. Study 1160.88 in adolescents.

The sponsor confirmed that the post-market observational study addressed under a. will be submitted as a Category 1 submission as soon as possible after completion. Furthermore, the sponsor confirmed that a Category 1 submission pertaining to Study 1160.88 will be submitted after approval of the ongoing DVT/PE application, currently under TGA review.

Sponsor's response to the Delegate's additional advice requested from ACPM

12. Does the advice in the PI, Pharmacodynamics section, that dabigatran does not require routine laboratory anticoagulant monitoring remain appropriate at present? It is noted that the EU SmPC, Canadian PI and the US PI all include similar statements.

Sponsor's response

It is critically important to consider that development of non-vitamin K antagonist oral anticoagulants (NOACs) was prompted primarily by the PK and PD limitations of vitamin K antagonists. Vitamin K antagonists are unique among antithrombotic drugs in their absolute requirement for routine coagulation monitoring. It is this requirement for monitoring and the challenges in achieving a stable therapeutic level that makes warfarin challenging to use, if not unpalatable, in many patients with AF. To put this in perspective, oral antiplatelet drugs such as clopidogrel produce variable effects but are not monitored. Unfractionated heparin is routinely monitored but 50 years after its introduction many questions remain concerning optimal dosing and monitoring targets and we learned from the FIDO trial that unfractionated heparin given subcutaneously in fixed doses without routine monitoring produces similar outcomes to those of LMWH. All of the LMWHs produce variable anticoagulant effects of a magnitude that is similar to the variability in the effects of the NOACs but they are routinely used in fixed doses without routine coagulation monitoring.

All currently available NOACs produce variable anticoagulant effects and there is nothing to suggest that dabigatran should be singled out in this regard. The magnitude of this variability is similar to that seen with LMWH and fondaparinux. Increasing blood levels of the drug or increasing coagulation effects of the drugs are associated with higher rates of bleeding and lower rates of stroke. The observation of an association between a drug level or a coagulation effect and outcome does not necessarily mean that adjusting the dose of

the drug will improve outcomes. In order to adopt such a position it needs to know the optimal drug level for a particular situation and also one needs to know that adjusting the dose based on the results of the test will yield benefits for patients. This is currently speculative and unproven. The pivotal RELY trial in over 18,000 patients demonstrated a superior clinical profile compared to well controlled warfarin for both fixed test doses of DE without any plasma level monitoring. While the higher dose 150 mg BD demonstrated superior stroke prevention and a comparable major bleeding rate, the lower dose 110 mg BD demonstrated a superior with respect to a lower major bleeding profile and a non-inferior stroke reduction versus warfarin. Both doses at the same time reduced significantly the intracranial bleed rate compared to warfarin. Any putative additional benefit in clinical outcomes with adjusted dosing based on monitoring would require a prospective clinical trial of a size similar to that of RE-LY, comparing fixed dosing of dabigatran with adjusted dosing.

In the period between January and September 2012 a number of simulation analyses were performed to explore whether exposure measurement, either directly using trough plasma concentration or indirectly using CrCl, might further improve the positive benefit-risk balance of DE versus warfarin. Simulations were based on PK and exposure-response models (which were based on models used for submission and were later published). Finally, the attempted internal validation of the model predictions and trial simulations by using the RE-LY trial data failed and the evaluation was discontinued. Therefore, exposure is only one factor determining outcome and compared with age (or renal function) it seems of less relevance.

Meanwhile numerous observational studies have been published reporting safety and effectiveness data of dabigatran compared to warfarin in the indication of SPAF. In the following, only the recently published study by Graham et al.[15] is briefly summarised as this presents currently the largest dataset of any NOAC in real world. Moreover, it has been evaluated and published independently of the sponsor via the US FDA.

In this observational cohort study more than 134,000 Medicare (USA) patients, all aged 65 years or older were evaluated, comprising 37,500 person-years of follow-up. In summary, dabigatran was associated with a lower risk of ischaemic stroke, intracranial haemorrhage and death compared to warfarin. The risk for major gastrointestinal bleeding was increased for dabigatran compared with warfarin (Table 26).

Table 26. Comparative effectiveness of dabigatran versus warfarin based on Medicare dataset.

