CLINICAL EVALUATION

Pradaxa
(Dabigatran etexilate)

Applicant: Boehringer Ingelheim (N.Z.) Limited

TT Number	TT50-7557
Date of this report:	09/06/10
Evaluator	

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CLINICAL CRITICAL ASSESSMENT

I. INTRODUCTION

I.1 Type of Application and aspects on development

Pradaxa is currently available in New Zealand and indicated for the prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery. It is available in 75mg and 110mg capsules. Boehringer Ingelheim has submitted a CMN relating to provision of an additional indication for the prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation. They have also submitted a NMA for an additional 150mg capsule strength. This clinical evaluation will cover both the additional indication and the additional capsule strength.

Dabigatran etexilate is an orally available prodrug of dabigatran, a competitive, reversible direct thrombin inhibitor. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. The inhibition of the thrombin dependent conversion of fibrinogen to fibrin prevents formation of thrombus.

For this clinical evaluation, the main study used for new and relevant (i.e. for the new indication and dose) clinical pharmacology, efficacy and safety data was the RE-LY study. This was a single, open-label, non-inferiority trial (n = 18,133). It was a large, multicentre, multinational study at 951 sites in 44 countries. The study consisted of three treatment arms: dabigatran 110mg bid; dabigatran 150mg bid; and warfarin. The two dabigatran doses were blinded.

I.2 GCP aspects

Trials were conducted following GCP. For the main study (RE-LY), all sites were monitored regularly for protocol and GCP compliance, including drug accountability, reporting of outcomes and adverse events, subject safety and responsibilities of the investigator.

II. CLINICAL PHARMACOLOGY

II.1 Pharmacokinetics

II.1.1 Introduction

The effects of dabigatran etexilate have been investigated in 40 Phase I studies, 6 completed Phase II studies in AF subjects and subjects undergoing orthopaedic surgery, and 4 completed Phase III studies. Over 10,000 subjects/subjects have been included in completed studies in the primary VTE prevention indication. Almost 700 subjects have been included in completed Phase II SPAF studies and over 18,000 in the Phase III study in AF subjects, RE-LY.

This clinical pharmacology overview will focus on the following PK and PD topics:

- The influence of age, gender, race, impaired hepatic and renal function on dabigatran pharmacokinetics
- The potential for pharmacokinetic or pharmacodynamic interactions with concomitant administration of drugs

- The pharmacokinetics and pharmacodynamics in orthopaedic surgery subjects and subjects with non-valvular atrial fibrillation
- The exposure-response relationship for efficacy and safety in the target subject population

There will be a specific focus on the PD and PK aspects for the proposed indication and the additional 150mg capsule strength.

II.1.2 Methods

- **Analytical methods**

n/a
Evaluator's comment

- **Pharmacokinetic data analysis**

Pharmacokinetic studies evaluated at least the following parameters: Cmax, Tmax, AUC and T1/2.

Evaluator's comment
Satisfactory

- **Statistical analysis**

Most statistical analysis used descriptive measures. Dose linearity and proportionality were also assessed where appropriate.

Evaluator's comment
Satisfactory

II.1.3 Absorption

- **Bioavailability**

The absolute bioavailability after oral administration is approximately 3% to 7%. This can vary depending intrinsic and extrinsic factors.

Evaluator's comment
Satisfactory

- **Bioequivalence**

n/a
Evaluator's comment

- **Influence of food**

A high fat, high caloric breakfast, delayed the time to peak from 2 to 4 hours post-dose, increased the average Cmax and AUC0-∞ values of dabigatran by about 9% and 27%, relative to the fasted state with the 150 mg HPMC capsule.

Evaluator's comment
There is some concern that with an increase for AUC of 27% that there is a possibility for accumulation, particularly with the higher dose. This should be addressed by the applicant.

II.1.4 Distribution

The volume of distribution of dabigatran is 60 – 70 L, which indicates no extensive extravascular distribution into tissue. The blood cell-plasma ratio of dabigatran is on average < 0.3, so dabigatran does not readily penetrate red blood cells.

Evaluator's comment
Satisfactory

II.1.5 Elimination

- **Excretion**

Renal plasma clearance (87 - 92 mL/min) of dabigatran accounts for about 80% of the total clearance (108 - 110 mL/min) following i.v. infusion of dabigatran. Thus, dabigatran is primarily excreted from plasma via the kidneys.

The terminal half-lives of dabigatran are on average 9.41 h and 10.1 h in young male and female subject, respectively, and 10.7 h and 11.2 h in healthy elderly (≥ 65 years) male and female volunteers, respectively.

Evaluator's comment
Care should be taken in administration of dabigatran in patients with renal insufficiency. The applicant needs to address the issue of dose adjustment for those with renal impairment.

- **Metabolism**

Dabigatran was by far the dominant compound in plasma, urine and faeces following both oral administration of dabigatran etexilate and intravenous administration of dabigatran. Dabigatran did not show any cytochrome P450 (CYP) catalysed metabolism.

Evaluator's comment
Satisfactory

- **Pharmacokinetics of metabolites**

Only trace amounts of dabigatran etexilate and the intermediate metabolites were detected and neither pro-drug nor intermediate metabolites were measurable beyond 4 h after administration of dabigatran etexilate.

Evaluator's comment
There are no significant active metabolites.

- **Consequences of possible genetic polymorphism**

n/a
Evaluator's comment

II.1.6 Dose proportionality and time dependency

- **Dose proportionality**

The area under the dabigatran plasma concentration-time curve and maximum plasma concentrations have been shown to increase linearly and dose proportional after single and multiple oral dosing of dabigatran etexilate in a dose range between 10-400 single dose and 50 to 400 mg tid, respectively. There was no unexpected accumulation of dabigatran on repeated

dosing. The average ratios of accumulation observed with 150 mg dabigatran etexilate given twice daily were about 1.7 and 1.5 fold for AUC and Cmax, respectively.

Evaluator's comment
Satisfactory

II.1.7 Intra- and inter-individual variability

The inter-individual variability in the exposure measures AUC and Cmax ranged (gCV) between 42.5-58.1% and 46.6-60.7%, respectively, in single dose bioequivalence studies. After multiple dosing the inter-subject variability became smaller ranging between 33.0 and 57.7% gCV and 31.4 and 53.5% for Cmax,ss and AUCτ,ss, respectively.

During long-term treatment (12 to 51 months) with 150 mg bid dabigatran etexilate, the trough concentrations within subjects had an intra-individual variability of ~39%.

Evaluator's comment
Satisfactory

II.1.8 Pharmacokinetics in target population

The pharmacokinetics of dabigatran in patients with non-valvular atrial fibrillation (AF) was demonstrated in three phase II and III studies (n > 12,500) with doses ranging from 50mg bid to 300mg bid. These studies indicate that it is expected that the pharmacokinetics of dabigatran is similar in AF patients as it is in the general population.

Evaluator's comment
Satisfactory

II.1.9 Special populations

- **Impaired renal function**

In a Phase I study, subjects with moderate renal impairment (CrCL 30 - < 50 mL/min) had dabigatran plasma levels 3.15 higher than subjects with normal renal function (> 80 mL/min). In subjects with severe renal impairment (CrCL < 30 mL/min), the mean AUC of dabigatran is increased 6.3 fold compared to normal renal function. The gMean half-lives were 13.4, 15.3, 18.4, and 27.2 hours in no (healthy subjects), mild, moderate and severe renal impairment, respectively.

Evaluator's comment
The amended product information sheet states that dabigatran is contraindicated in patients with severe renal impairment (<30 mL/min creatinine clearance). There is also a table summarising the half-life of dabigatran in healthy subjects and subjects with impaired renal function. This information is accurate. The need to modify dosing instructions for those with moderate renal impairment is not discussed in the product information sheet. This will need to be addressed by the applicant.

- **Impaired hepatic function**

Following a single dose of 150 mg dabigatran etexilate, the mean AUCs and half-lives in healthy controls and subjects with moderate hepatic impairment were similar.

Evaluator's comment
Satisfactory

- **Gender**

In the large phase III study, RE-LY, in AF patients, females had on average about 30% higher trough and post-dose concentrations compared with male patients. The effect was not associated with any increase in bleeding rate.

Evaluator's comment
This is similar to previous data on dabigatran. Currently in New Zealand there is no dose due to gender.

- **Race**

The phase III subgroup analyses in patients with AF (RE-LY) confirmed the lack of any meaningful differences in the PK of dabigatran between Asian, Caucasian and Black patients.

Evaluator's comment
Satisfactory

- **Weight**

No effect of weight or BMI on bleeding was seen in RE-LY.

Evaluator's comment
Satisfactory

- **Elderly**

Age effects on the PK of dabigatran paralleled the effect of age on renal function. Half-life increased from 9-10 hours in healthy young volunteers to 10.7 h and 11.2 h in healthy elderly (≥ 65 years) male and female volunteers. The effect of age was confirmed in the RE-LY study.

Evaluator's comment
As with patients with renal impairment, potential dose adjustment is not discussed in the product information sheet. This will need to be addressed by the applicant.

- **Children**

No studies performed in patients under 18 years of age. Use of dabigatran in children is not recommended.

Evaluator's comment
Satisfactory

Evaluator's overall comments on pharmacokinetics in special populations

Renal function was by far the most important subject factor affecting plasma concentrations of total dabigatran. The effects of gender, age, and body weight on plasma concentrations were less strong than creatinine clearance and had no impact on bleeding rates.

The RE-LY trial has confirmed previous studies on pharmacokinetics in special populations and has highlighted no further concerns regarding the use of dabigatran in patients with AF or of a 150mg dose.

However, given the effects of renal impairment and age, the potential for dose adjustment in these populations will need to be addressed with the product information sheet.

II.1.10 Interactions

- ***In vitro***

n/a

Evaluator's comment

- ***In vivo***

CYP 450 isoenzymes

Dabigatran etexilate is not metabolised by and does not inhibit or induce CYP 450 isoenzymes.

P-glycoprotein inhibitors

A series of in vivo drug interaction studies, designed to detect maximum effects, was performed in healthy volunteers using the following P-gp inhibitors or substrates: amiodarone, clarithromycin, verapamil, quinidine, ketoconazole, rifampicin and digoxin.

The data for these studies show that when there are high concentrations of a strong P-gp efflux inhibitor in the gut at the time of ingestion of dabigatran etexilate, a clinically meaningful increase in the bioavailability of dabigatran etexilate is expected, resulting in higher AUC and Cmax of the active moiety, dabigatran.

In patients with AF who were also taking verapamil or amiodarone, the effects are similar to other patients, with no clear correlation to major bleeding events. The number of subjects on ketoconazole, cyclosporine A, nelfinavir or saquinavir in the RE-LY study was too low to draw any final conclusion on the effect of these drugs on the incidence of major or any bleeding events.

Effects on drugs increasing the gastric pH

In the RE-LY study, proton-pump inhibitor (PPI) co-medication did not result in lower trough levels and on average only slightly reduced post-dose concentrations (- 11%). Accordingly, PPI co-medication was not associated with a higher incidence of stroke or SEE, especially in comparison with warfarin plus PPIs. Hence, the reduced bioavailability by pantoprazole co-administration seemed to be of no clinical relevance.

Evaluator's comment

Dose adjustment may be necessary for patients taking these medications. This issue will need to be addressed by the applicant.

Evaluator's overall comments on Interactions

Results from the RE-LY study have shown that patients with AF and a 150mg dose have not highlighted any further PK interaction concerns that were not previously known. All these interactions are appropriately identified in the product information sheet.

II.1.11 Exposure relevant for safety evaluation

n/a

Evaluator's comment

II.1.12 Evaluator's overall conclusions on pharmacokinetics

Pharmacokinetic analysis on patients with AF and on those taking the 150mg dose of Pradaxa have identified no further major concerns regarding the PK properties of dabigatran. With the

exception of the influence of food on absorption that requires further clarification, intrinsic and extrinsic factors are appropriately identified in the product information sheet.

II.2 Pharmacodynamics

II.2.1 Introduction

II.2.2 Mechanism of action

Dabigatran etexilate is an orally available prodrug of dabigatran, a competitive, reversible direct thrombin inhibitor. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. The inhibition of the thrombin dependent conversion of fibrinogen to fibrin prevents formation of thrombus.

Evaluator's comment
This is the same mechanism of action for the current indication of the prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.

II.2.3 Primary pharmacology

The close relationship between plasma concentrations and pharmacodynamic effect resulted in reproducible dose-dependent increases in clotting parameters. INR, TT and ECT increased linearly in direct proportion to the plasma concentration of dabigatran, whereas aPTT prolongation displayed a nonlinear increase with increasing dabigatran plasma concentrations.

Evaluator's comment
Satisfactory

II.2.4 Secondary pharmacology

There is no evidence that dabigatran, its pro-drug or intermediate metabolites had an adverse impact on cardiac electrophysiology, especially on cardiac repolarisation as assessed by mean changes or outliers in the QT interval.

Evaluator's comment
Satisfactory

II.2.5 Relationship between plasma concentration and effect

The close relationship between plasma concentrations and pharmacodynamic effect resulted in reproducible dose-dependent increases in clotting parameters. INR, TT and ECT increased linearly in direct proportion to the plasma concentration of dabigatran, whereas aPTT prolongation displayed a nonlinear increase with increasing dabigatran plasma concentrations.

In the RE-LY study there was no detectable association between ischemic stroke and plasma concentration of total dabigatran. Major bleeding events were associated with approximately 50% higher mean plasma concentrations. Subjects with major bleeding events also showed prolonged aPTT values. The median plasma concentration in subjects with any bleeding (minor+major) was ~20% higher (with a wide confidence interval) than in subjects who did not bleed.

Evaluator's comment
The relationship between plasma concentration and effect is mixed. There is a clear association between plasma concentration and coagulation time markers (e.g. aPTT, INR), but less of an

association between plasma concentration and clinical outcomes. The clinical outcomes, however, will be examined more closely in the clinical efficacy section.

II.2.6 Pharmacodynamic interactions with other medicinal products or substances

Acetylsalicylic acid (ASA) and clopidogrel co-medication increase the risk of bleeding when given together with dabigatran. Caution is warranted if combining dabigatran with ASA, clopidogrel or other platelet aggregation inhibitors.

Evaluator's comment

Although not entirely clear in the product information sheet, it appears that there is a warning against the co-medication of dabigatran with ASA or clopidogrel. Given the risk associated with co-medication, it is recommended that this is clearly identified under the contraindication section.

II.2.7 Genetic differences in PD response

No studies discussed

Evaluator's comment

II.2.8 Evaluator's overall conclusions on pharmacodynamics

As with the PK section, there are no further PD concerns regarding the use of dabigatran in patients with AF or for the 150mg dose. While there is no obvious association between plasma levels of dabigatran and ischaemic stroke (despite an association with markers of coagulation time), the efficacy of dabigatran will be examined in the clinical efficacy section.

III. CLINICAL EFFICACY

III.1 Introduction

The key evidence for efficacy of dabigatran in this indication comes from the RE-LY trial (1160.26), with approximately 30,000 subject-years of exposure to dabigatran or warfarin and a total of 513 adjudicated primary efficacy events.

Supportive data was provided by three phase II trials. These trials, however, contributed limited data for the assessment of efficacy. This is due to the fact that the incidence of the primary endpoint in stroke prevention, stroke and systemic embolic events, is in the order of 1.5-2.5% per year. With such a low event rate, Phase II trials were not of sufficient duration or sample size to record many primary efficacy events. This data was supportive for establishing dose-response.

Table 1.1: 1 Clinical trials referenced in the SCE – SPAF program

Study ID (Phase)	Study Design	Primary Endpoint	Treatment Groups	No. Subjects randomized
1160.26 (Phase III) [U09-3249-01, Module 5.3.5.1]	Randomized, parallel group, open-label for warfarin, double-blind for dabigatran doses	Stroke/SEE	Dabigatran etexilate 110 mg BID Dabigatran etexilate 150 mg BID Warfarin, adjusted dose	N = 6015 N = 6076 N = 6022 Total = 18,113
1160.20 (Phase II) [U06-1615-02, Module 5.3.5.1]	Randomized, parallel group, open-label for warfarin and ASA, double-blind for dabigatran doses	Safety and dose exploration	Dabigatran etexilate 50 mg BID Dabigatran etexilate 150 mg BID Dabigatran etexilate 300 mg BID Dabigatran etexilate 50 mg BID+ASA 81 mg QD Dabigatran etexilate 150 mg BID+ASA 81 mg QD Dabigatran etexilate 300 mg BID+ASA 81 mg QD Dabigatran etexilate 50 mg BID+ASA 325 mg QD. Dabigatran etexilate 150 mg BID+ASA 325 mg QD Dabigatran etexilate 300 mg BID+ASA 325 mg QD Warfarin, adjusted dose	N = 58 N = 99 N = 98 N = 20 N = 34 N = 33 N = 27 N = 33 N = 30 N = 70 Total = 502
1160.42 (Phase II) Extension of 1160.20 [U09-3247-01, Module 5.3.5.2]	Randomized, Double-blind, Parallel group	Long term safety	(treatments at the beginning of Study 1160.42; note that most subjects changed their dose regimen at least once during the trial) Dabigatran etexilate 150 mg QD Dabigatran etexilate 150 mg BID Dabigatran etexilate 300 mg QD Dabigatran etexilate 300 mg BID	(entered from 1160.20) N = 98 N = 88 N = 50 N = 125 Total = 361
1160.49 (Phase II) [U07-3126, Module 5.3.5.1]	Randomized, parallel group, open-label for warfarin, double-blind for dabigatran doses	Safety and dose exploration	Dabigatran etexilate 110 mg BID Dabigatran etexilate 150 mg BID Warfarin, adjusted dose	N = 53 N = 59 N = 62 Total = 174

Source Data: [U09-3249-01 Module 5.3.5.1], [U09-3247-01, Module 5.3.5.1], [U06-1615-02, Module 5.3.5.1], [U07-3126, Module 5.3.5.1]

III.2 Dose-response studies and main clinical studies

As commented above, the main clinical trial used to evaluate clinical efficacy was the RE-LY trial (1160.26 in the above table).

Evaluator's comment
Satisfactory

III.2.1 Dose response study(ies)

The RE-LY study examined two doses of dabigatran (110mg bid and 150mg bid). The phase II studies also explored other doses from 50mg bid up to 300mg qd.

Evaluator's comment
The RE-LY study uses the appropriate dose levels, including the additional 150mg capsule strength that is being applied for.

III.2.2 Main study(ies)

Methods

- **Study Participants**

Subjects included in the study were ≥18 years of age with non-valvular atrial fibrillation (AF) with at least one additional risk factor for stroke (i.e., previous ischemic stroke, transient ischemic attack [TIA], or systemic embolism; left ventricular dysfunction; age ≥75 years (or age ≥65 if subject has one of diabetes mellitus, history of coronary artery disease [CAD], or hypertension).

The baseline demographics are shown the table below.

Table 2.5.4.3: 1 Baseline demographics of RE-LY (Study 1160.26)

	DE 110mg bid	DE 150mg bid	Warfarin	Total
Randomized [N(%)]	6015 (100.0)	6076 (100.0)	6022 (100.0)	18,113 (100.0)
Age (mean, years)	71.4	71.5	71.6	71.5
Male (%)	64.3	63.2	63.3	63.6
Race: white (%)	70.0	70.2	69.8	70.0
Weight (mean, Kg)	82.9	82.4	82.6	82.6
VKA naïve (%)	50.0	49.8	51.4	50.4
Never on VKA (%)	31.1	31.4	32.7	31.7
CrCL (median, ml/min)	68.7	67.9	68.5	68.4
Systolic BP (mean, mmHg)	130.8	130.9	131.2	131.0
Diastolic BP (mean, mmHg)	77.0	77.0	77.1	77.0
AF type [N(%)]				
Persistent	1950 (32.4)	1909 (31.4)	1930 (32.0)	5789 (32.0)
Paroxysmal	1929 (32.1)	1978 (32.6)	2036 (33.8)	5943 (32.8)
Permanent	2132 (35.4)	2188 (36.0)	2055 (34.1)	6375 (35.2)
Regions [N(%)]				
USA, Canada	2166(36.0)	2200(36.2)	2167(36.0)	6533(36.1)
Central Europe	707(11.8)	706(11.6)	706(11.7)	2119(11.7)
Western Europe	1544(25.7)	1555(25.6)	1552(25.8)	4651(25.7)
Latin America	320(5.3)	320(5.3)	316(5.2)	956(5.3)
Asia	923(15.3)	933(15.4)	926(15.4)	2782(15.4)
Other	355(5.9)	362(6.0)	355(5.9)	1072(5.9)

Source data: 1160.26 [U09-1249-01, Module 5.3.5.1], Tables 15.1.4: 1, 3, 5, 7, and 9

Evaluator's comment
Satisfactory

- **Treatments**

Participants were randomised to one of three treatment arms: dabigatran etexilate 110mg bid; dabigatran etexilate 150mg bid; or warfarin (titrated to a target INR of 2-3). Given the known effectiveness of warfarin, it would be unethical in this study to have used a placebo group.

Evaluator's comment
Satisfactory

- **Objectives**

The primary objective of RE-LY was to demonstrate the efficacy and safety of dabigatran etexilate in subjects with non-valvular atrial fibrillation for the prevention of stroke and systemic embolism.

Evaluator's comment
Satisfactory

- **Outcomes/endpoints**

The primary efficacy endpoint was the incidence of stroke (including hemorrhagic) and systemic embolism (SEE).

Secondary efficacy endpoints are composites of:

- incidence of stroke (including hemorrhagic), systemic embolism, all death
- incidence of stroke (including hemorrhagic), systemic embolism, pulmonary embolism, acute myocardial infarction (MI), or vascular deaths (includes deaths from bleeding)

Other efficacy endpoints:

- individual occurrence or composites of any ischemic stroke (fatal and non-fatal), systemic embolism, pulmonary embolism, acute MI, TIAs, vascular death (includes deaths from bleeding), all deaths, and hospitalisations
- Net Clinical Benefit (NCB) as measured by the composite of the clinical endpoint of stroke, systemic embolism, pulmonary embolism, acute MI, all cause deaths, and major bleeds

Evaluator's comment
These primary and secondary end points are appropriate.

- **Sample size**

A total of 20,377 were screened for the study and 18,113 were randomised. The numbers in each treatment arm are in the above table.

Evaluator's comment
Satisfactory

- **Randomisation**

Participants were randomised to one of the three treatment groups with equal probability.

Evaluator's comment
Satisfactory

- **Blinding (masking)**

The dabigatran doses were administered in a blinded manner and warfarin was administered open-label. All study endpoints were blindly adjudicated.

The choice of an open-label design was based on several considerations. Most important was that treatment with dabigatran was fundamentally different from treatment with warfarin. Warfarin requires regular monitoring, dose adjustments, dietary considerations whereas dabigatran does not. An open-label Phase III trial, with appropriate measures to minimise bias, is more likely than a double-blind trial to represent the individual advantages and disadvantages of each therapy.

The PROBE design (**p**rospective, **r**andomized, **o**pen trial with **b**linded adjudication of **e**vents) was therefore selected as the design for the RE-LY trial.

The organisational structure of the study and its overall conduct was designed to ensure that neither sponsor nor anyone else involved in the conduct of the study except the Data Safety and Monitoring Board (DSMB) had access to aggregated, "by treatment" outcome data, unblinded safety data (other than expedited safety reports forwarded to regulators and investigators) or any "by treatment" data analyses until after database lock.

Evaluator's comment
Although this study was open-label, several measures were put in place in order to minimise the potential for bias. Given the differences in the administration of each treatment this design is satisfactory.

- **Statistical methods**

Four analysis sets were defined for the efficacy analyses: the randomised set (was called full analysis set [FAS] in the protocol), the safety analysis set (SAF), the treated set (all randomised subjects who took the randomised study medication for ≥70% of the time in the study or prior to the onset of a primary outcome event), and the per protocol set (PPS).

Table 9.7.1.3: 1 Analyses and analysis sets

Endpoint	Randomized set	Treated set	Safety set	PPS
Primary outcome	X	X (sensitivity analysis)	X (sensitivity analysis)	X (sensitivity analysis))
Important secondary outcome	X		X	
Other secondary outcome	X			
AEs			X	
Bleeds	X		X (sensitivity analysis)	
LFT			X	
Demographic/baseline endpoint	X			
Compliance			X	

PPS, per protocol set; PVs, protocol violations; AEs, adverse events; LFT, liver function test

Results

- **Participant flow**

Table 10.1: 2 Disposition of Subjects

	DE 110 N (%)	DE 150 N (%)	Warfarin N (%)	Total N (%)
Enrolled (screened)				20377
Not entered				2264
Entered (randomized)	6015	6076	6022	18113
Not Treated	31	17	23	71
Completed follow up	13	7	5	25
Withdrew consent or lost to follow up or other	18	10	18	46
Treated	5984 (100.0)	6059 (100.0)	5999 (100.0)	18042 (100.0)
Completed study	5775 (96.5)	5818 (96.0)	5744 (95.7)	17337 (96.1)
Completed on study medication	4593 (76.8)	4609 (76.1)	4832 (80.5)	14034 (77.8)
Completed follow up but stopped study medication prematurely*	1182 (19.8)	1209 (20.0)	912 (15.2)	3303 (18.3)
Outcome events^	417 (7.0)	427 (7.0)	329 (5.5)	1173 (6.5)
Serious AEs not related to outcome events	196 (3.3)	200 (3.3)	147 (2.5)	543 (3.0)
Subject preference	391 (6.5)	406 (6.7)	329 (5.5)	1126 (6.2)
Elevated LFT result	28 (0.5)	16 (0.3)	11 (0.2)	55 (0.3)
Hospitalisation#	142 (2.4)	154 (2.5)	156 (2.6)	452 (2.5)
Adverse Event	305 (5.1)	329 (5.4)	200 (3.3)	834 (4.6)
Other	452 (7.6)	504 (8.3)	379 (6.3)	1335 (7.4)
Premature discontinuation from study	209 (3.5)	241 (4.0)	255 (4.3)	705 (3.9)
Withdrew consent	129 (2.2)	146 (2.4)	141 (2.4)	416 (2.3)
Vital status available at study termination	82 (1.4)	98 (1.6)	108 (1.8)	288 (1.6)
Lost to follow up	17 (0.3)	33 (0.5)	39 (0.7)	89 (0.5)
Vital status available at study termination	6 (0.1)	19 (0.3)	22 (0.4)	47 (0.3)
Other	63 (1.1)	62 (1.0)	75 (1.3)	200 (1.1)

* Subjects may be counted in more than one of the sub-classes
^ Outcome events include: stroke, systemic emboli, myocardial infarction, pulmonary emboli, TIA, bleed and death (Section 9.5.1.4)
# Hospitalization could have been for elective procedures or those not otherwise specified.
Source: Table 15.1.1:1.1

Evaluator's comment
Satisfactory

- **Recruitment**

Recruitment was widespread across regions and countries, and included countries where anticoagulants are widely used as well as countries where they are not. The bulk of recruitment occurred in Western Europe and USA/Canada (~62%), where VKA use is widespread, but Asia was well-represented (~15% of subjects) as was central Europe (11.7%).

Approximately 11% of subjects were screened but not randomized, largely due to failure to meet the inclusion and exclusion criteria.

Evaluator's comment

Satisfactory

- **Conduct of the study**

The RE-LY study was a well-designed, GCP compliant study.

Evaluator's comment
Satisfactory

- **Baseline data**

Baseline demographic data was similar between all three treatment arms (see table under section III.2.2 *Study participants*). Distribution of the type of AF was similar across the participants with approximately one-third each having persistent, paroxysmal or permanent AF. Across the study, approximately 50% of participants were vitamin-K antagonist (VKA) naive.

Evaluator's comment
Satisfactory

- **Numbers analysed**

For all analyses, the randomised set (i.e. 18,113 participants) was used. There were also sensitivity analyses done for the primary outcome on the treated set, the safety analysis set and the per-protocol set.

Evaluator's comment
Satisfactory

- **Outcomes and estimation**

Primary outcome
Stroke or systemic embolism occurred in 183 subjects on DE110 BID (1.54%/year), 134 subjects on DE150 BID (1.11%/year) and 202 subjects on warfarin (1.71%/year). The test for non-inferiority to warfarin was significant for both doses of dabigatran ($p< 0.0001$). The high dose of dabigatran was superior to warfarin in the reduction of stroke or systemic embolism (RR 0.65, 95%CI 0.52-0.81, $p< 0.001$).

Secondary outcomes
A total of 1,710 stroke/SEEs/all cause deaths were observed during the trial: 577, 520 and 613 from the DE 110, DE 150 and the warfarin groups, respectively. The rates were DE110 BID 4.85%, DE150 BID 4.32%, and warfarin 5.20%. The DE110 BID dose was similar to warfarin (RR 0.93, 95%CI: 0.83-1.04, p=0.2206) but the high dose was superior to warfarin (RR 0.83, 95%CI: 0.74-0.93, p=0.0015) and different from D110: D110 vs. D150 (RR 1.13, 95%CI: 1.00-1.27, p=0.0503).

For the pre-specified composite endpoint for risk benefit (stroke/SEE/PE/MI/death/major bleed) dabigatran 150 mg BID is superior to warfarin. The annualized rates were 7.34%/year for DE110, 7.11%/year for DE150 and 7.91%/year for warfarin (DE110 vs. warfarin RR 0.91, 95%CI: 0.84-1.01, p=0.0968; DE150 vs. warfarin (RR 0.90, 95%CI: 0.82-0.99, p=0.0246).

The rate of MI was higher in the dabigatran groups compared to the warfarin group. The yearly event rates were 0.82% (n=98), 0.81% (n=97) and 0.64% (n=75) for DE 110, DE 150 and warfarin, respectively (p=0.093 and p=0.124 for DE 110 vs. warfarin and DE150 vs. warfarin). In the context of other cardiovascular events, namely vascular death, PE, stroke and SEE, the increased in frequency of MI on dabigatran is counterbalanced by the reduction in other events.

The benefits of dabigatran compared to warfarin still remain, with the high dose superior to warfarin (hazard ratio 0.84, p=0.0093).

Evaluator's comment
For the primary and secondary outcomes, both dabigatran 110mg and 150mg have been shown to be non-inferior to warfarin. Additionally, dabigatran 150mg was shown to be superior to warfarin for all outcomes. There is some indication that the rate of MI was higher in the dabigatran groups although this was not statistically significant. Overall, cardiovascular event rates were similar (for DE 110) or lower (for DE 150) than for warfarin.

- **Ancillary analyses**

In all primary endpoint analyses, both dabigatran doses (DE 110 and DE 150) were shown to be non-inferior to warfarin and DE 150 was shown to be superior to warfarin. Thus, the results of the analyses of the primary endpoint (stroke/SEE) are supported by analyses using different data sets (safety, treated and per protocol), different statistical approaches (stratified analyses by VKA use, ASA use, stroke history), and excluding sites that were closed for cause.

There was also a sensitivity analysis completed by INR control. This examined the frequency and yearly event rates for dabigatran compared to warfarin by INR control <65% or ≥65% for the primary endpoint.

Table 11.4.1.1.1: 2 Hazard ratios and 95% CIs for composite endpoint of stroke/SEE by INR control for warfarin- Safety Set

	Mean % of time of INR in range 2-3 ≥ 65%	
	DE 110 vs Warfarin	DE 150 vs Warfarin
Hazard ratio (SE)	1.03 (0.15)	0.69 (0.11)
95% CI	0.77, 1.37	0.50, 0.93
	Mean % of time of INR in range 2-3 <65%	
	DE 110 vs Warfarin	DE 150 vs Warfarin
Hazard ratio (SE)	0.74 (0.10)	0.49 (0.08)
95% CI	0.56, 0.97	0.36, 0.67

Source data: Table 15.2.1.2: 14 and Table 15.2.1.2: 16
The analyses included all DE subjects, and different warfarin subjects for each group.

Results of this sensitivity analysis show that subjects had better results on warfarin when their INR was controlled. Non-inferiority for both dabigatran doses compared to warfarin for stroke/SEE is maintained compared to well-controlled warfarin subjects.

Evaluator's comment
Sensitivity analyses support the findings from the primary and secondary outcomes.

III.3 Clinical studies in special populations

There were no clinical studies submitted by the applicant on special populations. However, there has been some subgroup analysis within the RE-LY study.

Age
When considering the primary endpoint the benefits of DE 110 versus warfarin were slightly less in subjects <65 years of age compared to older subjects. For DE 150, the benefits compared to warfarin were highest in the subjects <65 years of age.

Gender, ethnicity and renal function (i.e. CrCl)
When considering the primary endpoint there were no differences in hazard ratios between the treatment groups by gender, ethnicity or renal function.

Evaluator's comment
The subgroup analyses have supported the main findings and have not highlighted any concerns regarding particular subgroups.

III.4 Analysis performed across trials (pooled analyses AND meta-analysis)
None submitted

Evaluator's comment

III.5 Supportive study(ies)
As previously commented in the introduction, the Phase II supportive studies were of limited size and duration and are therefore unable to adequately detect the incidence of the primary endpoint in stroke prevention, stroke and systemic embolic events.

The 12 week dose-finding trial PETRO (1160.20), with 500 subjects, recorded 2 stroke/SEE events. The 12 week Phase II trial in Japan, (1160.49), recruited 174 subjects and recorded one primary event. The long-term extension of PETRO was PETRO-EX, with 361 subjects, was over 4 years' duration and collected multiple primary events but this trial was uncontrolled and subjects were exposed to more than 1 dose.

The supportive studies have demonstrated dose-response for bleeding over the range of 50 mg bid to 300 mg bid.

Evaluator's comment
Although very limited, the supportive Phase II studies have provided some dose-response evidence.

III.6 Evaluator's overall conclusions on clinical efficacy
The evidence from the single, large Phase III study (RE-LY) has demonstrated the non-inferiority of dabigatran 110mg and 150mg to warfarin. The higher dose of dabigatran was also shown to be superior to warfarin in relation to both primary and secondary outcomes. For the primary efficacy endpoint, stroke/SEE, the relative risk reductions for DE 110 and DE 150 were 10% and 35%, respectively.

The risk of death (all cause and vascular) was lower for both doses of dabigatran compared with warfarin. All cause mortality was reduced by 12% for DE150 compared to warfarin, p=0.0475.

The relative risk of MI in the dabigatran groups was 27-29% higher than in the warfarin group – these results were not statistically significant. However, a considerable amount of analysis was conducted on this result and the applicant commented that "the slightly higher incidence of MI on dabigatran is more than counterbalanced by the other cardiovascular endpoints", and concludes finally that "the incidence of MI in AF subjects treated with dabigatran is higher than the incidence in warfarin treated AF subjects."

The efficacy of dabigatran was consistent for all subgroups evaluated.

Although the relative risk reduction for DE 150 was 35% (hence, a third less chance of dying from stroke/SEE compared to warfarin), due to the low incidence rate of this outcome, absolute reductions will appear less impressive. However, given that the comparison is against an active treatment, these efficacy results are clinically significant.

IV. CLINICAL SAFETY

IV.1 Introduction

As for the efficacy data, clinical safety data is based almost exclusively on results from the RE-LY trial. Very limited supportive data is provided by the three Phase II trials.

The most important adverse event associated with dabigatran treatment is bleeding and the safety analysis has tended to focus on bleeding events from the clinical trials. For adverse events other than bleeding, analyses were conducted for adverse events by System Organ Class, serious adverse events (SAEs), discontinuations due to adverse events, and adverse events leading to death.

Evaluator's comment

IV.2 Patient exposure

Patient exposure in the RE-LY study is summarised below.

Table 12.1: 1 Treatment exposure, number (%) of subjects (safety set)

	DE 110	DE 150	Warfarin	Total
Total treated	5984 (100.0)	6059 (100.0)	5999 (100.0)	18042 (100.0)
Exposure category [N (%)]				
<=14 days	188 (3.1)	197 (3.3)	102 (1.7)	487 (2.7)
14 days < and <=1 month	128 (2.1)	133 (2.2)	75 (1.3)	336 (1.9)
1< and <=3 months	202 (3.4)	248 (4.1)	154 (2.6)	604 (3.3)
3< and <=6 months	220 (3.7)	231 (3.8)	157 (2.6)	608 (3.4)
6< and <=9 months	167 (2.8)	167 (2.8)	168 (2.8)	502 (2.8)
9< and <=12 months	148 (2.5)	144 (2.4)	146 (2.4)	438 (2.4)
12< and <=16 months	706 (11.8)	723 (11.9)	771 (12.9)	2200 (12.2)
16< and <=20 months	875 (14.6)	872 (14.4)	936 (15.6)	2683 (14.9)
20< and <=24 months	969 (16.2)	945 (15.6)	1022 (17.0)	2936 (16.3)
24< and <=28 months	879 (14.7)	889 (14.7)	946 (15.8)	2714 (15.0)
28< and <=32 months	965 (16.1)	989 (16.3)	1033 (17.2)	2987 (16.6)
32< and <=36 months	512 (8.6)	495 (8.2)	474 (7.9)	1481 (8.2)
>36 months	25 (0.4)	26 (0.4)	15 (0.3)	66 (0.4)
Summary statistics (months)				
Mean	20.51	20.31	21.33	20.71
SD	9.62	9.76	8.79	9.41
Median	21.88	21.32	22.54	22.08
Minimum	0.0	0.0	0.0	0.0
Maximum	36.7	37.3	36.7	37.3
Total subject-years	10229.2	10252.9	10661.2	31143.3

Exposure days are calculated as: the date of last study medication administration - date of first study drug administration +1; the calculated days are converted to months (12*days/365.25).
Total subject-years = sum of exposure days of all subjects / 365.25
Source data: Table 15.3.1: 1

Evaluator's comment
This exposure is satisfactory with over 80% of study participants being exposed to more than 12 months of dabigatran.

IV.3 Adverse events

The primary safety endpoint in RE-LY was major bleeding. Bleeding events were analysed in several categories: major bleeds, defined based on the ISTH definition, and minor bleeds were the primary divisions of bleeding events. All major bleeds were blindly adjudicated. The composite of major+minor bleeding, any bleeds, was also analysed.