Outcome event	Dabigatran	Warfarin	Adjusted HR (95% CI-interval)
Ischemic stroke	11.3	13.9	0.80 (0.67-0.96)
ICH	3.3	9.6	0.34 (0.26-0.46)
Major GI bleed	34.2	26.5	1.28 (1.14-1.44)
Acute MI	15.7	16.9	0.92 (0.78-1.08)
Mortality	32.6	37.8	0.86 (0.77-0.96)

In the US only 150 mg BD is approved as main dose and 75 mg BD only for patients with severe renal impairment. Table 27 shows the incidence rates by outcome after dose stratification.

[15] Graham DJ et al. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. *Circulation* 2015; 131: 157-164.

Table 27. The effect of daily dose of dabigatran on risk of ischemic stroke, major gastrointestinal-bleeding, intracranial hemorrhage and mortality compared with treatment with warfarin for nonvalvular-atrial fibrillation.*

	Ischemic stroke Hazard ratio (95% CI)	Major GI bleed Hazard ratio (95% CI)	Intracranial hemorrhage Hazard ratio (95% CI)	Mortality Hazard ratio (95% CI)
75 mg bid(n=10,522)	0.88 (0.60-1.27)	1.01 (0.78-1.31)	0.46 (0.26-0.81)	0.95 (0.78-1.16)
150 mg bid(n=56,576)	0.70 (0.57-0.85)	1.51 (1.32-1.73)	0.30 (0.21-0.42)	0.76 (0.67-0.86)

* Because of covariate imbalances between dabigatran and warfarin cohorts after stratification by dose, patients were matched within strata defined by daily dabigatran dose, resulting in a total of 67,098 patients in each cohort rather than 67,207 from the primary analysis.

In conclusion, the results of this observational study of the usage of fixed doses of dabigatran without monitoring in clinical practice are concordant with the results of the pivotal study RE-LY.

13. *In addition to the advice from ACSOM on laboratory monitoring, does ACPM have any further comments on the utility of laboratory monitoring for the VTE indications, including for special populations who may be at increased risk of bleeding, and if so what is the evidence to support such a recommendation?*

Sponsor's response

All clinical trials during the clinical development supporting the registered and proposed indications were performed with fixed doses of DE without any adjustment and without plasma level monitoring. It is unknown and unproven whether performing blood tests to rule out excess or inadequate anticoagulation of anticoagulant effects with dabigatran is possible, necessary or will lead to a net benefit.

14. *Should the PI include additional information on coagulation test thresholds that may be associated with an increased risk of bleeding, such as the information in EU SmPC? If so, should the threshold for the VTE indications be the same as for the NVAF indication?*

Sponsor's response

Please refer to the response to comments on the PI.

15. *In relation to ACPM questions 11, 12 and 13 in the original Request for ACPM's Advice, the sponsor proposes to align the dosing instructions for VTE subgroups at increased risk of bleeding with the dosing for the NVAF subgroups at increased risk of bleeding. In addition to these questions, if dosing in the elderly is lowered, should the age cut-off be ≥ 75 or ≥ 80 years?*

Sponsor's response

Please refer to refer to the response to comments on the PI.

16. *Changes to the PI/CMI*

Sponsor's response

The Delegate's recommended changes to the PI and CMI have been addressed by the sponsor.

Advisory committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Pradaxa capsules containing 75 mg, 110 mg and 150 mg of dabigatran etexilate to have an overall positive benefit–risk profile for the amended indication:

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE in adults.

In making this recommendation, the ACPM advised that the indication should be restricted to the adult population and the claim of prevention of related death should be removed from the sponsor's proposed indications.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration. It however, remained concerned about the current limited understanding of factors resulting in adverse effects. Intensive pharmacovigilance remained warranted. The ACPM recommended that in addition to the requirement for the submission of PSURs, the RMP should be amended to include a requirement that the sponsor provide each six months until further notice a cumulative analysis of adverse events reported in Australia including wherever known the dose, body weight, age, patient's renal function, dabigatran concentrations and measures of anticoagulant activity. If possible, similar information from reports in New Zealand and Europe should be included in each analysis.