Phase II studies
The PETRO trial (1160.20) demonstrated dose-response for bleeding over the range of 50 mg bid to 300 mg bid. In this 12 week trial, the bleeding rates of 150 mg bid and 300 mg bid without ASA were approximately the same.

In the PETRO-EX trial (1160.42) unacceptably high rates of major bleeding were seen with 300 mg bid

In trial 1160.49, the bleeding rates with 110 mg bid and 150 mg bid were comparable to that of warfarin. Thus Phase II identified 110 mg bid and 150 mg bid as doses with acceptable bleeding rates and defined the maximal tolerated dose to be less than 300 mg bid.

RE-LY

Both doses of dabigatran were associated with lower rates of life-threatening major bleeds, including lower rates of hemorrhagic stroke and ICH compared to warfarin. In addition, both doses also had lower rates of minor bleeding and any bleeding compared to warfarin.

Table 15.3.2.1: 1_NEW Frequency and yearly event rate (%) of major bleeds, randomized set

	DE 110mg bid N (%)	DE 150mg bid N (%)	Warfarin N (%)
Number of subjects	6015	6076	6022
Subject-years	11899	12033	11794
Major bleeds	342 (2.87)	399 (3.32)	421 (3.57)
Life threatening MBEs	147 (1.24)	179 (1.49)	218 (1.85)
Other MBEs	218 (1.83)	248 (2.06)	226 (1.92)
ICH	27 (0.23)	38 (0.32)	90 (0.76)

In case of recurrent events, the first event was considered.
Subject-years = sum(date of study termination - date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = # of subjects with event / subject-years * 100.
ICH consists of adjudicated hemorrhagic stroke and subdural and/or subarachnoid hemorrhage.
Source data: Appendix 16.2.6, Listing 6, Appendix 16.2.7, Listing 1.1
SCS Table 2.1.1.1.2: 3

Table 15.3.2.1: 9_NEW Hazard ratio and 95% CI for bleeds, randomized set

		DE 110mg bid vs Warfarin	DE 150mg bid vs Warfarin	DE 110mg bid vs DE 150mg bid
Adjudicated major bleeds	Hazard ratio (SE)	0.80 (0.06)	0.93 (0.07)	0.86 (0.06)
	95% CI	0.70, 0.93	0.81, 1.07	0.75, 1.00
	P-value	0.0026	0.3146	0.0429
Reported major bleeds	Hazard ratio (SE)	0.78 (0.06)	0.94 (0.06)	0.84 (0.06)
	95% CI	0.68, 0.90	0.82, 1.07	0.73, 0.96
	P-value	0.0006	0.3234	0.0134
Reported any bleeds	Hazard ratio (SE)	0.78 (0.03)	0.91 (0.03)	0.86 (0.03)
	95% CI	0.73, 0.83	0.85, 0.96	0.81, 0.92
	P-value	<.0001	0.0016	<.0001
Adjudicated hemorrhagic strokes	Hazard ratio (SE)	0.31 (0.09)	0.26 (0.08)	1.18 (0.46)
	95% CI	0.17, 0.56	0.14, 0.49	0.55, 2.55
	P-value	0.0001	<.0001	0.6750
Adjudicated life-threatening bleeds	Hazard ratio (SE)	0.67 (0.07)	0.80 (0.08)	0.83 (0.09)
	95% CI	0.54, 0.82	0.66, 0.98	0.67, 1.03
	P-value	0.0001	0.0305	0.0915
Adjudicated ICH	Hazard ratio (SE)	0.30 (0.06)	0.41 (0.08)	0.72 (0.18)
	95% CI	0.19, 0.45	0.28, 0.60	0.44, 1.18
	P-value	<.0001	<.0001	0.1875
Reported symptomatic intracranial bleeds	Hazard ratio (SE)	0.29 (0.06)	0.47 (0.09)	0.62 (0.15)
	95% CI	0.19, 0.44	0.33, 0.67	0.38, 1.00
	P-value	<.0001	<.0001	0.0502

In case of recurrent events, the first event was considered.
Source data: Appendix 16.1.9.2, Statdoc 7.2.1.3

The low dose of dabigatran DE 110 was associated with 20% less major bleeding than warfarin (p = 0.0026), while the high dose DE 150 had 7% less major bleeding (p = 0.3146).

The relative reduction in life-threatening bleeds was 33% (p<0.001) and 20% (p=0.0305) for the DE 110 and DE 150, respectively. The relative reductions of hemorrhagic stroke and ICH compared to warfarin ranged from 69% to 74%, with associated p-values of <0.0001.

Dabigatran treatment resulted in a higher number bleeding events in the gastrointestinal system (GI) compared with warfarin. For major bleeds, the high dose of dabigatran increased the risk of GI bleeds compared to warfarin, by ~50% (p=0.0004). However, both doses increased the risk of minor GI bleeds by ~40 to 50% (p<0.0001 both doses versus warfarin). A composite endpoint of stroke/SEE or major bleed was evaluated as measure of benefit/risk. In the overall population, the risk of stroke/SEE or major bleed was reduced 13% and 12% for the DE 110 bid and DE 150 bid dose groups compared to warfarin (Hazard ratio of 0.87 and 0.88, respectively). This was statistically significant for the DE 110 bid group (p = 0.0297) but not for DE 150 bid (p = 0.0527)

Table 15.3.2.2.8: 1_NEW Frequency and yearly event rate (%) of gastrointestinal bleeds randomized set

	DE 110mg bid N (%)	DE 150mg bid N (%)	Warfarin N (%)
Number of subjects	6015	6076	6022
GI Major bleeds	134 (1.14)	186 (1.57)	125 (1.07)
GI Life threatening MBEs	67 (0.57)	94 (0.79)	57 (0.49)
Any GI bleeds	600 (5.41)	681 (6.13)	452 (4.02)

In case of recurrent events, the first event was considered
For subjects with event, subject-years= (first onset date - date of randomization + 1) / 365.25
For subjects without event, subject-years= (study termination date - date of randomization + 1)/365.25
Yearly event rate (%) = # of subjects with event / subject-years * 100.
Source data: Appendix 16.2.6, Listing 6, Appendix 16.2.7, Listing 1.1

The most frequently occurring AEs for DE 110 bid, DE 150 bid, and warfarin subjects were dyspnoea (8.3%, 8.7%, and 9.2%, respectively), dizziness (7.6%, 7.6%, and 9.3%), and peripheral oedema (7.5%, 7.3%, and 7.6%). Dyspepsia was reported more frequently for DE 110 and DE 150 subjects compared with warfarin.

Table 2.5.5.2.1: 2 AEs with a frequency >5% in Study 1160.26 [N (%)] (safety set)

Adverse Event	DE110 BID	DE150 BID	Warfarin
Dyspepsia*	762 (12.7)	738 (12.2)	354 (5.9)
Dizziness	457 (7.6)	458 (7.6)	555 (9.3)
Dyspnoea	497 (8.3)	525 (8.7)	550 (9.2)
Oedema peripheral	446 (7.5)	442 (7.3)	453 (7.6)
Fatigue	370 (6.2)	367 (6.1)	353 (5.9)
Cough	319 (5.3)	310 (5.1)	345 (5.8)
Chest pain	288 (4.8)	355 (5.9)	342 (5.7)
Back pain	295 (4.9)	289 (4.8)	331 (5.5)
Arthralgia	249 (4.2)	313 (5.2)	328 (5.5)
Nasopharyngitis	314 (5.2)	309 (5.1)	327 (5.5)
Diarrhoea	355 (5.9)	367 (6.1)	327 (5.5)
Atrial fibrillation	303 (5.1)	313 (5.2)	326 (5.4)
Urinary tract infection	242 (4.0)	253 (4.2)	315 (5.3)
Upper respiratory tract infection	266 (4.4)	261 (4.3)	297 (5.0)

*includes dyspepsia, abdominal pain upper, abdominal pain, abdominal discomfort, epigastric discomfort
Percentages are calculated using total number of subjects per treatment as the denominator
Source data: [Module 2.7.4, Appendix 7, Table 2.1.1.2.1.11]

Evaluator's comment

The safety results demonstrate that dabigatran at both doses had fewer major bleeds than warfarin (although only the 110mg dose was statistically significant). Both dabigatran groups also had a lower percentage of minor bleeds than warfarin.

Both dabigatran doses displayed statistically significantly lower rates of haemorrhagic strokes, life-threatening bleeds and intracranial haemorrhages compared to warfarin, with the 110mg dose having the lowest rates overall.

Both dabigatran groups demonstrate a higher rate of any GI bleeding event in comparison to warfarin. However, a composite measure of stroke/SEE or major bleed showed a lower hazard ratio for the dabigatran groups compared to warfarin.

The rate of other adverse events was similar between all the groups with the exception of dyspepsia and related events. Rates of these events were twice as high in the dabigatran groups compared to warfarin.

The increased risk of GI bleeding has not been commented on in the product information sheet under either the *Haemorrhagic risk* section.

IV.4 Serious adverse events and deaths

Of the 1368 deaths that occurred during the RE-LY trial, 365 subjects had an adverse event with a fatal outcome identified by a study investigator. The incidence of fatal AEs was 2.0%, 1.8%, and 2.2% for DE 110 bid, DE 150 bid, and warfarin, respectively.

Pneumonia and cardiac failure were the most frequent fatal AEs during the study (0.1% to 0.2%). The incidence of fatal AEs was generally similar between treatment groups.

The incidence of serious AEs was similar across all treatment groups (21.2%, 21.3%, and 22.6% for DE 110, DE 150, and warfarin, respectively). SAEs were generally similar for dabigatran and warfarin subjects. The most frequently reported SAEs for DE 110, DE 150, and warfarin groups, respectively, were cardiac failure congestion (1.4%, 1.0%, and 1.2%), pneumonia (1.2%, 1.2%, and 1.0%), atrial fibrillation (1.1%, 0.9%, and 1.2%), and cardiac failure (0.9%, 1.0%, and 1.1%).

Serious GI disorders were reported in a greater percentage of DE 150 subjects compared with DE 110 or warfarin (3.5%, 4.0%, and 3.6% for DE 110, DE 150, and warfarin, respectively). Gastrointestinal haemorrhage was the most frequently reported GI SAE, which was reported in a higher percentage of DE 150 subjects compared with DE 110 and warfarin (0.6%, 0.9%, and 0.7% for DE 110, DE 150, and warfarin, respectively).

Evaluator's comment

Serious adverse events and deaths occurred at a similar frequency across the treatment groups. The dabigatran 150mg group did report a higher percentage of serious GI disorders and GI haemorrhage.

As under section IV.3 (*Adverse events*), the increased frequency of GI bleeding events has not been identified in the product information sheet.

IV.5 Laboratory findings

There was no evidence of increased frequencies on dabigatran compared to warfarin in transaminase elevations, or concomitant transaminase and bilirubin elevations. There were no statistically significant in hazard ratios between the treatment groups.

Table 2.5.5.4.1: 1 Summary of abnormal LFTs in Study 1160.26 (safety set)

LFT elevation	DE 110 bid N (%)	DE 150 bid N (%)	Warfarin N (%)
Total treated	5,984 (100.0)	6,059 (100.0)	5,999 (100.0)
ALT or AST > 1xULN and <= 2xULN	1,681 (28.1)	1,645 (27.1)	1,875 (31.3)
ALT or AST > 3xULN	121 (2.0)	111 (1.8)	126 (2.1)
ALT or AST > 5xULN	40 (0.7)	48 (0.8)	51 (0.9)
Bilirubin > 2xULN	126 (2.1)	116 (1.9)	127 (2.1)
ALT or AST > 3xULN + Bilirubin >2xULN	11 (0.2)	14 (0.2)	22 (0.4)

Subjects were counted in each category if the respective abnormal LFT event occurred between first dose of study medication and study termination visit.
Source: [Module 2.7.4, Appendix 7, Table 3.1.1.2]

Based on the pre-defined guidelines, a greater percentage of DE 150 bid subjects had clinically relevant changes in haemoglobin and haematocrit (haemoglobin: 7.7%, 8.4%, and 7.4% of DE 110 bid, DE 150 bid, and warfarin subjects, respectively; haematocrit: 4.2%, 4.5%, and 3.8%).

Evaluator's comment
Overall, there were few clinically relevant differences in laboratory findings between the treatment groups. The RE-LY study has demonstrated a laboratory safety profile for dabigatran (both does) similar to that of warfarin.

IV.6 Safety in special populations

Age was the only demographic variable with a significant treatment interaction ($p<0.0001$). The greater the age of the subject, the higher the yearly event rate for major bleeds. For subjects <75 years of age, DE 110 bid and DE 150 bid had a lower rate of major bleeds compared to warfarin; however, DE 150 bid subjects ≥75 years of age had a slightly higher rate of major bleeds compared to warfarin.

Renal dysfunction was associated with a high risk of bleeding for all treatments.

There is no data available on the safety of dabigatran in children (<18 years), and pregnant or lactating women.

Evaluator's comment
Safety of dabigatran in the elderly and those with renal impairment are of moderate concern. However, these concerns are appropriately identified in the product information sheet.

Dabigatran is not recommended for use in children (<18 years), or in pregnant or lactating women.

IV.7 Immunological events

No data provided

IV.8 Safety related to drug-drug interactions and other interactions

The use of ASA/clopidogrel nearly doubled the risk of major bleeds across all treatment groups but did not change the relative risks.

In the subgroup taking P-gp inhibitors (verapamil, diltiazem, and amiodarone) at baseline, for both doses of dabigatran the hazard ratio versus warfarin for the primary endpoint of stroke/SEE was approximately 50% lower.

Increases in the rate of major bleeding events were observed in both dabigatran and warfarin subjects with concomitant use of the calcium channel blockers verapamil and diltiazem, as well as with proton pump inhibitors and H2 blockers.

Antiplatelet drugs (ASA, clopidogrel, ASA+clopidogrel, NSAIDs) increased the risk of bleeding in subjects taking dabigatran or warfarin. For concomitant use of ASA or clopidogrel or the combination, the risk of bleeding was approximately doubled; for NSAIDs the bleeding risk increased by ~50%.

Evaluator's comment

The interaction with ASA and clopidogrel is appropriately identified in the product information sheet. The potential interaction with P-glycoprotein inhibitors is less clearly identified in the product information sheet.

Under the heading "Concomitant use of dabigatran etexilate with strong P-glycoprotein inhibitors i.e. amiodarone, quinidine or verapamil" the "i.e." should be changed to "e.g." and the list that follows should include "diltiazem".

There should also be some further comment regarding dose adjustment. Given the increased risk of bleeding with concomitant use of P-glycoproteins dose adjustment may well be necessary (see questions at the end of this evaluation).

The product information sheet should also identify the increased bleeding rate for patients also taking proton pump inhibitors and H2 blockers, and provide appropriate guidance on dose adjustment as required.

Advice and comment in the product data sheet on the use of NSAIDs is unclear. Under the Pharmacokinetics (Special populations) section it states that for NSAIDs "the use of regular NSAID medication with half-lives of less than 12 hours during treatment with dabigatran etexilate…has not suggested additional bleeding risk". This is contradictory to the findings of the RE-LY study and should be amended.

IV.9 Discontinuation due to AES

A higher percentage of dabigatran subjects discontinued study medication due to AEs compared with warfarin subjects (19.0%, 20.5%, and 15.6% for DE 110 bid, DE150 bid, and warfarin, respectively).

The number of subjects with permanent treatment discontinuation due to major bleeds was similar for all treatments, in the range of 1%. For minor bleeds, the number of subjects who permanently discontinued treatment was slightly higher for dabigatran (1.1% and 1.3% for DE 110 and DE 150, respectively) compared to warfarin (0.6%).

Evaluator's comment

The prevalence of adverse events was similar between all the three groups. It was therefore hypothesised that the difference in discontinuation rates between the groups may be a consequence of the open-label nature of the study, with a lower threshold for discontinuing an experimental drug.

IV.10 Post marketing experience/Risk management
None provided

IV.11 Proposals for post authorisation follow up (post marketing surveillance)
None provided

IV.12 Evaluator's overall conclusions on clinical safety
For the primary safety endpoint of major bleeding, DE 110 treatment had a significantly lower risk of major bleeding events compared with warfarin treatment (21% lower). DE 150 had similar risk of major bleeding compared with warfarin. Life-threatening bleeds, haemorrhagic stroke and intracranial bleeds were all statistically significantly lower in the dabigatran groups compared to the warfarin group.

Those within the dabigatran groups did experience higher rates of GI adverse events: dyspepsia/stomach discomfort/gastritis was twice as frequent for dabigatran as for warfarin. The DE 150 group also had a higher incidence of major bleeding events within the gastrointestinal tract when compared with warfarin.

The RE-LY study has also highlighted some potentially important drug-drug interactions, in particular, P-glycoprotein inhibitors, proton pump inhibitors and H2 blockers. The product information sheet does not adequately identify these interactions or provide appropriate advice regarding dose adjustment.

Given the higher risk of bleeding in patients with renal impairment, further information regarding dose adjustment is warranted.

V. BENEFIT RISK ASSESSMENT

The evidence from the single, large Phase III study (RE-LY) has demonstrated the non-inferiority of dabigatran 110mg and 150mg to warfarin. The dabigatran groups demonstrated lower stroke rates and lower overall mortality compared with warfarin. Reductions in occurrence of haemorrhagic stroke and intracranial haemorrhage were significantly reduced for both dabigatran dose compared with warfarin.

Although relative risk reductions were between 7% and 71% (depending on outcome and dose), absolute reductions would be less impressive given the low incidence of the endpoints. However, given that the comparison group was an active treatment and the study aimed to demonstrate non-inferiority, the efficacy results are clinically significant.

In contrast to these positive results, rates of MI were higher (27-29%) in the dabigatran groups (although not statistically significant). However, given the low rates of MI (0.64-0.82%) and low number of cases of MI (75-98) in the RE-LY study, it is unlikely that dabigatran causes MI.

When a composite measure of cardiovascular clinical outcomes (i.e. PE, MI, stroke, SEE and vascular death) was analysed, dabigatran 150mg was favourable to warfarin (hazard ratio 0.84,

p=0.0093). Dabigatran 110mg was similar to warfarin (hazard ratio 0.98, p=0.7508). Therefore, although MI rates were higher in the dabigatran groups, overall clinical benefit is achieved by a reduction in overall cardiovascular clinical outcomes.

The dabigatran groups demonstrated a similar or superior safety profile compared with warfarin for most outcomes including major bleeds and life-threatening bleeds. However, the gastrointestinal bleeding and dyspepsia (and related symptoms) were more frequent in the dabigatran groups. The composite endpoint of stroke/SEE or major bleed was evaluated and the risk of stroke/SEE or major bleed was reduced 13% and 12% for the DE 110 bid and DE 150 bid dose groups compared to warfarin (Hazard ratio of 0.87 and 0.88, respectively).

Concern has been noted regarding the use of dabigatran in the elderly and those with renal impairment, as well as potential drug interactions for the general population.

On overall balance, the results of the single, large Phase III study (RE-LY) have demonstrated that dabigatran is non-inferior to warfarin and is superior for some endpoints and dose levels. Dabigatran is also beneficial when compared to warfarin in its ease of use (e.g. no monitoring of INR, less drug and food interactions, improved compliance).

VI. RECOMMENDATION

Based on the review of the data and subject to the Applicant's response to the questions on the, safety and efficacy of this product, the Evaluator considers that consent to distribute Pradaxa 110mg and Pradaxa 150mg can be recommended for the prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation.

LIST OF QUESTIONS

1. Within the product information sheet there is very little comment regarding the potential for dose adjustment (i.e. from 150mg bid to 110mg bid). This seems particularly important for the elderly (>75 years of age) and those with renal impairment. It may also be important for those taking P-glycoprotein inhibitors or proton-pump inhibitors and H2 blockers. The applicant should provide an appropriate dose adjustment plan for these groups of patients (to be outlined in the product information sheet) or provide further evidence as to why such dose adjustment is not required.

2. Pharmacokinetic data suggest that co-medication with gastric pH-elevating agents could decrease dabigatran absorption by 25%. However, data from the RE-LY study indicate a higher rate of bleeding amongst patients taking PPIs or H2 blockers. This appears rather contradictory. Can the applicant please provide any further information that may be available regarding bleeding rates and stroke rates among these patients, and also how to most appropriately manage these patients in the clinical setting?

3. Pharmacokinetic evidence regarding the influence of food suggests that AUC may increase 27% when taken with food. There is some concern that this increase in AUC may lead to accumulation, particularly with the higher dose. The applicant should provide evidence that accumulation will not occur if dabigatran is taken regularly with food.

4. Results from the RE-LY study suggest that bleeding rates doubled for those taking concomitant ASA and/or clopidogrel (or any other oral anti-coagulant). The applicant should identify why the product information sheet does not explicitly recommend against the co-administration of these medications (i.e. as a contraindication). If no appropriate evidence can be provided, the applicant should amend the product information sheet to identify the co-administration of these medications as a contraindication.

5. The RE-LY study identified a greater risk of GI adverse events and GI bleeding in the dabigatran groups compared to warfarin. The applicant should provide any information available that may explain this result.

VII. PRODUCT INFORMATION

Product information sheet is provided in the Appendix.

(i) Under the *Dosage and Administration* (Recommended daily dose) section, it is recommended that, along with the recommended 150mg bid dose, it is identified that the lower 110mg bid dose can be used in the appropriate circumstances (e.g. elderly, those with renal impairment, etc.).

(ii) Under the *Dosage and Administration* section and the heading "Concomitant use of dabigatran etexilate with strong P-glycoprotein inhibitors i.e. amiodarone, quinidine or verapamil" the "i.e." should be changed to "e.g." and the list that follows should include "diltiazem".

(iii) Under the *Pharmacokinetics* (Special populations) section and the *Warnings and Precautions* section it states that for NSAIDs "the use of regular NSAID medication with half-lives of less than 12 hours during treatment with dabigatran etexilate…has not

suggested additional bleeding risk". After careful reading it appears that this relates to the use of dabigatran for the prevention of VTE in patients following major orthopaedic surgery. However, given the results of the RE-LY study that indicate a ~50% increased risk of bleeding for those taking concomitant NSAID medication, this is a potential area of confusion in the product information sheet. It is recommended that the statement is amended to more accurately describe the results from the RE-LY study and eliminate confusion regarding the concomitant use of NSAIDs.

(iv) Following on from the recommendation in point (ii) and question 3 above, it is stated under the *Warnings and Precautions* section that "co-administration of oral anti-platelet [medication] (including aspirin and clopidogrel) and NSAID therapies increase the risk of bleeding." It is recommended that that a further statement that recommends against the co-administration of these medications be added.

(v) Under the *Adverse Effects* (Bleeding) section, the bleeding rates of dabigatran in comparison to warfarin are identified. It is recommended that the higher rate of gastrointestinal bleeding in the dabigatran groups compared to the warfarin group found in the RE-LY study is noted and appropriately identified.

(vi) Under *Dosage and Administration* and *Warnings and Precautions* in the product information sheet a statement on hepatic impairment has been deleted ("Hepatic impairment: Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes > 2 ULN were excluded in clinical trials. Therefore the use of dabigatran etexilate is not recommended in this population."). The applicant should provide supporting evidence as to why this statement has been removed, and if this is not available, should reinstate the statement.

APPENDIX – Product Information Sheet

Name of Medicine

PRADAXA®
Dabigatran etexilate

Presentation

75 mg hard capsules: Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 2 filled with yellowish pellets. The cap is imprinted in black ink with the Boehringer Ingelheim company symbol, the body with R75.

110 mg hard capsules: Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 1 filled with yellowish pellets. The cap is imprinted in black ink with the Boehringer Ingelheim company symbol, the body with R110.

150 mg hard capsules: Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 0 filled with yellowish pellets. The cap is imprinted in black ink with the Boehringer Ingelheim company symbol, the body with R150.

Uses

Actions

Pharmacotherapy group: oral direct thrombin inhibitor
ATC Code: B01AE07 - dabigatran etexilate

Dabigatran etexilate is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma.

Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

In-vivo and ex-vivo animal studies have demonstrated antithrombotic efficacy and anticoagulant activity of dabigatran after intravenous administration and of dabigatran etexilate after oral administration in various animal models of thrombosis.

There is a close correlation between plasma dabigatran concentration and degree of anticoagulant effect. Dabigatran prolongs the activated partial thromboplastin time (aPTT).

Deleted: In patients who are bleeding aPTT tests may be useful to assist in determining an excess of anticoagulant activity - despite the aPTT being less sensitive to the activity of dabigatran at supratherapeutic levels. If available, thrombin time (TT) and ecarin clotting time (ECT) may be more sensitive tests to evaluate the anticoagulant effects of dabigatran. Prothrombin time (INR) is prolonged by dabigatran but it is less sensitive than TT and ECT.

Pharmacokinetics

After oral administration of dabigatran etexilate in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterised by a rapid increase in plasma concentrations with Cmax attained within 0.5 and 2.0 hours post administration. Cmax and the area under the plasma concentration-time curve were dose proportional. After Cmax, plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of 11 hours in healthy elderly subjects. After multiple dose a terminal half-life of about 12-14 hours was observed. The half-life was independent of dose. However, half-life is prolonged if renal function is impaired as shown below, in Table 1.

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Deleted: In young healthy volunteers and 12 - 14 hours in elderly subjects

Table 1: Half-life of total dabigatran in healthy subjects and subjects with impaired renal function

glomerular filtration rate (CrCl)	gMean (gCV%; range) half-life
[mL/min]	[h]
≥ 80	13.4 (25.7%; 11.0-21.6)
>50- ≤ 80	15.3 (42.7%;11.7-34.1)
> 30 - ≤ 50	18.4 (18.5%;13.3-23.0)
≤ 30	27.2 (15.3%; 21.6-35.0)

The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate was approximately 6.5 %.

Deleted: Cmax and the area under the plasma concentration-time curve were dose proportional.

Food does not affect the bioavailability of dabigatran etexilate but delays the time to peak plasma concentrations by 2 hours.

The oral bioavailability may be increased by 75% compared to the reference capsule formulation when the pellets are taken without the HPMC capsule shell. Hence, the integrity of the HPMC capsules should always be preserved in clinical use to avoid unintentionally increased bioavailability of dabigatran etexilate. Therefore, patients should be advised not to open the capsules and taking the pellets alone (e.g. sprinkled over food or into beverages) (see Dosage and Administration).

Deleted: The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate was approximately 6.5 %.¶

A study evaluating post-operative absorption of dabigatran etexilate, 1-3 hours following surgery, demonstrated relatively slow absorption compared with that in healthy volunteers, showing a smooth plasma concentration-time profile without high peak plasma concentrations. Peak plasma concentrations are reached at 6 hours following administration or at 7 to 9 hours following surgery (BISTRO Ib). It is noted however that contributing factors such as anaesthesia, gastrointestinal paresis, and surgical effects will mean that a proportion of patients will experience absorption delay independent of the oral drug formulation. Although this study did not predict whether impaired absorption persists with subsequent doses, it was demonstrated in a further study that slow and delayed absorption is usually only present on the day of surgery. On subsequent days absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after drug administration.

Metabolism and excretion of dabigatran were studied following a single intravenous dose of radiolabelled dabigatran in healthy male subjects. After an intravenous dose, the dabigatran-derived radioactivity was eliminated primarily in the urine (85%). Faecal excretion accounted for 6% of the administered dose. Recovery of the total radioactivity ranged from 88 - 94 % of the administered dose by 168 hours post dose.

After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran, which is the active form in plasma. The cleavage of the prodrug dabigatran etexilate by esterase-catalysed hydrolysis to the active principle dabigatran is the predominant metabolic reaction. Dabigatran is subject to conjugation forming pharmacologically active acylglucuronides. Four positional isomers, 1-O, 2-O, 3-O, 4-O-acylglucuronide exist, each accounts for less than 10% of total dabigatran in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods. Dabigatran is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 mL/min corresponding to the glomerular filtration rate.

Low (34-35%) concentration independent binding of dabigatran to human plasma proteins was observed. The volume of distribution of dabigatran of 60 – 70 L exceeded the volume of total body water indicating moderate tissue distribution of dabigatran.

Special populations

Renal impairment: The exposure (AUC) of dabigatran after the oral administration of dabigatran etexilate in a phase I study was approximately 2.7 fold higher in volunteers with moderate renal insufficiency (CrCL between 30 - 50mL/min) than in those without renal insufficiency.

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In a small number of volunteers with severe renal insufficiency (CrCL 10 - 30 mL/min), the exposure (AUC) to dabigatran was approximately 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal insufficiency (see Dosage and Administration and Contraindications sections).

Elderly patients: Specific pharmacokinetic studies with elderly subjects in phase 1 studies showed an increase of 40 to 60% in the AUC and of more than 25 % in Cmax compared to young subjects. The AUC_{ss} and $C_{max,ss}$ in male and female elderly subjects (> 65 y) were approximately 1.9 fold and 1.6-fold higher for elderly females compared to young females and 2.2 and 2.0 fold higher for elderly males than in male subjects of 18 - 40 years of age. The observed increase of dabigatran exposure correlated with the age-related reduction in creatinine clearance.

Deleted: Population-based pharmacokinetic studies have evaluated the pharmacokinetics of dabigatran after repeated doses in patients (up to 88 years)

The effect by age on exposure to dabigatran was confirmed in the RE-LY study with an about 31 % higher trough concentration for subjects ≥ 75 years and by about 22 % lower trough level for subjects < 65 years compared to subjects of age between 65 and 75 years.

Hepatic insufficiency: No change in dabigatran exposure was seen in 12 subjects in a phase 1 study with moderate hepatic insufficiency (Child Pugh B) compared to 12 controls.

Prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.

Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes ≥ 2 Upper Limit Normal (ULN) were excluded in clinical trials.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation.

Patients with active liver disease including but not limited to the persistent elevation of liver enzymes ≥ 2 Upper Limit Normal (ULN), or hepatitis A, B or C were excluded in clinical trials.

Body weight: The dabigatran trough concentrations were about 20% lower in patients with a BW > 100 kg compared with 50 - 100 kg. The majority (80.8%) of the subjects were in the ≥ 50 kg and < 100 kg category with no clear difference detected. Limited data in patients ≤ 50 kg are available.

Deleted: Population pharmacokinetic studies have evaluated the pharmacokinetics of dabigatran in patients of 48 to 120 kg body weight. Body weight had a minor effect on the plasma clearance of dabigatran resulting in higher exposure in patients with low body weight.

Gender: Drug exposure in the primary VTE prevention studies was about 40% to 50% higher in female patients. In atrial fibrillation patients females had on average 30 % higher trough and post-dose concentrations. This finding had no clinical relevance.

Deleted: There were no differences in the phase 3 clinical studies for efficacy and safety data between men and women.

Ethnic origin: The pharmacokinetics of dabigatran was investigated in Caucasian and Japanese volunteers after single and multiple doses. Ethnic origin does not affect the pharmacokinetics of dabigatran in a clinically relevant manner. Limited pharmacokinetic data in black patients are available which suggest no relevant differences.

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Pharmacokinetic interactions: In vitro interaction studies did not show any inhibition or induction of the principal isoenzymes of cytochrome P450. This has been confirmed by in vivo studies with healthy volunteers, who did not show any interaction between dabigatran treatment and the

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following drugs: atorvastatin (CYP3A4), digoxin (P-gp transporter interaction) and diclofenac (CYP2C9).

Atorvastatin: When dabigatran etexilate was coadministered with atorvastatin a CYP3A4 substrate, exposure of atorvastatin, atorvastatin metabolites and of dabigatran were unchanged indicating a lack of interaction.

Diclofenac: When dabigatran etexilate was coadministered with diclofenac, a CYP2C9 substrate, pharmacokinetics of both drugs remained unchanged indicating a lack of interaction between dabigatran etexilate and diclofenac.

P-gp inhibitor / inducer interactions

The pro-drug dabigatran etexilate but not dabigatran is a substrate of the efflux transporter P-glycoprortein (P-gp). Therefore co-medications with P-gp transporter inhibitors and inducers had been investigated.

Co-medication with P-gp inhibitors

Amiodarone: When dabigatran etexilate was coadministered with a single oral dose of 600 mg amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The dabigatran AUC and Cmax were increased by about 60 % and 50 %, respectively.

Verapamil: When dabigatran etexilate was coadministered with oral verapamil, the C_{max} and AUC of dabigatran were increased depending on timing of administration and formulation of verapamil.

The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to dabigatran etexilate intake (increase of C_{max} by about 180% and AUC by about 150%). The effect was progressively decreased with administration of an extended release formulation (increase of C_{max} by about 90% and AUC by about 70%) or administration of multiple doses of verapamil (increase of C_{max} by about 60% and AUC by about 50%). This can be explained by the induction of P-gp in the gut by chronic verapamil treatment.

There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increase of C_{max} by about 10% and AUC by about 20%). This is explained by completed dabigatran absorption after 2 hours. (See Dosage and Administration).

No data are available for the parenteral application of verapamil; based on the mechanism of the interaction, no meaningful interaction is expected.

Ketoconazole: Ketoconazole increased total dabigatran $AUC_{0-\infty}$ and C_{max} values by 138 % and 135 %, respectively, after a single dose of 400 mg , and 153 % and 149 %, respectively, after multiple dosing of 400 mg ketoconazole qd.. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole.

Clarithromycin: When clarithromycin 500 mg twice daily was administered together with dabigatran etexilate no clinically relevant PK-interaction was observed (increased of C_{max} by about 19% and AUC by about 15%).

Quinidine: Quinidine was given as 200 mg dose every 2nd hour up to a total dose of 1000 mg. Dabigatran etexilate was given bid over 3 consecutive days, on the 3rd day either with or without quinidine. Dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ were increased on average by 53 % and 56 %, respectively with concomitant quinidine.

Co-medication with P-gp substrates

Digoxin: When dabigatran etexilate was coadministered with digoxin, a P-gp substrate, no PK-interaction was observed. Neither dabigatran nor the pro-drug dabigatran etexilate is a clinically relevant P-gp inhibitor.

Co-medication with P-gp inducers

Rifampicine: Pre-dosing of the probe inducer rifampicin at a dose of 600 mg qd for 7 days decreased total dabigatran peak and total exposure by 65.5 and 67 %, respectively. The inducing effect was diminished resulting in dabigatran exposure close to the reference by day 7 after cessation of rifampicin treatment. No further increase in bioavailability was observed after another 7 days.

Co-medications with platelet-inhibitors:

Acetylsalycilic acid (ASA): The effect of concomitant administration of dabigatran etexilate and acetylsalicylic acid (ASA) on the risk of bleeds was studied in patients with atrial fibrillation in a phase II study in which a randomized ASA coadministration was applied. Based on logistic regression analysis, co-administration of ASA and 150 mg dabigatran etexilate twice daily may increase the risk for any bleeding from 12 % to 18 % and 24% with 81 mg and 325 mg ASA, respectively. From the data gathered in the phase III study RE-LY it was observed that ASA or clopidogrel co-medication with dabigatran etexilate at dosages of 110 or 150 mg bid may increase the risk of major bleeding. The higher rate of bleeding events by ASA or clopidogrel co-medication was, however, also observed for warfarin.

NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. There is limited evidence regarding the use of regular NSAID medication with half-lives of less than 12 hours during treatment with dabigatran etexilate and this has not suggested additional bleeding risk.

Clopidogrel: In a phase I study in young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times (CBT) compared to clopidogrel monotherapy. In addition, dabigatran $AUC_{T,ss}$ and $C_{max,ss}$ and the coagulation measures for dabigatran effect, aPTT, ECT or TT (anti FIIa), or the inhibition of platelet aggregation (IPA) as measure of clopidogrel effect remained essentially unchanged comparing combined treatment and the respective mono-treatments. With a loading dose of 300 or 600 mg clopidogrel, dabigatran $AUC_{T,ss}$ and $C_{max,ss}$ were increased by about 30 to 40%.

Co-medication with gastric pH-elevating agents:

Pantoprazole: When dabigatran etexilate was coadministered with pantoprazole, a decrease in dabigatran area under the plasma concentration - time curve of approximately 30 % was observed. Pantoprazole and other proton-pump inhibitors were co-administered with dabigatran etexilate in clinical trials and no effects on bleeding or efficacy were observed.

Ranitidine: Ranitidine administration together with dabigatran etexilate had no meaningful effect on the extent of absorption of dabigatran.

The changes in dabigatran exposure determined by population pharmacokinetic analysis caused by PPIs and antacids were not considered clinically relevant because the magnitude of the effect were minor (fractional decrease in bioavailability not significant for antacids and 14.6 % for PPIs. In the phase III study, RE-LY, PPI co-medication did not result in lower trough levels and on average only slightly reduced post-dose concentrations (- 11 %). Accordingly, PPI comedication seemed to be not associated with a higher incidence of stroke or SEE, especially in comparison with warfarin, and

with warfarin, and hence, the reduced bioavailability by pantoprazole co-administration seemed to be of no clinical relevance.

Indications

Prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation.

Dosage and Administration

Dabigatran etexilate hard capsules should be taken with water, with or without food. Do not open the capsule.

Adults:

Prevention of Venous Thromboembolism (VTE) in patients following major orthopaedic surgery:
The recommended dose of dabigatran etexilate is 220 mg once daily taken as 2 capsules of 110 mg. Patients with moderate renal impairment have an increased risk for bleeding. For those patients the recommended dose of dabigatran etexilate is 150 mg once daily, taken as 2 capsules of 75 mg.

Treatment with dabigatran etexilate should be initiated orally within 1 – 4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for the required duration. If haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

VTE prevention following knee replacement surgery:
Treatment with dabigatran etexilate should be initiated orally within 1 – 4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for a total of 10 days. If haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

VTE prevention following hip replacement surgery:
Treatment with dabigatran etexilate should be initiated orally within 1 - 4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for a total of 28 – 35 days. If haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:
The recommended daily dose of Pradaxa is 300 mg taken orally as 150 mg hard capsules twice daily. Therapy should be continued life-long.