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 stronger warning and additional information against the concomitant use with P-gp inhibitors and dabigatran, particularly in patients with moderate renal impairment.
- Provide additional information regarding dosing adjustment with concomitant use of dabigatran and verapamil, amiodarone or quinidine.
- Preference should be given to using accepted international terminology used in renal failure that ischronic kidney disease status and eGFR.
- Mild renal impairment should be added to the precautions section as causing increased plasma levels of dabigatran.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission.[16]

1. *Should the indication exclude the claim of prevention of related death from both indications and provide a revised single indication? Should adults be specified?*

The ACPM agreed with the Delegate that the claim of prevention of related death from both indications should not be included and that the proposed indications should be restricted to adult patients, which is supported by the data provided.

2. *Should a reduced dose of dabigatran be considered for patients with moderate renal impairment and if so what would be the most appropriate dose? Pradaxa is contraindicated in patients with severe renal impairment and the sponsor is not proposing a reduced dose for moderate renal impairment.*

See Response for Question 4.

3. *Should a reduced dose of dabigatran be considered in patients aged ≥ 75 years and if so what would be the most appropriate dose? The sponsor is not proposing a dose adjustment for this group.*

[16] Note the numbering of the questions is rearranged and questions 1 to 8 below corresponds to questions 10 to 17 from the request for advice for the ACPM meeting of August 2014. Questions 9 to 12 were in the Delegate's request for advice from the June 2015 ACPM (meeting 304) (which correspond to questions 12 to 15).

See Response for Question 4

4. *Should a reduced dose of dabigatran be considered for patients with an increased risk of bleeding and if so what would be the most appropriate dose? The sponsor is not proposing a dose adjustment for this group.*

The ACPM noted the reduced dose (110 mg twice a day) was not included as part of the clinical trials for DVT but was of the view that the reduced dose would be appropriate in certain groups of patients, including patients with moderate renal impairment (30 to 50 mL/min CrCl), patients aged ≥ 75 years and patients with a high risk of major bleeding or those who have a past history of GI bleeds. The ACPM noted that the sponsor has agreed to harmonise the posology for the VTE indication and the SPAF (stroke and stystemic embolism prevention in patients with non-valvular atrial fibrillation) indication.

5. *Should specific mention be made of patients with gastritis, esophagitis or gastroesophageal reflux disease as having an increased risk of gastrointestinal bleeding and that the use of a lower dose of dabigatran should be considered for these patients in the PI? The sponsor is not proposing to specifically mention these groups in the PI.*

The ACPM was of the view that for patients with a past history of gastrointestinal bleed or an increased risk of gastrointestinal bleed, a lower dose would be necessary. The ACPM did not consider that gastritis itself caused bleeding and that it is not necessary to make specific mention of patients with gastritis or gastro-oesophgeal reflux being at higher risk of gastrointestinal bleeding. The ACPM advised that the PI should provide a stronger warning regarding the importance of dose reduction in the patients who had an increased risk of bleeding.

6. *Should the PI recommend against the concomitant use of P-gp inhibitors with dabigatran in those with moderate renal impairment? At present, the sponsor is not proposing to include this statement in the PI.*

The ACPM noted that the sponsor had amended the PI in their pre-ACPM response to include cyclosporin and itraconazole (P-gp inhibitors) in the contrainidcations section of the PI. The ACPM advised that the PI should also include a stronger warning against the use of P-gp inhibitors with dabigatran particularly in patients with moderate renal impairment.

7. *Are the dosing instructions in the PI, stating no dose adjustment is necessary in relation to concomitant use with P-gp inhibitors, appropriate or should information be included that there is limited data and that results may vary depending on the individual P-gp inhibitor?*

The ACPM noted that the PI states no dosage adjustment is necessary with concomitant use of dabigatran and verapamil, amiodarone or quinidine. The ACPM was of the view that the dosing instructions in the PI are inadequate and additional information regarding dosing adjustment should be included.

8. *The PI is proposing treatment for up to 6 months and then lifelong for the prevention indication. Are these clinically appropriate or would the statements included in the EU SmPC be more appropriate?*

The ACPM was of the view that there was insufficient evidence to support lifelong treatment and duration of treatment should be based on the clinical judgement.

9. *Does ACPM have any comments on the advice in the PI that dabigatran does not require routine laboratory anticoagulant monitoring? It is noted that the EU SmPC, Canadian PI and the US PI all include similar statements.*

See response to question 10.