Children: Dabigatran etexilate has not been investigated in patients <18 years of age. Treatment of children with dabigatran etexilate is not recommended.

Renal impairment:
There are no data to support use in patients with severe renal impairment (< 30 mL/min creatinine clearance); treatment in this population with dabigatran etexilate is not recommended.

Prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.

Deleted: Dabigatran exposure in healthy subjects was increased by 60% in the presence of amiodarone.¶
¶
The population pharmacokinetic analysis of comedication effects supports the use of antacids and gastric acids suppressants without dose adjustment of dabigatran etexilate in patients and revealed the absence of dabigatran drug interactions with the most commonly used drugs in the study population: Opioids, diuretics, paracetamol, non-steroidal antiinflammatory drugs, Cyclo-oxygenase-2 inhibitors, hydroxymethylglutary-CoenzymeA (HMG-CoA) reductase inhibitors, non statin cholesterol /triglyceride lowering drugs, angiotensin II antagonists, angiotensin converting enzyme inhibitors, ß-adrenoceptor antagonists, dihydropyridine Ca2+-channel blockers, anti GI-motility drugs, benzodiazepine derivatives and drugs known to inhibit the P-glycoprotein (P-gp) efflux transporter, and P-gp substrates.¶

Deleted: Dabigatran etexilate should be taken with water, with or without food.

Deleted: Treatment for a total of 10 days.¶

Deleted: Treatment for a total of 28 – 35 days.

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Hepatic impairment: Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes > 2 Upper Limit Normal (ULN) were excluded in clinical trials. Therefore the use of dabigatran etexilate is not recommended in this population.¶

Dosing should be reduced to 150 mg dabigatran etexilate taken once daily as 2 capsules of 75 mg in patients with moderate renal impairment (30-50 mL/min creatinine clearance).

Deleted: After i.v. application 85% of dabigatran in plasma is cleared through the kidneys. Patients with moderate renal impairment (30-50 mL/min creatinine clearance) appear to be at higher risk of bleeding.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

No dose adjustment necessary, patients should be treated with a daily dose of 300 mg taken orally as 150 mg hard capsules twice daily.

Dabigatran can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies.

Elderly:
Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure in those patients with age-related decline of renal function, (see dosagee and administration in renal impairment).

Prevention of Venous Thromboembolism in patients following major orthopaedic surgery:

No dose adjustment necessary, patients should be treated with 220 mg dabigatran etexilate taken once daily as 2 capsules of 110 mg.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

No dose adjustment necessary, patients should be treated with a daily dose of 300 mg taken orally as 150 mg hard capsules twice daily.

Weight:
No dose adjustment necessary.

Concomitant use of dabigatran etexilate with strong P-glycoproetin inhibitors i.e. amiodarone, quinidine or verapamil:

Prevention of Venous Thromboembolism in patients following major orthopaedic surgery:

Dosing should be reduced to dabigatran etexilate 150 mg taken once daily as 2 capsules of 75 mg in patients who concomitantly receive dabigatran etexilate and amiodarone, quinidine or verapamil (see Interactions).

Treatment initiation with verapamil should be avoided in patients following major orthopaedic surgery who are already treated with dabigatran etexilate. Simultaneous initiation of treatment with dabigatran etexilate and verapamil should also be avoided.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

No dose adjustment necessary, patients should be treated with a daily dose of 300 mg taken orally as 150 mg hard capsules twice daily.

Patients at risk of bleeding:

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation.

For patients with a potentially higher risk of major bleeding, e.g. age ≥ 75 years, CHADS$_2$ score of ≥ 3, moderate renal impairment (30-50 ml CrCL/min), or concomitant treatment with strong P-gp inhibitors (see specific population in kinetics), previous gastro-intestinal bleed a reduced daily dose of 220 mg given as 110 mg twice daily may be considered.

Switching from dabigatran etexilate treatment to parenteral anticoagulant:

Prevention of Venous Thromboembolism in patients following major orthopaedic surgery:

Wait 24 hours after the last dose before switching from dabigatran etexilate to a parenteral anticoagulant.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

Wait 12 hours after the last dose before switching from dabigatran etexilate to a parenteral anticoagulant.

Switching from parenteral anticoagulants treatment to dabigatran etexilate:
Dabigatran etexilate should be given 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous UFH).

Switching from Vit. K antagonists to dabigatran etexilate:
The Vit. K antagonist should be stopped. Dabigatran etexilate can be given as soon as the INR is < 2.0.

Cardioversion
Patients can stay on dabigatran etexilate while being cardioverted.

Missed dose

Prevention of Venous Thromboembolism in patients following major orthopaedic surgery:

Continue with your remaining daily doses of dabigatran etexilate at the same time of the next day. Do not take a double dose to make up for missed individual doses.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

A forgotten dabigatran etexilate dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose on, the missed dose should be omitted. Do not take a double dose to make up for missed individual doses.

Contraindications

- Known hypersensitivity to dabigatran or dabigatran etexilate or to one of the excipients of the product
- Severe renal impairment (CrCl < 30mL/min)
- Haemorrhagic manifestations, patients with a bleeding diathesis, or patients with spontaneous or pharmacological impairment of haemostasis
- Organ lesions at risk of clinically significant bleeding, including haemorrhagic stroke within the last 6 months
- Indwelling spinal or epidural catheter and during the first hour after removal (see Warnings and Precautions).
- Concomitant treatment with systemic ketokonazole (see Interactions)

Deleted: Treatment in patients with severe renal impairment creatinine clearance (< 30 mL/min) with dabigatran etexilate is not recommended. There are no data to support use in this population.¶
¶
Weight: Population PK modelling shows that patients with a body weight of 120 kg have about 20% lower drug exposure and patients with a body weight of 48 kg have about 25% higher drug exposure compared to patients with an average weight. Since there was no difference in efficacy and bleeding rates, no dose adjustment is necessary.¶
¶
Concomitant use of dabigatran etexilate with amiodarone or verapamil: Dosing should be reduced to dabigatran etexilate 150 mg daily in patients who concomitantly receive dabigatran etexilate and amiodarone or verapamil.¶
¶
Switching from dabigatran etexilate treatment to parenteral anticoagulant: Wait 24 hours after the last dose before switching from dabigatran etexilate to a parenteral anticoagulant. ¶

Deleted: Switching from parenteral anticoagulants treatment to dabigatran etexilate: No data are available, therefore it is not recommended to start the administration of dabigatran etexilate before the next scheduled dose of the parenteral anticoagulant would have been due.¶

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Warnings and Precautions

Haemorrhagic risk

As with all anticoagulants, dabigatran etexilate should be used with caution in conditions with an increased risk of bleeding. Bleeding can occur at any site during therapy with dabigatran. An unexplained fall in hemoglobin and/or hematocrit or blood pressure should lead to a search for a bleeding site.

The aPTT test is widely available and provides an approximate indication of the anticoagulation intensity achieved with dabigatran. In patients who are bleeding, the aPTT test maybe useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity. An aPTT greater than 80 sec is associated with a higher risk of bleeding.

Pharmacokinetic studies demonstrated an increase in drug exposure in patients with reduced renal function including age-related decline of renal function. Dabigatran etexilate is contraindicated in cases of severe renal impairment (CrCL < 30 ml/min).

Patients who develop acute renal failure should discontinue dabigatran etexilate.

Factors, such as decreased renal function (30 - 50ml/min CrCL), age ≥ 75 years, or strong P-gp-inhibitor comedication are associated with increased dabigatran plasma levels. The presence of one or more than one of these factors may increase the risk of bleeding (see Dosage and Administration).

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, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfinpyrazone, rivaroxaban, prasugrel, vitamin K antagonists, and the P-gp inhibitors itraconazole, tacrolismus, cyclosporine, ritonavir, tipranavir, nelfinavir and saquinavir.

In situations where there is an increased haemorrhagic risk (e.g. recent biopsy or major trauma, bacterial endocarditis) close observation (looking for signs of bleeding or anaemia) is generally required.

Prevention of Venous Thromboembolism in patients following major orthopaedic surgery:

NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. There is limited evidence regarding the use of regular NSAID medication with half-lives of less than 12 hours during treatment with dabigatran etexilate and this has not suggested additional bleeding risk.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

Co-administration of oral anti-platelet (including aspirin and clopidogrel) and NSAID therapies increase the risk of bleeding.

Interaction with P-gp inducers:
The concomitant use of dabigatran etexilate with the strong P-gp inducer rifampicin reduces dabigatran plasma concentrations. Other P-gp inducers such as St. John's Wort or carbamazepine are also expected to reduce dabigatran plasma concentrations, and should be co-administered with caution (see interaction and special population).

Deleted: Hepatic impairment¶
Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes > 2 ULN. were excluded in clinical trials. Therefore the use of dabigatran etexilate is not recommended in this population. ¶

Deleted: The following treatments should not be administered concomitantly with dabigatran etexilate: unfractionated heparins and heparin derivatives, low molecular weight heparins (LMWH), factor Xa inhibitors like fondaparinux, other thrombin inhibitors like desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, anti-thrombotic agents like clopidogrel, ticlopidine, dextran, sulfinpyrazone and vitamin K antagonists. It should be noted that unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter. ¶
¶
The risk of bleeding increases when aspirin at doses of 75 to 325 mg was given concomitantly with dabigatran etexilate at high doses (above those recommended for VTE prevention). There was no evidence of an excess bleeding risk when dabigatran was given at the recommended dose to patients receiving low-dose aspirin for the prevention of cardiovascular events. However, the information is limited and the co-administration of low-dose aspirin and dabigatran etexilate should be accompanied by clinical observation for bleeding.¶
¶
Close observation (looking for signs of bleeding or anaemia) is required in the following situations that may increase the haemorrhagic risk:¶
¶
Recent biopsy or major trauma. ¶
¶
Patients receiving treatments liable to increase the haemorrhagic risk. The association of dabigatran etexilate with treatments that act on haemostasis or coagulation may increase the haemorrhagic risk (See Warnings and Precautions, Interactions sections).¶
¶

... [1]

Surgery and Interventions:

Patients on dabigatran etexilate who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore surgical interventions may require the temporary discontinuation of dabigatran etexilate.

Preoperative Phase
In advance of invasive or surgical procedures dabigatran etexilate should be stopped temporarily due to an increased risk of bleeding. If possible, dabigatran etexilate should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete hemostasis may be required consider stopping dabigatran etexilate 2-4 days before surgery. Clearance of dabigatran in patients with renal insufficiency may take longer. This should be considered in advance of any procedures.

Dabigatran etexilate is contraindicated in patients with severe renal dysfunction (CrCl <30 mL/min) but should this occur then dabigatran etexilate should be stopped at least 5 days before major surgery.

If an acute intervention is required, dabigatran etexilate should be temporarily discontinued. A surgery / intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed there may be an increase in the risk of bleeding. This risk of bleeding should be weighed together with the urgency of intervention.

Spinal Anesthesia/Epidural Anesthesia/Lumbar Puncture
Procedures such as spinal anesthesia may require complete hemostatic function.

The risk of spinal or epidural hematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 1 hour should elapse before the administration of the first dose of dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms of spinal or epidural hematoma.

Post Procedural Period

Resume treatment after complete haemostasis is achieved.

The product contains the excipient sunset yellow, which may cause allergic reactions.

Effects on Fertility
In the fertility study in rats, no toxicologically remarkable parental findings were noted. With respect to litter parameters, a slight decrease in corpora lutea and an increase in pre-implantation loss led to a decrease in the mean number of implantations in the 200 mg/kg (free base equivalent) dose group.

Use in Pregnancy
No clinical data on exposed pregnancies are available. The potential risk for humans is unknown.

Teratology studies were performed with up to 200 mg/kg (free base equivalent) in rats and rabbits. A slight effect on the morphogenesis of foetuses was observed in rats at 200 mg/kg (free base equivalent). No teratogenic effects were noted in rabbits.

Women of child-bearing potential should avoid pregnancy during treatment with dabigatran etexilate and when pregnant, women should not be treated with dabigatran etexilate unless the expected benefit is greater than the risk.

Deleted: <#>The oral application of a strong P-gp inhibitor (e.g. verapamil) concomitantly with dabigatran etexilate may elevate dabigatran plasma concentrations resulting in an increased bleeding risk. Treatment initiation with verapamil should be avoided in patients following major orthopaedic surgery who are already treated with dabigatran etexilate. Simultaneous initiation of treatment with dabigatran etexilate and verapamil should also be avoided¶
¶
<#>Bacterial endocarditis.¶
¶
Renal Insufficiency¶
Pharmacokinetic studies demonstrated an increase in drug exposure in patients with reduced renal function including age-related decline of renal function. Dose reduction to 150 mg daily is recommended for patients with moderate renal impairment (50-30 mL/min). Dabigatran etexilate is contraindicated in cases of severe renal impairment (CrCL < 30 mL/min). Patients who develop acute renal failure should discontinue dabigatran etexilate.¶
¶
Spinal Anaesthesia/Epidural Anaesthesia/Lumbar Puncture¶
The risk of spinal or epidural haematoma may be increased in cases of traumatic or repeated puncture and by the prolonged postoperative use of epidural catheters. After removal of a catheter, an interval of at least 1 hour should elapse before the administration of the first dose of dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms.¶
¶

Use in Lactation
No clinical data are available. As a precaution, breast-feeding should be stopped.

Effect on Fertility
No data available

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Effects on Ability to Drive and Use Machines
No studies on the effects on the ability to drive and use machines have been performed.

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Paediatric use
There is no experience in children. Dabigatran etexilate has not been investigated in patients <18 years of age. Treatment of children with dabigatran etexilate is not recommended.

Use in the elderly
The clinical studies have been conducted in a patient population with a mean age > 65 years. In general, patients should be treated with the standard dose of 220 mg dabigatran etexilate daily. Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure in those patients with age-related decline of renal function (see Precautions, Renal Insufficiency section).

Carcinogenicity
The tumorigenic potential of dabigatran etexilate is currently being investigated in rats and mice at maximum doses of 200 mg/kg (free base equivalent).

Genotoxicity
Comprehensive in vitro- and in vivo studies revealed no evidence of a mutagenic potential.

Adverse Effects
The safety of dabigatran etexilate has been evaluated overall in 22,687 patients.

In the primary VTE prevention trials after major orthopaedic surgery a total of 10,596 patients were treated in 5 controlled studies with at least one dose of study medication. Of these 5,674 were treated with 150 or 220 mg once daily of dabigatran etexilate, while 522 received doses less than 150 mg once daily and 1168 received doses in excess of 220 mg once daily.

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Deleted: VTE prevention trials

In the RE-LY trial investigating the prevention of stroke and systemic embolism in patients with atrial fibrillation a total of 12,091 patients were randomized. Of these 6,076 were treated with 150 mg twice daily of dabigatran etexilate, while 6,015 received doses of 110 mg twice daily.

In total, about 9 % of patients treated for elective hip or knee surgery (short-term treatment for up to 42 days) and 22 % of patient with atrial fibrillation treated for the prevention of stroke and systemic embolism (long-term treatment for up to 3 years) experienced adverse reactions.

Bleeding

Bleeding is the most relevant side effect of dabigatran etexilate; dependant of the indication bleeding of any type or severity occurred in approximately 14 % of patients treated short-term for elective hip or knee replacement surgery and in long-term treatment in yearly 16.5 % of patient with atrial fibrillation treated for the prevention of stroke and systemic embolism.

Although rare in frequency in clinical trials, major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

Deleted: The adverse reactions that can with reasonable certainty be attributed to dabigatran, and occurred with a similar frequency with enoxaparin, are those of bleeding or signs of bleeding e.g. anaemia and wound discharge. The definition of major bleeding events (MBE) followed the ISTH (International Society on Thrombosis and Haemostasis) criteria and the EMEA guideline. According to the MedDRA coding system, bleeding events are distributed over several System Organ Classes (SOC); therefore, a summary description of major and any bleeding is given in Table 1 below.¶

Prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.

Overall bleeding rates were similar between treatment groups and not significantly different.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

Major bleeding fulfilled one or more of the following criteria:

- Bleeding associated with a reduction in hemoglobin of at least 20 grams per liter or leading to a transfusion of at least 2 units of blood or packed cells;
- Symptomatic bleeding in a critical area or organ: Intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding.

Major bleeds were classified as life-threatening if they fulfilled one or more of the following criteria:

- Fatal bleed; symptomatic intracranial bleed; reduction in hemoglobin of at least 50 grams per liter; transfusion of at least 4 units of blood or packed cells; a bleed associated with hypotension requiring the use of intravenous inotropic agents; a bleed that necessitated surgical intervention.

Subjects randomized to dabigatran etexilate 110 mg twice daily and 150mg twice daily had a significantly lower risk for life-threatening bleeds, haemorrhagic stroke and intracranial bleeding compared to warfarin ($p < 0.05$). Both dose strengths of dabigatran etexilate had also a statistically significant lower total bleed rate. Subjects randomized to dabigatran etexilate 110mg twice daily had a signficantly lower risk for major bleeds comapred with warfarin (hazard ratio 0.79, p= 0.0021)

Side effects:

Adverse reactions classified by SOC and MedDRA preferred terms reported from any treatment group per population of all controlled studies are shown in the listings below. Table 2 lists identified side effects applicable to both indications. Table 3 lists indication specific side effects identified.

Side effects are generally associated to the pharmacological mode of action of dabigatran etexilate and represent bleeding associated events that may occur in different anatomical regions and organs.

In patients treated for VTE prevention after hip or knee replacement surgery the observed incidences of side effects of dabigatran etexilate were in the range of enoxaparin.

The observed incidences of side effects of dabigatran etexilate in patients treated for stroke prevention after atrial fibrillation were in the range of warfarin except gastrointestinal disorders which appeared at a higher rate in the dabigatran etexilate arms.

Table 2: Side effects identified from the *Primary VTE prevention studies after major orthopaedic surgery program* and the *Prevention of thromboembolic stroke and systemic embolism in patients with atrial fibrillation at moderate to high risk of stroke program.*

Blood and lymphatic system disorders
Anaemia, Thrombocytopenia
Immune system disorders
Drug hypersensitivity including urticaria, rash and pruritus, bronchospasm

Deleted: Table 1 shows the number (%) of patients experiencing major and total bleeding event rates during the treatment period in the VTE prevention RCT, according to dose.¶
¶
Table 1: Bleeding broken down to randomisation procedure, severity and dosage of dabigatran etexilate and enoxaparin¶
Pre-operative randomisation trials ... [2]

Deleted: Adverse reactions classified by System Organ Class (SOC) and preferred terms reported from any treatment group of all controlled VTE prevention studies are shown in the listing below.¶
¶
Blood and lymphatic system disorders ... [3]

Nervous system disorders
Intracranial haemorrhage
Vascular disorders
Haematoma, Haemorrhage
Respiratory, thoracic and mediastinal disorders
Epistaxis, haemoptysis
Gastrointestinal disorders
Gastrointestinal haemorrhage, Abdominal pain, diarrhoea, dyspepsia, nausea, gastrointestinal ulcer, gastrooesophagitis, gastrooesophageal reflux disease, vomiting, dysphagia
Hepatobiliary disorders
Hepatic function abnormal
Skin and subcutaneous tissue disorders
Skin haemorrhage
Musculoskeletal, connective tissue and bone disorders
Haemarthrosis
Renal and urinary disorders
Urogenital haemorrhage, Haematuria
General disorders and administration site conditions
Injection site haemorrhage, Catheter site haemorrhage
Injury, poisoning and procedural complications
Traumatic haematoma, Incision site haemorrhage

Table 3: Additional specific side effects identified per indication

Prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.
Vascular disorders
Wound haemorrhage
General disorders and administration site conditions
Bloody discharge
Injury, poisoning and procedural complications
Post-procedural haematoma, Post-procedural haemorrhage, Anaemia post-operative, Post-procedural discharge, Wound secretion,
Surgical and medical procedures
Wound drainage, Post-procedural drainage,
Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

None

Interactions

The concomitant use of dabigatran etexilate with treatments that act on haemostasis or coagulation including Vitamin K antagonists can markedly increase the risk of bleeding.

Dabigatran etexilate and dabigatran are not metabolised by the cytochrome P450 system and had no effects in vitro on human cytochrome P450 enzymes. Therefore related drug-drug interactions are not expected with dabigatran etexilate or dabigatran (see Pharmacokinetcs - special populations).

P-gp interactions:

P-glycoprotein inhibitors:

Amiodarone: Dabigatran exposure in healthy subjects was increased by 60 % in the presence of amiodarone (see Pharmacokinetcs - special populations).

Verapamil: When dabigatran etexilate (150 mg) was coadministered with oral verapamil, the C_{max} and AUC of dabigatran were increased but magnitude of this change differs depending on timing of administration and formulation of verapamil (see Pharmacokinetcs - special populations).

Quinidine: Dabigatran exposure in healthy subjects was increased by 53 % in the presence of quinidine (see Pharmacokinetcs - special populations).

Clarithromycin: Dabigatan exposure in healthy subjects was increased by 15 % in the presence of clarithromycine without any clinical safety concern (see Pharmacokinetcs - special populations).

Ketoconazole: Dabigatran exposure was 150 % increased after single and multiple doses of Ketoconazole (see Contraindications and Pharmacokinetcs - special populations).

P- glycoprotein substrate:
Digoxin: In a study performed with 24 healthy subjects, when Rradaxa was coadministered with digoxin, no changes on digoxin and no clinical relevant changes on dabigatran exposure have been observed (see Pharmacokinetcs - special populations).

P-glycoprotein inducers:
After 7 days of treatment with 600 mg rifampicin qd, total dabigatran AUC0-∞ and Cmax were reduced by 67% and 66% compared to the reference treatment, respectively. Caution should be exercised with strong P- glycoprotein inducers (see Warnings and Precautions and Pharmacokinetcs - special population).

Overdosage

Overdose following administration of dabigatran etexilate may lead to haemorrhagic complications due to its pharmacodynamic properties. A specific antidote antagonising the pharmacodynamic effect of dabigatran etexilate is not available. Doses of dabigatran etexilate beyond those recommended expose the patient to increased risk of bleeding. Excessive anticoagulation may require discontinuation of dabigatran etexilate. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. Appropriate standard treatment, e.g., surgical haemostasis as indicated and blood volume replacement, should be undertaken. In addition, consideration may be given to the use of fresh whole blood or fresh

Deleted: Other anticoagulants:

Deleted: Metabolic profile of dabigatran etexilate and dabigatran:

Deleted: Amiodarone: When dabigatran etexilate was coadministered with a single oral dose of 600 mg amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The dabigatran AUC and C_{max} were increased by about 60 % and 50 %, respectively. ¶
¶
Verapamil: When dabigatran etexilate was coadministered with oral verapamil, the C_{max} and AUC of dabigatran were increased depending on timing of administration and formulation of verapamil.¶
¶
The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to dabigatran etexilate intake (increase of C_{max} by about 180% and AUC by about 150%). The effect was progressively decreased with administration of an extended release formulation (increase of C_{max} by about 90% and AUC by about 70%) or administration of multiple doses of verapamil (increase of C_{max} by about 60% and AUC by about 50%). This can be explained by the induction of P-gp in the gut by chronic verapamil treatment.¶
¶
There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increase of C_{max} by about 10% and AUC by about 20%). This is explained by completed dabigatran absorption after 2 hours. (See Dosage and Administration).¶
¶
No data are available for the parenteral application of verapamil; based on the mechanism of the interaction, no meaningful interaction is expected.¶
¶
Clarithromycin: When clarithromycin 500 mg bid was administered together with dabigatran etexilate no clinically relevant PK-interaction was observed (increased of Cmax by about 19% and AUC by about 15%).¶
¶
Atorvastatin: When dabigatran etexilate was coadministered with atorvastatin, exposure of ... [4]

frozen plasma. As protein binding is low, dabigatran is dialysable, however there is limited clinical experience in using dialysis in this setting [2].

Activated prothrombin complex concentrates (e.g., FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX or X, may be considered. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatran but their usefulness in clinical settings has not yet been systematically demonstrated. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet drugs have been used. All symptomatic treatment has to be given according to the physician's judgement.

Deleted: In case of poisoning or overdose, advice should be sought from a Poisons Information Centre.¶
¶
There is no antidote to PRADAXA or dabigatran. Doses of PRADAXA beyond those recommended expose the patient to increased risk of bleeding. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. The initiation of appropriate treatment, e.g. surgical haemostasis or the transfusion of fresh frozen plasma should be considered. ¶
¶
Dabigatran can be dialysed; there is no clinical experience to demonstrate the utility of this approach in clinical studies.¶
¶

Pharmaceutical Precautions

CAPSULES (blister packs): Store below 30°C. Protect from moisture.

CAPSULES (bottle): Store below 30°C. Protect from moisture. Once opened, the bottle must be used within 30 days. Keep the bottle tightly closed.

Medicine Classification

Prescription Medicine

Package Quantities

Capsules 75 mg: Blister packs: 10, 30, 60 capsules.
Bottle: 60 capsules.

Capsules 110mg : Blister packs: 10, 30, 60 capsules.
Bottle: 60 capsules.

Capsules 150mg : Blister packs: 10, 30, 60 capsules.
Bottle: 60 capsules.

Not all pack sizes may be marketed.

Further Information

PRADAXA® is a registered Trademark

Excipients

Capsule fill: Tartaric acid, acacia, hypromellose, dimethicone 350, talc, hydroxypropylcellulose
HPMC capsule shell: Sodium carrageenan, potassium chloride, titanium dioxide, sunset yellow FCF (E110), indigo carmine (E132), hypromellose, water - purified
Printing ink: Shellac, tert-butyl alcohol, isopropyl alcohol, methylated spirit - industrial, iron oxide black (E172), water - purified, propylene glycol.

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Clinical Trials

Clinical trials in primary VTE prevention following major joint replacement surgery:

In 2 large randomised, parallel group, double-blind, dose–confirmatory trials, patients undergoing elective major orthopaedic surgery (one for knee replacement surgery and one for hip replacement surgery) received dabigatran etexilate 75 mg or 110 mg within 1-4 hours of surgery followed by 150 or 220 mg once daily thereafter, haemostasis having been secured, or enoxaparin 40 mg on the day prior to surgery and once daily thereafter.

In the RE-MODEL trial (knee replacement) treatment was for 6 – 10 days and in the RE-NOVATE trial (hip replacement) for 28 – 35 days. Totals of 2076 patients (knee) and 3494 (hip) were treated respectively.

The results of the knee study (RE-MODEL) with respect to the primary end-point, total venous thromboembolism (VTE) including asymptomatic venous (VTE) plus all-cause mortality showed that the antithrombotic effect of both doses of dabigatran etexilate were statistically non-inferior to that of enoxaparin.

Similarly, total VTE including asymptomatic VTE and all-cause mortality constituted the primary end-point for the hip study (RE-NOVATE). Again dabigatran etexilate at both once daily doses was statistically non-inferior to enoxaparin 40 mg daily.

Furthermore in a third randomized, parallel group, double-blind, trial (RE-MOBILIZE), patients undergoing elective total knee surgery received dabigatran etexilate 75 mg or 110 mg within 6-12 hours of surgery followed by 150 mg and 220 mg once daily thereafter. The treatment duration was 12-15 days. In total 2615 patients were randomised and 2596 were treated. The comparator dosage of enoxaparin was 30 mg twice daily according to the US label. In the RE-MOBILIZE trial non–inferiority was not established. There were no statistical differences in bleeding between the comparators.

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In addition a randomized, parallel group, double-blind, placebo-controlled phase II study in Japanese patients where dabigatran etexilate 110 mg, 150 mg, and 220 mg was administered at the next day after elective total knee replacement surgery was evaluated. The Japanese study showed a clear dose response relationship for the efficacy of dabigatran etexilate and a placebo like bleeding profile.

In RE-MODEL and RENOVATE the randomisation to the respective study medication was done pre-surgery, and in the RE-MOBILIZE and the Japanese placebo controlled trial the randomisation to the respective study medication was done post-surgery. This is of note especially in the safety evaluation of these trials. For this reason the trials are grouped in pre- and post surgery randomised trials in the previous Table 1 above.

Data for the major VTE and VTE-related mortality end-point and adjudicated major bleeding endpoints are shown in table 4 below. VTE was defined as the composite incidence of deep vein thrombosis and Pulmonary Embolism.

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Table 4 - Analysis of major VTE and VTE-related mortality during the treatment period in the RE-MODEL and the RE-NOVATE orthopaedic surgery studies

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Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
RE-NOVATE (hip)			
N	909	888	917
Incidences (%)	28 (3.1)	38 (4.3)	36 (3.9)
Risk differences vs. enoxaparin (%)	- 0.8	0.4	
95 % CI	- 2.5, 0.8	- 1.5, 2.2	
Risk ratio over enoxaparin	0.78	1.09	
95% CI	0.48, 1.27	0.70, 1.70	
RE-MODEL (knee)			
N	506	527	511
Incidences (%)	13 (2.6)	20 (3.8)	18 (3.5)
Risk differences vs.	- 1.0	0.3	

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
enoxaparin (%)			
95 % CI	- 3.1, 1.2	-2.0, 2.6	
Risk ratio over enoxaparin	0.73	1.08	
95% CI	0.36, 1.47	0.58, 2.01	
RE-MOBILIZE (knee) [2]			Enoxaparin 60 mg
N	618	656	668
Incidences (%)	21 (3.4)	20 (3.0)	15 (2.2)
Risk differences vs. enoxaparin (%)	1.2	0.8	
95 % CI	(-0.7, 3.0)	(-0.9, 2.5)	
Risk ratio over enoxaparin	1.51	1.36	
95% CI	(0.79, 2.91)	(0.70, 2.63)	
Japanese knee study [2]			
			Placebo
N	102	113	104
Incidences (%)	0	2 (1.8)	6 (5.8)
Risk differences vs. placebo (%)	-5.8	-4.0	
95 % CI	(-10.3, -1.3)	(-9.1, 1.1)	

[1] pre-operative randomisation studies
[2] post-operative randomisation studies

Clinical trials in prevention of stroke and systemic embolism in patients with atrial fibrillation:

The clinical evidence for the efficacy of dabigatran etexilate is derived from the RE-LY study (Randomized Evaluation of Long –term anticoagulant therapy) a multi-center, multi-national, randomized parallel group study of two blinded doses of dabigatran (110 mg bid and 150 mg bid) compared to open-label warfarin in patients with atrial fibrillation at moderate to high risk of stroke or systemic embolism. The primary objective in this study was to determine if dabigatran was non-inferior to warfarin in reducing the occurrence of the composite endpoint, stroke and systemic embolic events (SEE).

In the RE-LY study, a total of 18,113 patients were randomized, with a mean age of 71.5 years and a mean CHADS$_2$ score of 2.1. The population had approximately equal proportions of patients with CHADS$_2$ score 1, 2 and ≥ 3. The patient population was 64% male, 70% Caucasian and 16% Asian. RE-LY had a median treatment of 20 months with dabigatran etexilate given as fixed dose without coagulation monitoring. In addition to documented non-valvular atrial fibrillation (AF) e.g., persistent AF or paroxysmal, patients had one of the following additional risk factors for stroke:

- Previous stroke, transient ischemic attack, or systemic embolism
- Left ventricular ejection fraction <40 %
- Symptomatic heart failure, ≥ NYHA Class 2
- Age ≥ 75 years
- Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension

The concomitant diseases of patients in this trial included hypertension 79%, diabetes 23% and CAD 28%. 50% of the patient population was VKA naïve defined as less than 2 months total life time exposure. 32% of the population had never been exposed to a VKA. For those patients

randomized to warfarin, the time in therapeutic range (INR 2 to 3) for the trial was a median of 67%. Concomitant medications included aspirin (25% of subjects used at least 50% of the time in study), clopidogrel (3.6%), ASA+clopidogrel (2%), NSAIDs (6.3%), beta-blockers (63.4%), diuretics (53.9%), statins (46.4%), ACE-inhibitors (44.6%), angiotensin receptor blockers (26.1%), oral hypoglycemics (17.5%), insulin (5.2%), digoxin (29.4%), amiodarone (11.3%), diltiazem (8.9%), verapamil (5.4%), and proton pump inhibitors (17.8%).

For the primary endpoint, stroke and systemic embolism, no subgroups (i.e., age, weight, gender, renal function, ethnicity, etc.) were identified with a different risk ratio compared to warfarin.

This study demonstrated that dabigatran etexilate, at a dose of 110 mg twice daily, is non-inferior to warfarin in the prevention of stroke and systemic embolism in subjects with atrial fibrillation, with a reduced risk of intracranial hemorrhage and total bleeding. The higher dose of 150 mg twice daily, reduces significantly the risk of ischemic and hemorrhagic stroke, vascular death, intracranial hemorrhage and total bleeding compared to warfarin. The lower dose of dabigatran has a signficiantly lower risk of major bleeding compared to warfarin.

Figure 1 and tables 5 - 9 display details of key results:

Table 5: Analysis of first occurrence of stroke or systemic embolism (primary endpoint) during the study period in the RE-LY

	Dabigatran etexilate 150 mg bid	Dabigatran etexilate 110 mg bid	Warfarin
Subjects randomized	6076	6015	6022
Stroke and/or SEE			
Incidences (%)	133 (1.10)	182 (1.53)	199 (1.69)
Hazard ratio over warfarin (95% CI)	0.66 (0.53, 0.82)	0.91 (0.75, 1.12)	
p value superiority	p < 0.001	p = 0.370	

% refers to yearly event rate

Figure 1: Kaplan-Meyer curve estimate of time to first stroke or systemic embolism

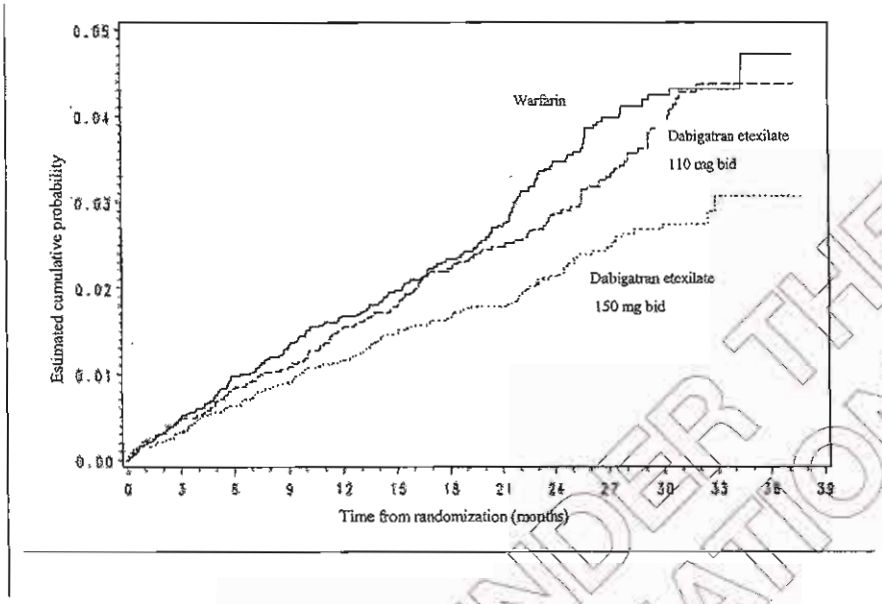


Table 6: Analysis of first occurrence of ischemic or haemorrhagic strokes during the study period in the RE-LY

	Dabigatran etexilate 150 mg bid	Dabigatran etexilate 110 mg bid	Warfarin
Subjects randomized	6076	6015	6022
Stroke			
Incidences (%)	121 (1.01)	171 (1.44)	184 (1.56)
Hazard ratio vs. warfarin (95% CI)	0.64 (0.51, 0.81)	0.92 (0.75, 1.14)	
p-value	<0.001	0.443	
SEE			
Incidences (%)	13 (0.11)	14 (0.12)	19 (0.16)
Hazard ratio vs. warfarin (95% CI)	0.67 (0.33, 1.36)	0.73 (0.37, 1.46)	
p-value	0.271	0.378	
Ischemic stroke			
Incidences (%)	102 (0.85)	152 (1.28)	132 (1.12)
Hazard ratio vs. warfarin (95% CI)	0.76 (0.58, 0.98)	1.14 (0.91, 1.44)	
p-value	0.034	0.258	
Hemorrhagic stroke			
Incidences (%)	12 (0.10)	14 (0.12)	45 (0.38)
Hazard ratio vs. warfarin (95% CI)	0.26 (0.14, 0.49)	0.31 (0.17, 0.56)	
p-value	<0.001	<0.001	

% refers to yearly event rate

Table 7: Analysis of all cause and cardiovascular survival during the study period in the RE-LY

	Dabigatran etexilate 150 mg bid	Dabigatran etexilate 110 mg bid	Warfarin
Subjects randomized	6076	6015	6022
All-cause mortality			
Incidences (%)	437 (3.63)	445 (3.74)	487 (4.13)
Hazard ratio vs. warfarin (95% CI)	0.88 (0.77, 1.00)	0.90 (0.79, 1.03)	
p-value	0.051	0.123	
Vascular mortality			
Incidences (%)	273 (2.27)	288 (2.42)	317 (2.69)
Hazard ratio vs. warfarin (95% CI)	0.84 (0.72, 0.99)	0.90 (0.79, 1.06)	
p-value	0.039	0.194	

% refers to yearly event rate

The net clinical benefit as measured by the composite clinical endpoint of stroke, systemic embolism, pulmonary embolism, acute myocardial infarction, vascular deaths, and major bleeds was assessed and is presented as part of Table 8. The yearly event rates for the dabigatran etexilate groups were lower compared to the warfarin group. The risk reduction for this composite endpoint was 8% and 10% for the dabigatran etexilate 110 mg bid and 150 mg bid treatment groups. Other components evaluated included all hospitalizations which had statistically significant fewer hospitalizations at dabigatran etexilate 110 mg bid compared to warfarin (7% risk reduction, 95% CI 0.87, 0.99, p=0.021).