10. *In addition to the advice from ACSOM on laboratory monitoring, does ACPM have any further comments on the utility of laboratory monitoring for the VTE indications, including for special populations who may be at increased risk of bleeding, and if so what is the evidence to support such a recommendation?*

The ACPM considered that valuable information could be discerned if there was a study of the use of dabigatran and the effect of monitoring dabigatran, especially for high risk patients. The ACPM was of the view that dabigatran monitoring may be of value in certain groups of patients, who had a higher risk of bleeding.

11. *Should the PI include additional information on coagulation test thresholds that may be associated with an increased risk of bleeding, such as the information in the EU SmPC? If so, should the threshold for the VTE indications be the same as for the NVAF indication?*

The ACPM was of the view that there are not enough trial data to provide insight into the use of coagulation test thresholds in a clinical setting. The ACPM noted that the sponsor had amended the PI in their pre ACPM response to include the same table of coagulation test thresholds that appears in the EU SmPC. This was considered appropriate.

12. *In relation to ACPM questions 11, 12 and 13[13] in the original request for ACPM's advice, the sponsor proposes to align the dosing instructions for VTE subgroups at increased risk of bleeding with the dosing for the NVAF subgroups at increased risk of bleeding. In addition to these questions, if dosing in the elderly is lowered, should the age cut-off be ≥ 75 or ≥ 80 years?*

The ACPM advised that the cut-off age should be 75 years of age. For patients > 75 years, a reduced dose of 110 mg BD should be used.

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

Additional advice

Following advice on the substantive application at the 304 meeting of ACPM, the Delegate requested further advice specific issues concerning the PI.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Pradaxa capsules containing 75 mg, 110 mg and 150 mg of dabigatran etexilate to have an overall positive benefit–risk profile for the indication:

> *Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE in adults.*

Specific advice

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

- *Should the Australian PI Table 14 include the additions factors listed in the comparable tables in the EU and/or HC (Health Canada) product monographs (and therefore prescribers should consider dose reduction in the presence of these factors) or are they adequately covered in the Contraindications and Precautions sections? Is the sponsor's proposal acceptable? If not, which factors should be included in amended table, and why?*

The ACPM advised that inclusion of the additional factors proposed for the PI table on factors which increase haemorrhagic risk would be helpful for clinicians. The table format is easy to read and can be used as a 'quick reference'.

Although no direct evidence of the need for dose reduction in these additional points was submitted these are known haemorrhagic risk factors and it would be prudent for prescribers to consider dose reduction.

The ACPM was of the view that duplication of the information contained in the Precautions and Contraindications sections in the table is acceptable as it reinforces the information about risk factors.

The ACPM advised the most satisfactory outcome would be the updating of the Australian PI to align the proposed Table 14 with the corresponding table in the Health Canada Product Monograph.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Pradaxa dabigatran etexilate (as dabigatran etexilate mesilate) 75 mg, 110 mg and 150 mg capsules for oral administration, indicated for:

> *Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE in adults.*

Specific conditions of registration applying to these goods

1. The dabigatran EU-RMP version 31.2, dated 29 May 2015, (data lock point 18 March 2015) with ASA version to EU-RMP version 31.2 dated 10 July 2015, included with the submission, and any subsequent revisions, as agreed with the TGA will be implemented in Australia
2. You are to continue to perform pharmacokinetic analyses in the ongoing and upcoming clinical trials, to check the consistency of the results between studies on the correlation of PK data to major bleeding events and ischaemic events and provide the results of these analyses within the upcoming PSURs.
3. You are to provide each six months until further notice a cumulative analysis of adverse events reported in Australia including wherever known the dose, body weight, age, patient's renal function, dabigatran concentrations and measures of anticoagulant activity. If possible, similar information from reports in New Zealand and Europe should be included in each analysis. These could be provided with the six-monthly PSURs.
4. You are to further investigate/analyse the pharmacokinetics of dabigatran to determine if laboratory monitoring could provide an improved safety and efficacy profile
5. The final study reports for the following studies must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission or submissions:
    a. The worldwide post-market observational study in 6,000 patients with acute DVT and/or PE to compare the rate of major bleeding and clinically relevant non-major bleeding in patients treated with dabigatran versus warfarin on a background of a low molecular weight heparin.
    b. Study 1160.88 in adolescents.

Attachment 1. Product Information

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

Attachment 2. Extract from the Clinical Evaluation Report

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