Table 8: Other Measures Evaluated

	Dabigatran etexilate 150 mg bid	Dabigatran etexilate 110 mg bid	Warfarin
Subjects randomized	6076	6015	6022
Stroke/SEE/death			
Incidences (%)	518 (4.30)	575 (4.83)	610 (5.17)
Hazard ratio vs. warfarin (95%CI)	0.83 (0.74, 0.93)	0.93 (0.83, 1.05)	
p-value	0.002	0.234	
Stroke/SEE/PE/MI/death/major bleed (net clinical benefit)			
Incidences (%)	830 (6.89)	842 (7.08)	900 (7.63)
Hazard ratio vs. Warfarin (95%CI)	0.90 (0.82, 0.99)	0.92 (0.84, 1.02)	
p-value	0.037	0.100	
Pulmonary embolism			
Incidences (%)	18 (0.15)	14 (0.12)	11 (0.09)
Hazard ratio vs. Warfarin (95%CI)	1.61 (0.76, 3.41)	1.26 (0.57, 2.79)	
p-value	0.214	0.560	
Myocardial infarction			
Incidences (%)	89 (0.74)	86 (0.72)	63 (0.53)
Hazard ratio vs. Warfarin (95%CI)	1.38 (1.00, 1.91)	1.35 (0.98, 1.87)	
p-value	0.049	0.070	
All hospitalizations			
Incidences (%)	4773 (41.56)	4470 (39.51)	4780 (42.60)
Rate ratio over warfarin	0.98	0.93	
95%CI	0.92, 1.04	0.87, 0.99	
p-value	0.443	0.021	

Table 9 Liver Function Tests
In the RE-LY study, potential abnormalities of liver function tests (LFT) occurred with a comparable or lower incidence in dabigatran etexilate vs. warfarin treated patients

	Dabigatran etexilate 150 mg bid N (%)	Dabigatran etexilate 110 mg bid N (%)	Warfarin N (%)
Total treated	6059 (100.0)	5984 (100.0)	5999 (100.0)
ALT or AST > 3xULN	111 (1.8)	121 (2.0)	126 (2.1)
ALT or AST > 5xULN	48 (0.8)	40 (0.7)	51 (0.9)
ALT or AST > 3xULN + Bilirubin >2xULN	14 (0.2)	11 (0.2)	22 (0.4)

Pre-clinical Toxicology

Acute oral toxicity studies were conducted in rats and mice. In both species, the approximate lethal dose after single oral administration was above 2000 mg/kg. In dogs and Rhesus monkeys, oral administration of 600 mg/kg dabigatran etexilate did not induce any toxicologically meaningful changes.

In repeat-dose toxicity studies over a maximum of 26 weeks in rats and 52 weeks in Rhesus monkeys, dosages up to 300 mg/kg (free base equivalent) were used. Generally, these doses were tolerated remarkably well by both, rats and Rhesus monkeys. Bleeding problems were observed in association with traumata (e.g. blood sampling) within the first 4 – 6 hours after administration and are directly related to the pharmacodynamic activity of dabigatran.

Teratology studies were performed with up to 200 mg/kg (free base equivalent) in rats and rabbits. A slight effect on the morphogenesis of foetuses was observed in rats at 200 mg/kg (free base equivalent). No teratogenic effects were noted in rabbits.

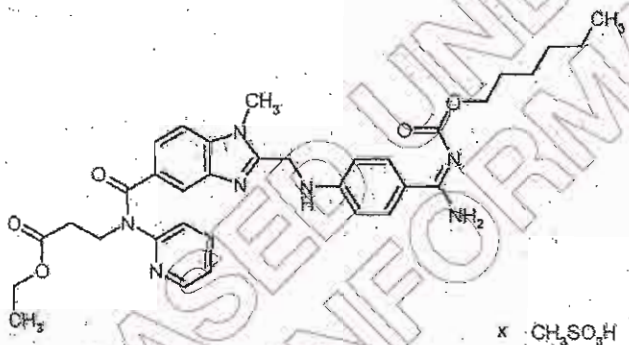
In the fertility study in rats, no toxicologically remarkable parental findings were noted. With respect to litter parameters, a slight decrease in corpora lutea and an increase in pre-implantation loss led to a decrease in the mean number of implantations in the 200 mg/kg (free base equivalent) dose group.

Comprehensive in vitro- and in vivo-studies revealed no evidence of a mutagenic potential.

In lifetime toxicology studies in rats and mice, there was no evidence for a tumorigenic potential of dabigatran up to maximum doses of 200 mg/kg (free base equivalent).

Chemical Structure

Dabigatran etexilate is beta-Alanine, N-[[2-[[[4(hexyloxy)carbonyl]amino]iminomethyl] phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-, ethyl ester, methane-sulfonate.



x CH_3SO_3H

Molecular Formula: $C_{35}H_{45}N_7O_5S$

CAS Registry Number: 211915-06-9 (free base)
593282-20-3 (mesilate)

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Date of Preparation

13 November 2009

CCDS 0266-03 4.11.09

Deleted: 24 April 2009

Deleted: 2

Deleted: 9.4.09

CLINICAL EVALUATION OF ADDITIONAL INFORMATION

Pradaxa
(Dabigatran etexilate)

Applicant: Boehringer Ingelheim (N.Z.) Limited

TT Number	TT50-7557/1, -/1a
Date of this report:	22 December 2010
Evaluator	

EVALUATION OF APPLICANT'S RESPONSE

Question

1. *Within the product information sheet there is very little comment regarding the potential for dose adjustment (i.e. from 150mg bid to 110mg bid). This seems particularly important for the elderly (>75 years of age) and those with renal impairment. It may also be important for those taking P-glycoprotein inhibitors or proton-pump inhibitors and H2 blockers. The applicant should provide an appropriate dose adjustment plan for these groups of patients (to be outlined in the product information sheet) or provide further evidence as to why such dose adjustment is not required.*

Applicant's Response

P-glycoprotein inhibitors or proton-pump inhibitors and H2 blockers
The sponsor has provided data comparing rates of major bleeding events and stroke/systemic embolism (SEE) based on risk categorisation of the patient population. The sponsor argues that the reduced bleeding events for the 110mg group are not offset by the higher number of stroke/SEE in comparison to the 150mg group.

Table 1.1: Occurrence of major bleeding events (Safety) or stroke/SEE (Efficacy) in AF patients from RE-LY categorized to high or low risk to develop a major bleeling event under dabigatran therapy

			total	no event		event on treatmnet	
			N	N	%	N	%
Safety	High risk	150 mg bid	533	487	91.37	46	8.63
		110 mg bid	531	489	92.09	42	7.91
	Low risk	150 mg bid	3961	3812	96.24	149	3.76
		110 mg bid	3946	3821	96.83	125	3.17
Efficacy	High risk	150 mg bid	544	535	98.35	9	1.65
		110 mg bid	539	528	97.96	11	2.04
	Low risk	150 mg bid	3988	3938	98.75	50	1.25
		110 mg bid	3974	3901	98.16	73	1.84

The sponsor has suggested adding in the *Warnings and precautions* section that P-glycoprotein-inhibitor co-medication increases haemorrhagic risk, and should therefore be considered in the prescribing of dabigatran.

Elderly

The sponsor has provided a relatively detailed analysis regarding the risks and benefits of the two dabigatran doses based on age (both ≥75 years and ≥80 years). This includes an analysis of the Net Clinical Benefit (a composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, all cause death and major bleeds) for age subgroups ≥75 years and ≥80 years.

Table 1.6 Subjects ≥75 years, Net Clinical Benefit

Age (years)		DE 110 vs. warfarin	DE 150 vs. warfarin	DE110 vs. DE150
<75	hazard ratio	0.86	0.79	1.09
	95% CI	(0.76, 0.99)	(0.69, 0.91)	
≥ 75	hazard ratio	0.99	1.01	0.98
	95% CI	(0.87, 1.13)	(0.89, 1.15)	

P for interaction= 0.0330, Source: RE-LY (1160.26), NZ response appendix, August, 2010, Table 4.1.2

Table 1.7 Subjects ≥80 years, Net Clinical Benefit

Age (years)		DE 110 vs. warfarin	DE 150 vs. warfarin	DE110 vs. DE150
<80	hazard ratio	0.87	0.83	1.05
	95% CI	(0.78, 0.97)	(0.74, 0.92)	
≥ 80	hazard ratio	1.12	1.13	1.00
	95% CI	(0.93, 1.36)	(0.94, 1.35)	

P for interaction= 0.0115, Source: RE-LY (1160.26), NZ response appendix, August, 2010, 2010, Table 4.1.4

Table 1.8 Subjects <80 and ≥80 years: annual event rates of stroke/SEE, MBE and ICH

	Age (years)	DE 110 (%/year)	DE 150 (%/year)	Warfarin (%/year)
Stroke/ SEE	<80	1.48	0.98	1.52
Stroke/ SEE	≥ 80	1.88	1.78	2.72
MBE	<80	2.43	2.73	3.35
MBE	≥ 80	5.25	6.24	4.70
ICH	<80	0.21	0.24	0.66
ICH	≥ 80	0.32	0.69	1.31

Source: RE-LY (1160.26); NZ response appendix, August 2010, Tables 4.1.5-4.1.10

These results suggest that the Net Clinical Benefit between the 110mg and 150mg groups is similar for those ≥75 years (HR = 0.98) and for those ≥80 years (HR = 1.00). Table 1.8 suggests that for patients aged 80 years or over the benefit of 110mg bid and 150mg bid for stroke/SEE prevention are almost comparable, whereas 110mg bid has less major bleeding than 150mg bid (HR 0.83, 95% CI 0.64-1.08).

Based on these results the sponsor has suggested adding to the *Dosage and administration* section that "*patients aged 80 years and above should be treated with a daily dose of 220mg taken orally as 110mg hard capsules twice daily*". The sponsor has also added to the *Warnings and precautions* section that age ≥75 years increases haemorrhagic risk, and should therefore be considered in the prescribing of dabigatran.

Renal function

The sponsor has provided an analysis of efficacy and safety stratified by renal function level. Regardless of treatment, bleeding risk increased with decreasing renal function. However, stroke risk increased with decreasing renal function in all groups, but much less so in the dabigatran 150mg bid group. This suggests that 150mg was more effective in reducing stroke risk in patients with moderate renal impairment (CrCl 30-50ml/min).

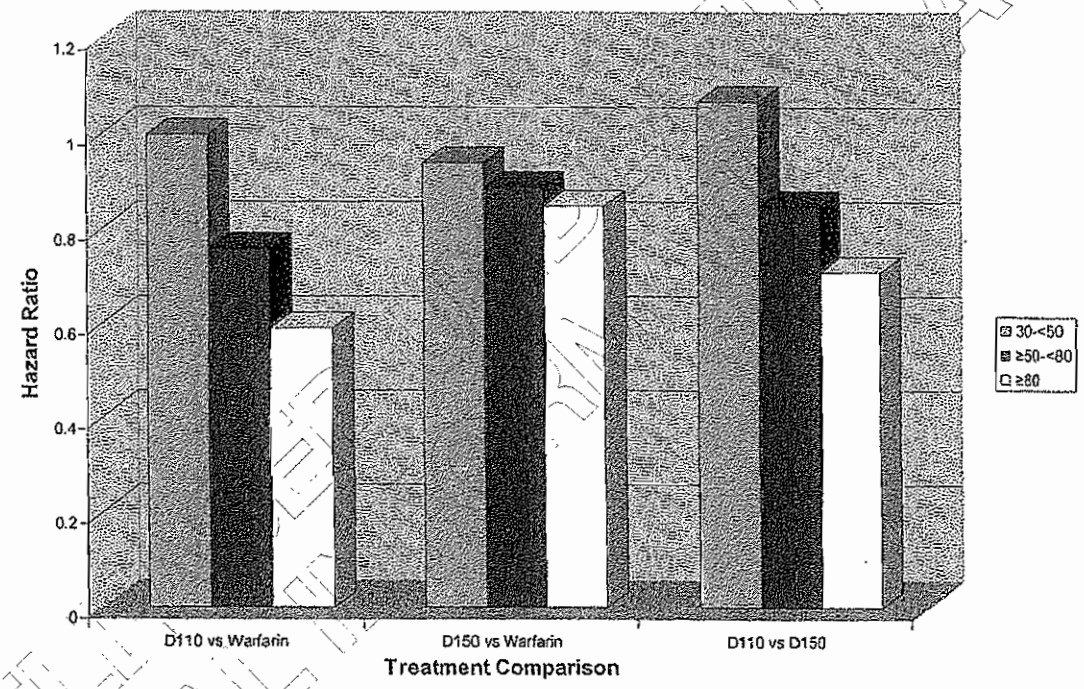

Figure 1.2 Hazard ratios for major bleeding in subgroups of renal function.

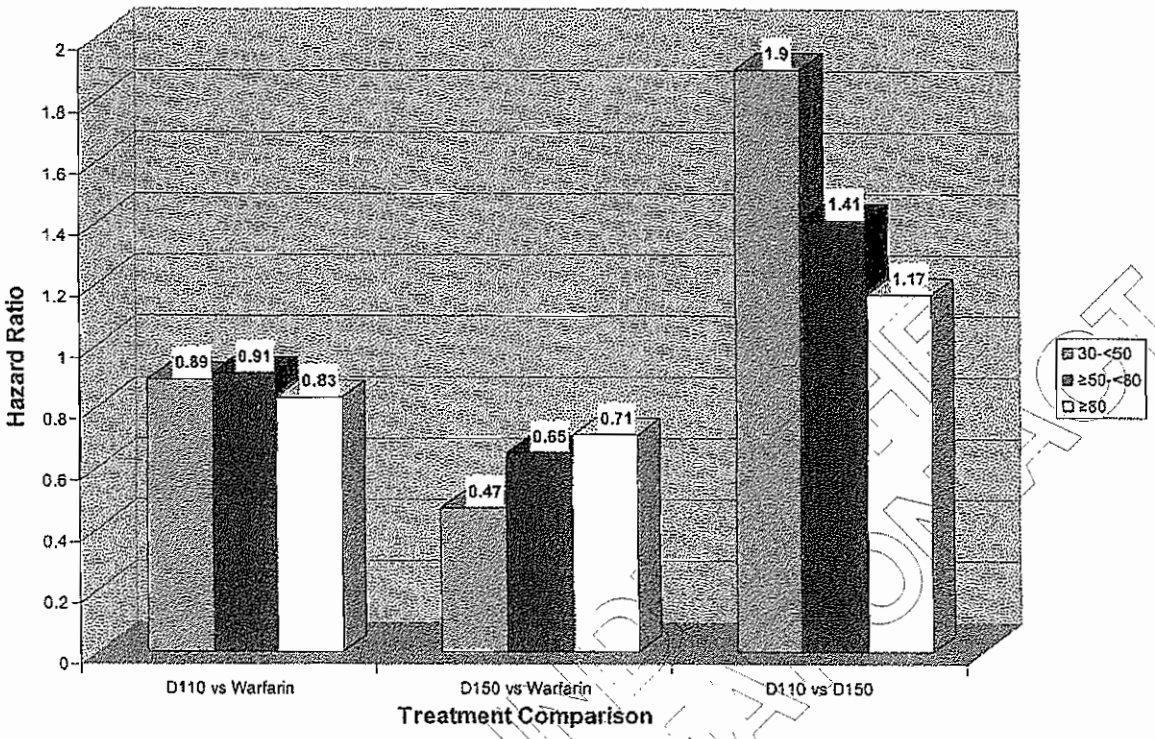

Figure 1.4 Hazard ratios for Stroke/SEE by treatment, subgrouped by renal function

The sponsor has suggested adding in the *Warnings and precautions* section that Moderate renal impairment (30-50ml/min CrCl) increases haemorrhagic risk, and should therefore be considered in the prescribing of dabigatran.

Overall addition to Product Information sheet

Under *Warnings and Precautions* section:

Haemorrhagic risk:
As with all anticoagulants, dabigatran etexilate should be used with caution in conditions with an increased risk of bleeding. Bleeding can occur at any site during therapy with dabigatran. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site.
Close clinical surveillance (looking for signs of bleeding or anaemia) is recommended throughout the treatment period, especially if risk factors are combined.

The Table summarises factors which may increase the haemorrhagic risk as identified in clinical studies.

Factors increasing dabigatran plasma levels	• Moderate renal impairment (30-50ml/min CrCL) • P-glycoprotein-inhibitor comedication
Pharmacodynamic interactions	• Acetylsalicylic acid • NSAID • Clopidogrel
Diseases / procedures with special haemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Active ulcerative gastrointestinal disease • Recent gastro-intestinal bleeding • Recent biopsy or major trauma • Recent intracranial haemorrhage • Brain, spinal or ophthalmic surgery • Bacterial endocarditis
Others	• Age ≥ 75 years

The measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors.
In patients who are bleeding, the aPTT test may be useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity. An aPTT > 80 sec at trough (when the next dose is due) is associated with a higher risk of bleeding.

Patients who develop acute renal failure must discontinue Pradaxa.

Under *Dosage and administration* section:

Patients at risk of bleeding:

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

Patients with an increased bleeding risk (see section warnings and precautions) should be closely clinically monitored (looking for signs of bleeding or anaemia). A coagulation test (see section warnings and precautions), may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. In such patients a dose of 220 mg given as 110 mg twice daily may be considered.

Elderly:

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:
Patients aged 80 years and above should be treated with a daily dose of 220 mg taken orally as 110 mg hard capsules twice daily.

Evaluation of Response
This analysis and discussion is satisfactory. The additions and changes to the product information sheet are acceptable.

Question

2. *Pharmacokinetic data suggest that co-medication with gastric pH-elevating agents could decrease dabigatran absorption by 25%. However, data from the RE-LY study indicate a higher rate of bleeding amongst patients taking PPIs or H2 blockers. This appears rather contradictory. Can the applicant please provide any further information that may be available regarding bleeding rates and stroke rates among these patients, and also how to most appropriately manage these patients in the clinical setting.*

Applicant's Response

The sponsor has provided an analysis based on participants who: had never used PPIs (or H2 blockers); were using PPIs at baseline; or started PPIs (or H2 blockers) after randomisation.

Table 2.1 Major GI bleed rates in subjects with or without proton pump inhibitors.

Subgroup	DE 110	DE 150	Warfarin
not on PPI	1.2%	1.5%	1.1%
baseline use of PPI	2.7%	3.4%	2.5%
PPI started post-rand.	6.2%	10.2%	8.2%

Source: NZ response appendix, August 2010, Table 4.2.3

Table 2.2 Major GI bleed rates in subjects with or without H2 blockers.

Subgroup	DE 110	DE 150	Warfarin
not on H2 blockers	1.8%	2.4%	1.6%
baseline use of H2 blockers	3.3%	6.4%	1.5%
H2 blockers started post-rand.	5.3%	6.0%	9.9%

Source: NZ response appendix, August 2010, Table 4.2.4)

Subjects on PPIs/H2 blockers have an elevated risk of bleeding compared to those not taking PPIs/H2 blockers. It is suggested that this may be more of an indicator of a patient population at higher risk of bleeding, rather than bearing a higher risk of bleeding caused by the concomitant use of these drugs. When examining the demographics of the patient population, patients using PPIs were older, more likely to be female, have slightly lower renal function, and more likely to have concomitant use of NSAIDs, ASA or clopidogrel.

Based on these results, consideration should be given to using a 110mg bid dose in patients who had recent GI bleeding or active ulcerative GI disease who are often treated with PPIs or H2 blockers.

Proposed changes to the Product Information sheet are shown in response to Question 1 above.

Evaluation of Response

The response is satisfactory. The issue is resolved.

Question

3. *Pharmacokinetic evidence regarding the influence of food suggests that AUC may increase 27% when taken with food. There is some concern that this increase in AUC may lead to accumulation, particularly with the higher dose. The applicant should provide evidence that accumulation will not occur if dabigatran is taken regularly with food.*

Applicant's Response

The sponsor has provided a pharmacokinetic analysis based on the effect of food on Cmax and AUC levels.

An estimate of the accumulation factor for dabigatran taken regularly with food is 1.575, and for dabigatran taken always fasted is 1.533.

It was calculated that in the most extreme condition (i.e. dabigatran always taken with a high fat meal) the predicted risk of bleeding was less than the overall rate of major bleeds in the warfarin group and only marginally higher than the overall rate for dabigatran patients in the main study. The difference was considered to be of no clinical relevance.

Evaluation of Response

This response is satisfactory and any accumulation is unlikely to cause clinically significant differences. The issue has been resolved.

Question

4. *Results from the RE-LY study suggest that bleeding rates doubled for those taking concomitant ASA and/or clopidogrel (or any other oral anti-coagulant). The applicant should identify why the product information sheet does not explicitly recommend against the co-administration of these medications (i.e. as a contraindication). If no appropriate evidence can be provided, the applicant should amend the product information sheet to identify the co-administration of these medications as a contraindication.*

Applicant's Response

The sponsor claims that although the use of ASA or clopidogrel increases major bleeding event rates with dabigatran, these results may be biased because those who are prescribed these medications during the study may be at higher risk for the occurrence of strokes and/or bleeding due to their underlying diseases.

The sponsor recommends close clinical surveillance with the concomitant use of ASA and clopidogrel, and has proposed the addition in the *Warnings and precautions* section that concomitant use with ASA, NSAIDs and clopidogrel increases haemorrhagic risk, and should therefore be considered in the prescribing of dabigatran (see proposed table under question 1 response above).

The following is also proposed for the *Interactions* section:

Anticoagulants and platelet aggregation agents:
The following treatments have not been studied and may increase the risk of bleeding when used concomitantly with Pradaxa: unfractionated heparins and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfinpyrazone, rivaroxaban, prasugrel, vitamin K antagonists, dronaderone, itraconazole, posaconazole, tacrolismus, cyclosporine A, nelfinavir, ritonavir and combinations of ritonavir and lopinavir or ritonavir and tipranavir and saquinavir.

The following interactions have been studied:

Clopidogrel: In a phase I study in young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times compared to clopidogrel monotherapy. In addition, dabigatran AUCτ,ss and Cmax,ss and the coagulation measures for dabigatran effect or the inhibition of platelet aggregation as measure of clopidogrel effect remained essentially unchanged comparing combined treatment and the respective mono-treatments. With a loading dose of 300 mg or 600 mg clopidogrel, dabigatran AUCτ,ss and Cmax,ss were increased by about 30-40 %.

Acetylsalicylic acid (ASA): The effect of concomitant administration of dabigatran etexilate and ASA on the risk of bleeds was studied in patients with atrial fibrillation in a phase II study in which a randomized ASA coadministration was applied. Based on logistic regression analysis, co-administration of ASA and 150 mg dabigatran etexilate twice daily may increase the risk for any bleeding from 12 % to 18 % and 24 % with 81 mg and 325 mg ASA, respectively.

From the data collected in the phase III study RE-LY it was observed that ASA or clopidogrel co-medication with dabigatran etexilate at dosages of 110 mg or 150 mg twice daily may increase the risk of major bleeding. The higher rate of bleeding events by ASA or clopidogrel co-medication was also observed for warfarin.

Evaluation of Response

This is an inadequate response. The evaluator considers that the concomitant use of ASA and clopidogrel poses a level of risk that needs to be appropriately conveyed within the product information sheet. The paragraphs proposed under the *Anticoagulants and platelet aggregation agents* (see Applicant's response above) should be removed (with the exception of the last paragraph beginning "From the data collected in the phase III study RE-LY...") and replaced with wording from the current product information sheet (see below). This information should be placed in the *Warnings and Precautions* section.

<u>Anticoagulants and platelet aggregation agents</u>

The following treatments should not be administered concomitantly with dabigatran etexilate: unfractionated heparins and heparin derivatives, low molecular weight heparins (LMWH), factor Xa inhibitors like fondaparinux, other thrombin inhibitors like desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, anti-thrombotic agents like clopidogrel, ticlopidine, dextran, sulfinpyrazone and vitamin K antagonists. It should be noted that unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter.

The risk of bleeding increases when aspirin at doses of 75 to 325 mg was given concomitantly with dabigatran etexilate at high doses (above those recommended for VTE prevention). There was no evidence of an excess bleeding risk when dabigatran was given at the recommended dose to patients receiving low-dose aspirin for the prevention of cardiovascular events. However, the information is limited and the co-administration of low-dose aspirin and dabigatran etexilate should be accompanied by clinical observation for bleeding.

From the data collected in the phase III study RE-LY it was observed that ASA or clopidogrel co-medication with dabigatran etexilate at dosages of 110mg or 150mg twice daily may increase

the risk of major bleeding. The higher rate of bleeding events by ASA or clopidogrel co-medication was also observed for warfarin.

Question

5. *The RE-LY study identified a greater risk of GI adverse events and GI bleeding in the dabigatran groups compared to warfarin. The applicant should provide any information available that may explain this result.*

Applicant's Response

The sponsor has provided some discussion on the issue of GI adverse events and GI bleeding. Although the increase in these adverse events is recognised, the excess is counterbalanced by a decrease in other major bleeds on dabigatran. Hence, the overall major bleed rate was 20% lower with 110mg than for warfarin and 7% lower with 150mg than for warfarin.

There is no known mechanism or explanation as to why the oral administration of dabigatran is associated with an increased incidence of GI AEs or GI bleeds compared to warfarin.
In the ongoing RE-LYABLE trial (BI study 1160.71) a questionnaire regarding whether various approaches (e.g. intake of food, use of PPIs) impact measures of dyspepsia has been implemented.

The sponsor has proposed the addition in the *Warnings and precautions* section that certain diseases increase haemorrhagic risk, and should therefore be considered in the prescribing of dabigatran (see proposed table under question 1 response above). This list includes recent GI bleeding.

The following is also proposed for under the *Dosage and administration* section:

Patients at risk of bleeding:

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

Patients with an increased bleeding risk (see section warnings and precautions) should be closely clinically monitored (looking for signs of bleeding or anaemia). A coagulation test (see section warnings and precautions), may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. In such patients a dose of 220 mg given as 110 mg twice daily may be considered.

Evaluation of Response

This response is satisfactory and the issue has been resolved.

Product Information Question

(i) *Under the Dosage and Administration (Recommended daily dose) section, it is recommended that, along with the recommended 150mg bid dose, it is identified that the lower 110mg bid dose can be used in the appropriate circumstances (e.g. elderly, those with renal impairment, etc.).*

Applicant's Response

For a full response to this please see response to question 1 above. The sponsor has proposed a lower dose (i.e. 110mg bid) for patients aged 80 years and above.

Evaluation of Response

The issue is resolved.

Product Information Question

(ii) Under the Dosage and Administration section and the heading "Concomitant use of dabigatran etexilate with strong P-glycoprotein inhibitors i.e. amiodarone, quinidine or verapamil" the "i.e." should be changed to "e.g." and the list that follows should include "diltiazem".

Applicant's Response

From the database survey diltiazem was not identified as a drug which may lead to effects on the bioavailability of dabigatran as observed with sub-chronic verapamil, amiodarone or quinidine. This is confirmed by the data from RE-LY where essentially no effect was observed on dabigatran trough- and post-dose concentrations where diltiazem was co-medicated. At therapeutic dosages diltiazem is not expected to affect dabigatran PK in a clinically meaningful way and it is proposed not to include it in the list of P-gp inhibitors.

The sponsor has accepted the change from "i.e." to "e.g.".

Evaluation of Response

The response is satisfactory and the issue is resolved.

Product Information Question

(iii) Under the Pharmacokinetics (Special populations) section and the Warnings and Precautions section it states that for NSAIDs "the use of regular NSAID medication with half-lives of less than 12 hours during treatment with dabigatran etexilate…has not suggested additional bleeding risk". After careful reading it appears that this relates to the use of dabigatran for the prevention of VTE in patients following major orthopaedic surgery. However, given the results of the RE-LY study that indicate a ~50% increased risk of bleeding for those taking concomitant NSAID medication, this is a potential area of confusion in the product information sheet. It is recommended that the statement is amended to more accurately describe the results from the RE-LY study and eliminate confusion regarding the concomitant use of NSAIDs.

Applicant's Response

Along with the proposed changes to the *Warnings and precautions* section (see proposed changes under applicant's response to question 1 above, the following changes to the *Pharmacokinetics (Special populations)* section has also been proposed:

NSAIDs:

VTE prevention following knee or hip replacement surgery:
When Pradaxa was coadministered with diclofenac, the plasma exposure of both medicinal products remained unchanged indicating a lack of a pharmacokinetic interaction between dabigatran etexilate and diclofenac. NSAIDs given for short-term perioperative analgesia for primary VTE prevention following major orthopedic surgery have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

Due to the increased risk of haemorrhage, notably with NSAIDs with elimination half-lives > 12 hours, close observation for signs of bleeding is recommended (see section "warnings and precautions").

Evaluation of Response

Satisfactory response and the issue is resolved.

Product Information Question

(iv) Following on from the recommendation in point (ii) and question 4 above, it is stated under the Warnings and Precautions section that "co-administration of oral anti-platelet [medication] (including aspirin and clopidogrel) and NSAID therapies increase the risk of bleeding." It is recommended that that a further statement that recommends against the co-administration of these medications be added.

Applicant's Response

For a full response to this please see response to question 4 above.

Evaluation of Response

As stated under question 4 above, the response is inadequate. The evaluator considers that the concomitant use of ASA and clopidogrel poses a level of risk that needs to be appropriately conveyed within the product information sheet. The paragraphs proposed under the *Anticoagulants and platelet aggregation agents* (see Applicant's response from question 4) should be removed (with the exception of the last paragraph beginning "From the data collected in the phase III study RE-LY...") and replaced with wording from the current product information sheet (see below). This information should be placed in the *Warnings and Precautions* section.

Anticoagulants and platelet aggregation agents

The following treatments should not be administered concomitantly with dabigatran etexilate: unfractionated heparins and heparin derivatives, low molecular weight heparins (LMWH), factor Xa inhibitors like fondaparinux, other thrombin inhibitors like desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, anti-thrombotic agents like clopidogrel, ticlopidine, dextran, sulfinpyrazone and vitamin K antagonists. It should be noted that unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter.

The risk of bleeding increases when aspirin at doses of 75 to 325 mg was given concomitantly with dabigatran etexilate at high doses (above those recommended for VTE prevention). There was no evidence of an excess bleeding risk when dabigatran was given at the recommended dose to patients receiving low-dose aspirin for the prevention of cardiovascular events. However, the information is limited and the co-administration of low-dose aspirin and dabigatran etexilate should be accompanied by clinical observation for bleeding.

From the data collected in the phase III study RE-LY it was observed that ASA or clopidogrel co-medication with dabigatran etexilate at dosages of 110mg or 150mg twice daily may increase the risk of major bleeding. The higher rate of bleeding events by ASA or clopidogrel co-medication was also observed for warfarin.

Product Information Question

(v) *Under the Adverse Effects (Bleeding) section, the bleeding rates of dabigatran in comparison to warfarin are identified. It is recommended that the higher rate of gastrointestinal bleeding in the dabigatran groups compared to the warfarin group found in the RE-LY study is noted and appropriately identified.*

Applicant's Response

The sponsor acknowledges the comment and has proposed adding the following table to the *Adverse Effects (Bleeding)* section:

Table X Bleeding events broken down to major and any bleeding in the pivotal study testing the prevention of thromboembolic SSE in patients with atrial fibrillation.

	Dabigatran etexilate 110 mg twice daily	Dabigatran etexilate 150 mg twice daily	Warfarin
Subjects randomized	6,015	6,076	6,022
Major Bleeding	342 (2.87 %)	399 (3.32 %)	421 (3.57 %)
Intracranial bleeding	27 (0.23 %)	38 (0.32 %)	90 (0.76 %)
Gastrointestinal bleeding	134 (1.14 %)	186 (1.57 %)	125 (1.07 %)
Fatal bleeding	23 (0,19 %)	28 (0,23 %)	39 (0,33 %)
Minor bleeding	1,566 (13.16 %)	1,787 (14.85%)	1,931 (16.37%)
Any bleeding	1,754 (14.74 %)	1,993 (16.56 %)	2,166 (18.37 %)

Evaluation of Response

The response is satisfactory and the issue is resolved.

Product Information Question

(vi) *Under Dosage and Administration and Warnings and Precautions in the product information sheet a statement on hepatic impairment has been deleted ("Hepatic impairment: Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes > 2 ULN were excluded in clinical trials. Therefore the use of dabigatran etexilate is not recommended in this population."). The applicant should provide supporting evidence as to why this statement has been removed, and if this is not available, should reinstate the statement.*

Applicant's Response

The sponsor acknowledges the comment and proposes the following in the *Dosage and administration* section:

Hepatic impairment:

Patients with elevated liver enzymes > 2 upper limit of normal (ULN) were excluded in clinical trials investigating the VTE prevention following elective hip or knee replacement surgery as well as in RE-LY study investigating the prevention of stroke and systemic emboli associated with atrial fibrillation. No treatment experience is available for this subpopulation of patients,and therefore the use of Pradaxa is not recommended in this population (see sections 4.4 and 5.2).

The sponsor also states they are unclear as to why this section needs to be presented under the *Dosage and Administration* section instead of under *Warnings and Precautions*.

Evaluation of Response

The proposed change is satisfactory. In the current product information sheet the statement on hepatic impairment was in both the *Dosage and Administration* and *Warnings and Precautions* sections. It is recommended that the statement is placed in the *Warnings and Precautions* section.

REQUEST FOR INFORMATION

1. The issue regarding concomitant use of ASA and clopidogrel has not been resolved. The evaluator considers that the concomitant use of ASA and clopidogrel poses a level of risk that needs to be appropriately conveyed within the product information sheet. The new paragraphs proposed under the *Anticoagulants and platelet aggregation agents* (see response to question 4) should be removed (with the exception of the last paragraph beginning "From the data collected in the phase III study RE-LY...") and replaced with the following wording from the current product information sheet (see below). This information should be placed in the *Warnings and Precautions* section.

Anticoagulants and platelet aggregation agents
The following treatments should not be administered concomitantly with dabigatran etexilate: unfractionated heparins and heparin derivatives, low molecular weight heparins (LMWH), factor Xa inhibitors like fondaparinux, other thrombin inhibitors like desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, anti-thrombotic agents like clopidogrel, ticlopidine, dextran, sulfinpyrazone and vitamin K antagonists. It should be noted that unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter.

The risk of bleeding increases when aspirin at doses of 75 to 325 mg was given concomitantly with dabigatran etexilate at high doses (above those recommended for VTE prevention). There was no evidence of an excess bleeding risk when dabigatran was given at the recommended dose to patients receiving low-dose aspirin for the prevention of cardiovascular events. However, the information is limited and the co-administration of low-dose aspirin and dabigatran etexilate should be accompanied by clinical observation for bleeding.

From the data collected in the phase III study RE-LY it was observed that ASA or clopidogrel co-medication with dabigatran etexilate at dosages of 110mg or 150mg twice daily may increase the risk of major bleeding. The higher rate of bleeding events by ASA or clopidogrel co-medication was also observed for warfarin.

2. The proposed addition of the comment on hepatic impairment is acceptable. In the current product information sheet the statement on hepatic impairment was in both the *Dosage and Administration* and *Warnings and Precautions* sections. It is recommended that the statement is placed in the *Warnings and Precautions* section.

CLINICAL EVALUATION OF ADDITIONAL INFORMATION II

Pradaxa
(Dabigatran etexilate)

Applicant: Boehringer Ingelheim (N.Z.) Limited

TT Number	TT50-7557
Date of this report:	1 February 2011
Evaluator	

EVALUATION OF APPLICANT'S RESPONSE

Question

1. The issue regarding concomitant use of ASA and clopidogrel has not been resolved. The evaluator considers that the concomitant use of ASA and clopidogrel poses a level of risk that needs to be appropriately conveyed within the product information sheet. The new paragraphs proposed under the *Anticoagulants and platelet aggregation agents* (see response to question 4) should be removed (with the exception of the last paragraph beginning "From the data collected in the phase III study RE-LY...") and replaced with the following wording from the current product information sheet (see below). This information should be placed in the *Warnings and Precautions* section.

Anticoagulants and platelet aggregation agents
The following treatments should not be administered concomitantly with dabigatran etexilate: unfractionated heparins and heparin derivatives, low molecular weight heparins (LMWH), factor Xa inhibitors like fondaparinux, other thrombin inhibitors like desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, anti-thrombotic agents like clopidogrel, ticlopidine, dextran, sulfinpyrazone and vitamin K antagonists. It should be noted that unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter.

The risk of bleeding increases when aspirin at doses of 75 to 325 mg was given concomitantly with dabigatran etexilate at high doses (above those recommended for VTE prevention). There was no evidence of an excess bleeding risk when dabigatran was given at the recommended dose to patients receiving low-dose aspirin for the prevention of cardiovascular events. However, the information is limited and the co-administration of low-dose aspirin and dabigatran etexilate should be accompanied by clinical observation for bleeding.

From the data collected in the phase III study RE-LY it was observed that ASA or clopidogrel co-medication with dabigatran etexilate at dosages of 110mg or 150mg twice daily may increase the risk of major bleeding. The higher rate of bleeding events by ASA or clopidogrel co-medication was also observed for warfarin.

Applicant's Response
The applicant has responded by partially accepting the requested changes. The applicant has included a statement regarding bridging situations when switching medications. They have also removed clopidogrel from the first paragraph with the justification that the increased risk of bleeding with clopidogrel will be highlighted in the third paragraph and in the following suggested addition:

"The co-administration of aspirin and/or clopidogrel with dabigatran should be accompanied by clinical observation for bleeding."

They have also suggested the removal of the redundant second paragraph.

Evaluation of Response
These changes are satisfactory and the issue is now resolved.

Question

2. The proposed addition of the comment on hepatic impairment is acceptable. In the current product information sheet the statement on hepatic impairment was in both the *Dosage and Administration* and *Warnings and Precautions* sections. It is recommended that the statement is placed in the *Warnings and Precautions* section.

Applicant's Response
This recommendation has been accepted.

Evaluation of Response
The issue is now resolved.

I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the questions on the, safety and efficacy, the Evaluator considers that under Section 20 of the Medicines Act consent to distribute Pradaxa 110mg and Pradaxa 150mg can be recommended for the prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation.