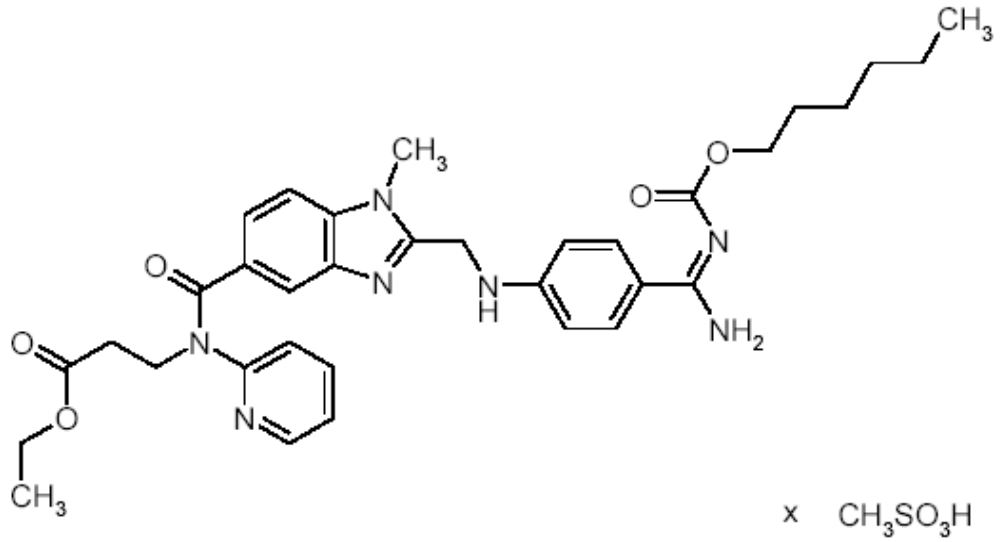
Attachment 1: Product information for AusPAR Pradaxa Boehringer Ingelheim Pty Ltd PM-2013-02038-1-3 Final 4 January 2016. This Product Information was approved at the time this AusPAR was published.

PRADAXA®

(dabigatran etexilate)
75 mg, 110 mg, 150 mg

NAME OF THE MEDICINE

Dabigatran etexilate mesilate is Ethyl N-{[2-({[4-((E)-amino{[hexyloxy)carbonyl]imino}methyl) phenyl]amino}methyl)-1-methyl-1H-benzimidazol-5-yl]carbonyl}-N-pyridin-2-yl-β-alaninate methanesulfonate.



Molecular Formula:	$C_{35}H_{45}N_7O_8S$
Molecular Weight:	627.75 (free base)
	723.86 (mesilate salt)
CAS Registry Number:	211915-06-9 (free base)
	593282-20-3 (mesilate)

DESCRIPTION

Dabigatran etexilate mesilate is a yellow-white to yellow crystalline powder; the crystals have a rod-like habit. It contains two weak basic centers with pKa-values of 4.0 ± 0.1 (benzimidazol moiety) and 6.7 ± 0.1 (carbamic acid hexyl ester moiety). Its solubility in water is strongly pH dependent with rather high solubility in acidic media (>50 mg/mL in 0.1 N HCl) and very poor solubility in neutral and basic media (0.003 mg/mL at pH 7.4). The solubility in water is 1.8 mg/mL (0.18%). In its neutral form it is very lipophilic (log P = 3.8, determined in different mixtures of aqueous solution and n-octanol).

PRADAXA are hard capsules for oral administration.

PRADAXA 75 mg hard capsules contain 75 mg dabigatran etexilate.

PRADAXA 110 mg hard capsules contain 110 mg dabigatran etexilate.

PRADAXA 150 mg hard capsules contain 150 mg dabigatran etexilate.

Excipients

Capsule fill: Tartaric acid, acacia, hypromellose, dimeticone 350, talc, hydroxypropylcellulose.

HPMC capsule shell: Carrageenan, potassium chloride, titanium dioxide, sunset yellow FCF CI15985, indigo carmine CI73015, hypromellose, water - purified.

Printing ink: TekPrint SW-9008 Black Ink.

PHARMACOLOGY

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 competitive (K_i = 4.5 nM) and reversible direct thrombin inhibitor and is the main metabolite of dabigatran etexilate 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 venous thrombosis.

There is a close correlation between plasma dabigatran concentration and degree of anticoagulant effect. Prothrombin time (PT, expressed as International Normalised Ratio (INR)) is too insensitive to reliably detect anticoagulant activity of dabigatran and is therefore not recommended as a suitable tool for monitoring anticoagulant activity. Ecarin Clotting Time (ECT), Thrombin Time (TT) and diluted Thrombin Time (dTT) are sensitive assays that increase in direct proportion to dabigatran plasma concentration without any deviation from linearity at high plasma concentrations. However, ECT is not readily available in clinical practice. Activated Partial Thromboplastin Time (aPTT) increases in a non-linear manner to dabigatran concentration and is less proportional at higher dabigatran concentrations (see Precautions, Effect on laboratory tests). ECT, TT and aPTT are not standardised or validated with dabigatran for commercial use. In cases of emergency, TT and aPTT are the most accessible qualitative methods for determining the presence or absence of the anticoagulant effect of dabigatran.

Interpretation of coagulation assay results should consider time of dabigatran etexilate administration relative to time of blood sampling (see Pharmacokinetics, Absorption).

In patients undergoing elective hip replacement surgery, greater test variability with aPTT and ECT was observed. The mechanisms for this variability immediately after surgery are unclear and aPTT and ECT levels measured in the first 2-3 days following surgery should be interpreted with caution.

Whilst PRADAXA does not require routine laboratory anticoagulant monitoring, careful clinical monitoring including renal function testing is required for all patients (see PRECAUTIONS, Haemorrhagic risk and DOSAGE AND ADMINISTRATION, Special patient populations).

PHARMACOKINETICS

Absorption

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 C_{max} attained within 0.5 and 2.0 hours post administration. C_{max} and the area under the plasma concentration-time curve were dose proportional. After C_{max}, plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of 12–14 hours in elderly healthy volunteers and 14–17 hours in patients undergoing major orthopaedic surgery. The half-life was independent of dose. However, half-life is prolonged if renal function is impaired as shown below, in Table 1.

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

Glomerular filtration rate (CrCL) [mL/min]	gMean (gCV%; range) half-life [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)

gMean – Geometric mean
gCV% - Geometric coefficient of variation

Upon administration of the dabigatran etexilate HPMC capsules together with a high fat, high caloric breakfast, the average total exposure (AUC) of dabigatran increased by 27% and the maximum exposure on average by 8.5%. The time to peak plasma concentrations was delayed by 2 hours. The relative increase of bioavailability was considered of no clinical relevance.

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

The oral bioavailability was increased by about 1.8-fold (+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 take the pellets alone (e.g. sprinkled over food or into beverages) (see Dosage and Administration).

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. 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.

Distribution

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.

Metabolism and elimination

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. 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.

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.

Special populations

Renal impairment

An open, parallel-group single-centre study compared dabigatran pharmacokinetics in healthy subjects and patients with mild to moderate renal impairment receiving a single dose of dabigatran etexilate 150 mg. Based on pharmacokinetic modeling, estimated exposure to dabigatran increases with the severity of renal function impairment (Table 2).

Table 2: Estimated Pharmacokinetic Parameters of Dabigatran by Renal Function

Renal Function	CrCL (mL/min)	Increase in AUC	Increase in Cmax	$t_{1/2}$ (h)
Normal	80	1x	1x	13
Mild	50	1.5x	1.1x	15
Moderate	30	3.2x	1.7x	18

Similar findings were observed in the RE-LY study. The median CrCL in RE-LY was 68.4 mL/min. Almost half (45.8%) of the RE-LY patients had a CrCL between 50-80 mL/min. When compared with patients without renal impairment (CrCL ≥ 80 mL/min), patients with moderate renal impairment (CrCL between 30-50 mL/min) had pre- and post-dose dabigatran plasma concentrations 2.29-fold and 1.81-fold higher on average, respectively.

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).

Clearance of dabigatran by haemodialysis was investigated in patients with end- stage renal disease (ESRD) without atrial fibrillation. Dialysis was conducted with 700 mL/min dialysate flow rate, four hour duration, a blood flow rate of either 200 mL/min or 350 – 390 mL/min. This resulted in a removal of 50% or 60% of free- or total dabigatran concentrations, respectively. The amount of drug cleared by dialysis is proportional to the blood flow rate. The anticoagulant activity of dabigatran decreased with decreasing plasma concentrations and the PK/PD relationship was not affected by the procedure. Upon cessation of haemodialysis, a redistribution effect of approximately 7% to 15% is seen.

The median CrCL in the RE-COVER study was 100.4 mL/min. 21.7% of patients had mild renal impairment (CrCL > 50-< 80 mL/min) and 4.5% of patients had moderate renal impairment (CrCL between 30-50 mL/min). Patients with mild and moderate renal impairment had on

average 1.8-fold and 3.6-fold higher steady state dabigatran trough concentrations compared with patients with CrCL > 80 mL/min. Similar values for CrCL were found in RE-COVER II.

The median CrCL in the RE-MEDY and RE-SONATE studies were 99.0 mL/min and 99.7 mL/min respectively. 22.9 % and 22.5% of the patients had a CrCL > 50-< 80 mL/min, and 4.1% and 4.8% had a CrCL between 30-50 mL/min in the RE-MEDY and RE-SONATE studies.

Elderly patients

The $AUC_{\tau,ss}$ and $C_{max,ss}$ in male and female elderly subjects (>65 years) 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. The effect by age on exposure to dabigatran was confirmed in the RE-LY and RE-COVER studies: in RE-LY, compared with subjects aged < 65 years, dabigatran trough concentrations were 28% higher in subjects aged between 65 and 75 years and 68% higher in subjects aged ≥75 years. In RE-COVER, compared with patients aged between 50 and < 65 years, dabigatran trough concentrations were 20% and 106% higher in patients aged between 65 and 75 years and ≥ 75 years, respectively (see Precautions, Use in the elderly and Dosage and Administration).

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 (VTE) in adult 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 X 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 X ULN or hepatitis A, B or C were excluded in clinical trials.
- *Treatment of, and prevention of recurrent, deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in adults*: 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.

Body weight

The dabigatran trough concentrations were about 20% lower in subjects with a body weight >100 kg compared with subjects of 50–100 kg. The dabigatran trough concentrations were about 20% higher in subjects with a body weight <50 kg compared with subjects of 50-100 kg. Comparing the extremes, <50 kg versus >100 kg, the median dabigatran trough concentrations differed by 53%. The majority (80.8%) of the subjects were in the ≥50 kg and <100 kg category with no clear difference detected.

Gender

Drug exposure in the primary VTE prevention studies was about 1.4- to 1.5-fold (+40% to 50%) higher in female patients. In atrial fibrillation, female patients had on average 1.3-fold (+30%) higher trough and post-dose concentrations. This finding had no clinical relevance.

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.

CLINICAL TRIALS

Prevention of venous thromboembolic events (VTE) in adult patients who have undergone major orthopaedic surgery (pVTEp orthopaedic 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.

Both trials were performed in centres of countries located on 3 continents (Africa, Australia and Europe).

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.

Enrolled patients were scheduled to have total knee or hip replacement surgery; 18 years of age or older and weighing at least 40 kg. Patients were excluded if there was a history of bleeding diathesis; coagulation disorders; major surgery or trauma (e.g. hip fracture) within the last 3 months; recent unstable cardiovascular disease or history of myocardial infarction within the last 3 months; greater than 3 attempts or traumatic placement for spinal or epidural anaesthesia; history of haemorrhagic stroke or intracranial pathology such as bleeding, neoplasm, AV malformation or aneurysm; history of VTE or pre-existing condition requiring anticoagulant therapy; clinically relevant bleeding within the last 6 months; gastric or duodenal ulcer within the last 6 months; liver disease which was expected to have a potential impact on survival; elevated AST or ALT >2 X ULN; severe renal insufficiency (CrCl <30 mL/min); elevated creatinine which contraindicated venography; treatment within 7 days with anticoagulants – clopidogrel, ticlopidine, abciximab, aspirin >160 mg/day or NSAID with $t_{1/2}$ >12 hours or requiring these medicines during the study treatment period; intermittent pneumatic compression and electric stimulation of lower limb; pregnant or nursing women and pre-menopausal women without acceptable birth control; allergy to radio-opaque contrast media or iodine; thrombocytopenia or platelet count <100,000 cells/µL; allergy to heparins or dabigatran and dabigatran etexilate; active malignant disease or currently receiving cytostatic treatment; participated in a clinical trial in the last 30 days; leg amputee; alcohol or drug abuse and contraindications to enoxaparin.

For the knee study (RE-MODEL), the median age was 68 years for all treatment groups. The majority of patients were female in all treatment groups (64.2–68.9%). The mean BMI was also similar in all 3 treatment groups with 29.9 (dabigatran etexilate 220 mg), 30.1 (dabigatran etexilate 150 mg), and 29.8 kg/m^2 (enoxaparin), respectively.

For the hip study (RE-NOVATE), the median age was 65 years for all treatment groups. The majority of patients were female in all treatment groups (55.5–57.4%) and almost all patients were of white ethnic origin. The median BMI was 27.3 kg/m^2 in both dabigatran etexilate groups and 27.1 kg/m^2 in the enoxaparin group.

The most widely used type of anaesthesia was spinal anaesthesia. The second most frequent type of anaesthesia was general anaesthesia.

Both the knee (RE-MODEL) and the hip (RE-NOVATE) studies were non-inferiority studies. For determination of the minimal important difference against enoxaparin, the placebo-controlled studies with enoxaparin 40 mg QD were pooled and the incidences of deep vein thrombosis (DVT), total VTE and all-cause mortality for enoxaparin against placebo for each indication analysed. For the knee study (RE-MODEL), one third of the lower boundary of the 95% CI, i.e. 9.2%, was chosen to represent a rather strict and conservative estimate of the non-inferiority margin. For the hip study (RE-NOVATE), one third of the lower boundary of the 95% CI, 7.7% was chosen as the non-inferiority margin.

The results of the knee study (RE-MODEL) with respect to the primary end-point, total venous thromboembolism (VTE) including asymptomatic 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.

Data for the major VTE and VTE-related mortality end-point and adjudicated major bleeding endpoints are shown in Table 3 below. VTE was defined as the composite incidence of deep vein thrombosis and pulmonary embolism.

A third trial involving patients undergoing total knee replacement 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 for 12–15 days (RE-MOBILIZE). 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.

A fourth trial involving patients undergoing hip replacement surgery received dabigatran etexilate 110 mg on the day of surgery followed by 220 mg once daily thereafter, or enoxaparin 40 mg on the day prior to surgery and daily thereafter (RE-NOVATE II). The duration of treatment was 28-35 days. In the RE-NOVATE II trial, dabigatran etexilate was statistically non-inferior to enoxaparin 40 mg daily for total VTE events and all-cause mortality.

In addition, a randomised, parallel group, double-blind, placebo-controlled phase II study, in Japanese patients where dabigatran etexilate 110 mg, 150 mg and 220 mg was administered once daily beginning the next day after elective total knee replacement surgery, was evaluated. The Japanese study showed an inverse relationship between dabigatran etexilate dose and the incidence of the primary endpoint (total VTE and all-cause mortality). The highest dabigatran etexilate dose resulted in the lowest incidence of total VTE and all-cause mortality.

In RE-MODEL and RE-NOVATE and RE-NOVATE II the randomisation to the respective study medication was done pre-surgery, and in the RE-MOBILIZE and 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. In Table 3, three of the trials have been grouped in to pre- and post-surgery randomised trials.

Table 3: Analysis of major VTE and VTE-related mortality during the treatment period in the orthopaedic surgery studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
Pre-operative randomisation studies			
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-NOVATE II (hip)			
N	805		794
Incidences (%)	18 (2.2)		33 (4.2)
Risk differences vs. enoxaparin (%)	- 1.92		
95% CI	- 3.64, - 0.2		
Risk ratio over enoxaparin	0.49		
95% CI	0.28, 0.86		
RE-MODEL (knee)			
N	506	527	511
Incidences (%)	13 (2.6)	20 (3.8)	18 (3.5)
Risk differences vs. enoxaparin (%)	- 1.0	0.3	
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	
Post-operative randomisation studies			
Japanese knee study			
			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)	

Table 4 presents the combined incidences of major VTE and VTE related mortality for RE-MODEL and RE-NOVATE trials. The most frequent component of the composite endpoint was proximal DVT in all three treatment groups. Non-fatal pulmonary embolism (PE) during the treatment period in the two trials were observed in 1 patient in the dabigatran etexilate 150 mg group, 3 patients receiving enoxaparin and 5 patients receiving dabigatran etexilate 220 mg. VTE related mortality was observed for 1 patient in each of the dabigatran etexilate 220 mg and enoxaparin groups and for 4 patients in the dabigatran etexilate 150 mg group.

Table 4: Summary of primary endpoint components (N [%]) in the RE-NOVATE and RE-MODEL trials

Trial	Worst event	Dabigatran etexilate 220 mg N (%)	Dabigatran etexilate 150 mg N (%)	Enoxaparin 40 mg N (%)
RE-MODEL and RE-NOVATE Knee/Hip Pivotal	FAS-major*	1415 (100.0)	1415 (100.0)	1428 (100.0)
	VTE-death	1 (0.1)	4 (0.3)	1 (0.1)
	PE	5 (0.4)	1 (0.1)	3 (0.2)
	Proximal DVT	35 (2.5)	53 (3.7)	50 (3.5)
	Major VTE/VTE mortality	41 (2.9)	58 (4.1)	54 (3.8)

* Full analysis set – major

Table 5: Major bleeding events by treatment in the individual RE-MODEL and the RE-NOVATE studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
RE-NOVATE (hip)			
Treated patients N	1146	1163	1154
Number of MBE N(%)	23 (2.0)	15 (1.3)	18 (1.6)
RE-NOVATE II (hip)			
Treated patients N	1010		1003
Number of MBE N(%)	14 (1.4)		9 (0.9)
RE-MODEL (knee)			
Treated patients N	679	703	694
Number of MBE N(%)	10 (1.5)	9 (1.3)	9 (1.3)

Major bleeding events (MBE) followed the International Society on Thrombosis and Haemostasis (ISTH) criteria and the EMEA guideline (including surgical wound site bleedings)

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF)

The clinical evidence for the efficacy of dabigatran etexilate is derived from the RE-LY study (Randomised Evaluation of Long–term anticoagulant therapy) a multi-centre, multinational, randomised parallel group study of two blinded doses of dabigatran (110 mg twice daily and 150 mg twice daily) compared to open-label warfarin in patients with non-valvular atrial fibrillation (AF) at moderate to high risk of stroke or systemic embolism. This trial used the Prospective Randomised Open label trial with Blinded Evaluation of outcomes (PROBE) design. 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 randomised, 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 AF e.g. persistent, paroxysmal or permanent AF, patients had one of the following additional risk factors for stroke:

- Previous stroke, transient ischaemic 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 (CAD), or hypertension.

Patients were excluded if they had prosthetic heart valves requiring anticoagulation or with haemodynamically relevant valve disease that was expected to require surgical intervention during the course of the study; severe disabling stroke within the previous 6 months or any stroke within the previous 14 days; conditions associated with an increased risk of bleeding – major surgery in the previous month, planned surgery or intervention in the next 3 months, history of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding unless the causative factor has been permanently eliminated or repaired (e.g. by surgery); gastrointestinal haemorrhage within the past year unless the cause has been permanently eliminated (e.g. surgery); symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days; haemorrhagic disorder or bleeding diathesis; need for anticoagulant treatment for disorders other than atrial fibrillation; fibrinolytic agents within 48 hours of study entry; uncontrolled hypertension (SBP >180 mmHg and/or DBP >100 mmHg); recent malignancy or radiation therapy (≤6 months) and not expected to survive 3 years; contraindication to warfarin treatment; reversible causes of atrial fibrillation (e.g. cardiac surgery, pulmonary embolism, untreated hyperthyroidism); plan to perform a pulmonary vein ablation or surgery for cure of the AF; severe renal impairment (estimated creatinine clearance ≤30 mL/min); active infective endocarditis; active liver disease, including but not limited to persistent ALT, AST, alkaline phosphatase ≥2 X ULN, known active hepatitis C, active hepatitis B, active hepatitis A; women who were pregnant, lactating or of childbearing potential who refused to use a medically acceptable form of contraception throughout the study; anaemia (haemoglobin <100 g/L) or thrombocytopenia (platelet count <100 X 10^9/L); patients who had developed transaminase elevations upon exposure to ximelagatran; patients who had received an investigational drug in the past 30 days or were participating in another drug study; patients considered unreliable by the investigator concerning the requirements for follow-up during the study and/or compliance with study drug administration.

The concomitant diseases of patients in this trial included hypertension 79%, diabetes 23% and CAD 28%. 50% of the patient population was vitamin K antagonist (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 randomised to warfarin, the time in therapeutic range (INR 2.0 to 3.0) for the trial was a median of 67%. Concomitant medications included acetylsalicylic acid (ASA) (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 hypoglycaemics (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.

Based on the intent to treat population analysis, this study demonstrated that dabigatran etexilate, at a dose of 150 mg twice daily, is superior to warfarin in the prevention of stroke and systemic embolism in patients with atrial fibrillation. The lower dose of 110 mg twice daily is non-inferior to warfarin (see Table 6).

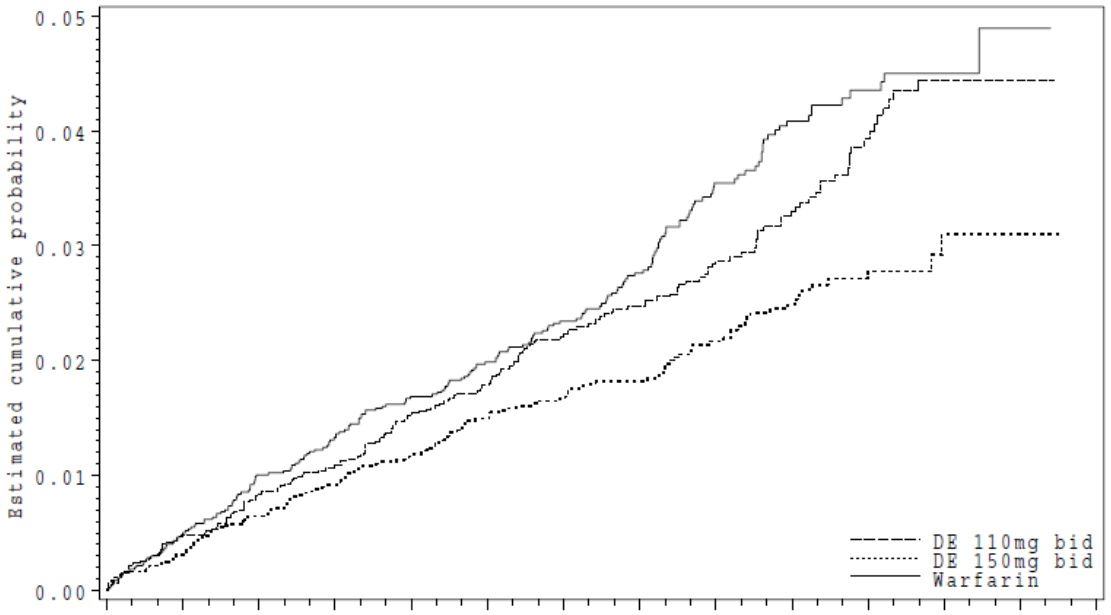
Dabigatran etexilate 150 mg twice daily reduces other clinically relevant endpoints: ischaemic stroke, haemorrhagic stroke, intracranial haemorrhage and total bleeding compared to warfarin, with similar rates of major bleeding (see Tables 7 and 21). Dabigatran etexilate 110 mg twice

daily reduces the risk of intracranial haemorrhage, major bleeding and total bleeding (see Table 20). The yearly event rate for vascular death for dabigatran etexilate 150 mg twice daily was 2.28%, 110 mg twice daily was 2.43% and warfarin was 2.69%.

There was an increased frequency in myocardial infarction events in subjects treated with dabigatran etexilate compared to warfarin treated subjects, which was not statistically significant (yearly event rate: 150 mg twice daily 0.81%, 110 mg twice daily 0.83%, warfarin 0.64%). Patients had similar baseline characteristics across the treatment groups, with respect to cardiovascular risk factors: hypertension, diabetes, prior coronary artery disease, prior MI, prior stroke, and active smoking. The baseline use of anti-platelet and antithrombotic therapies was similar across the three treatment groups. The reason for this finding is unknown.

Gastrointestinal (GI) haemorrhage occurred at a higher frequency with dabigatran etexilate compared to warfarin. The underlying mechanism of the increased rate of GI bleeding has not been established.

Figure 1: Kaplan-Meier curve estimate of time to first stroke or systemic embolism in RE-LY



Subjects at risk													
DE 110mg bid	6015	5927	5862	5797	5713	5481	4615	3778	3132	2386	1446	495	87
DE 150mg bid	6076	6010	5940	5861	5782	5555	4700	3847	3238	2428	1481	494	90
Warfarin	6022	5937	5862	5782	5719	5438	4615	3702	3091	2338	1364	383	76

Table 6: Analysis of first occurrence of stroke or systemic embolism (primary endpoint) during the study period in RE-LY (randomised set)

	Dabigatran etexilate 150 mg twice daily	Dabigatran etexilate 110 mg twice daily	Warfarin
Subjects randomised	6076	6015	6022
Subject-years	12033	11899	11794
Stroke and/or SEE			
Yearly event rate (%)	135 (1.12)	183 (1.54)	203 (1.72)
Hazard ratio over warfarin (95% CI)	0.65 (0.52, 0.81)	0.89 (0.73, 1.09)	
p-value superiority	0.0001	0.2721	
p-value noninferiority	<0.0001	<0.0001	

% refers to yearly event rate (calculated as number of subjects with events divided by subject-years and multiplied by 100)

Table 7: Analysis of first occurrence of stroke, systemic embolism, ischaemic or haemorrhagic strokes during the study period in RE-LY (randomised set)

	Dabigatran etexilate 150 mg twice daily	Dabigatran etexilate 110 mg twice daily	Warfarin
Subjects randomised	6076	6015	6022
Subject-years	12033	11899	11794
Stroke			
Yearly event rate (%)	123 (1.02)	171 (1.44)	187 (1.59)
Hazard ratio vs. warfarin (95% CI)	0.64 (0.51, 0.81)	0.91 (0.74, 1.12)	
SEE			
Yearly event rate (%)	13 (0.11)	15 (0.13)	21 (0.18)
Hazard ratio vs. warfarin (95% CI)	0.61 (0.30, 1.21)	0.71 (0.37, 1.38)	
Ischaemic stroke			
Yearly event rate (%)	104 (0.86)	152 (1.28)	134 (1.14)
Hazard ratio vs. warfarin (95% CI)	0.76 (0.59, 0.98)	1.13 (0.89, 1.42)	
Haemorrhagic stroke			
Yearly event rate (%)	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)	

% refers to yearly event rate (calculated as number of subjects with events divided by subject-years and multiplied by 100)

Table 8: Analysis of pulmonary embolism and myocardial infarction during the study period in RE-LY (randomised set)

	Dabigatran etexilate 150 mg twice daily	Dabigatran etexilate 110 mg twice daily	Warfarin
Subjects randomised	6076	6015	6022
Subject-years	12033	11899	11794
Pulmonary embolism			
Yearly event rate (%)	18 (0.15)	14 (0.12)	12 (0.10)
Hazard ratio vs. warfarin (95% CI)	1.41 (0.71, 3.06)	1.16 (0.54, 2.51)	
Myocardial infarction			
Yearly event rate (%)	97 (0.81)	98 (0.82)	75 (0.64)
Hazard ratio vs. warfarin (95% CI)	1.27 (0.94, 1.71)	1.29 (0.96, 1.75)	

% refers to yearly event rate (calculated as number of subjects with events divided by subject-years and multiplied by 100)

Table 9: Major bleeding events by age group during the study period in RE-LY

Age (years)	# of subjects	Dabigatran etexilate 110 mg twice daily Yearly event rate (%/ year)	Dabigatran etexilate 150 mg twice daily Yearly event rate (%/ year)	Warfarin Yearly event rate (%/ year)
<65	2981	0.81	0.88	2.48
>65 - <75	7894	2.31	2.68	3.24
≥ 75	7238	4.52	5.24	4.47

% refers to yearly event rate (calculated as number of subjects with events divided by subject-years and multiplied by 100)

The RE-LY extension study (RELY-ABLE) provided additional safety information for a large cohort of patients which continued the same dose of dabigatran etexilate as assigned in the RE-LY trial. Patients were eligible for the RELY-ABLE trial if they had not permanently discontinued study medication at the time of their final RE-LY study visit. Enrolled patients continued to receive the same double-blind dabigatran etexilate dose randomly allocated in RE-LY, for up to 43 months of follow up after RE-LY (total mean follow-up RE-LY + RELY-ABLE, 4.5 years). There were 5897 patients enrolled, representing 49% of patients originally randomly assigned to receive dabigatran etexilate in RE-LY and 86% of RELY-ABLE–eligible patients.

During the additional 2.5 years of treatment in RELY-ABLE, with a maximum exposure of over 6 years (total exposure in RELY + RELY-ABLE), the long-term safety profile of dabigatran etexilate was confirmed for both test doses. No new safety findings were observed.

The rates of outcome events including major bleed and other bleeding events were consistent with those seen in RE-LY.

Treatment of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in adults

The efficacy and safety was investigated in two multi-centre, randomised, double blind, parallel-group, replicate studies RE-COVER and RE-COVER II. These studies compared dabigatran etexilate (150 mg twice daily) with warfarin (target INR 2.0-3.0) in patients with acute DVT and/or PE. Patients were to be included in the studies if they had objectively confirmed symptomatic uni-or bi-lateral DVT of the leg and/or confirmed symptomatic PE. Patients were not eligible to participate in any study if they had of any of the following at screening: excessive

risk of bleeding, CrCL below 30 mL/min, known liver disease expected to have any potential impact on survival or pregnancy, breast feeding, or not using adequate contraceptive methods. The primary objective of these studies was to determine if dabigatran was non-inferior to warfarin in reducing the occurrence of the primary endpoint which was the composite of recurrent symptomatic DVT and/or PE and related deaths within the 6 month acute treatment period. The lower bound of the non-inferiority margin was 2.75 in hazard ratio.

In the pooled RE-COVER and RE-COVER II studies, a total of 5,153 patients were randomised and 5,107 were treated. The index events at baseline: DVT - 68.5%, PE -22.2%, PE and DVT - 9.1%. The most frequent risk factors were history of DVT and/or PE - 21.5%, surgery/trauma - 18.1%, venous insufficiency -17.6%, and prolonged immobilisation -14.6%. Patients' baseline characteristics: mean age was 54.8 years, males 59.5%, Caucasian 86.1%, Asian 11.8%, blacks 2.1%. The co-morbidities included: hypertension 35.5%, diabetes mellitus 9.0%, CAD 6.8% and gastric or duodenal ulcer 4.1%.

The duration of treatment with fixed dose of dabigatran was 174.0 days without coagulation monitoring. For patients randomised to warfarin, the median time in therapeutic range (INR 2.0 to 3.0) was 60.6%. Concomitant medications included vasodilators 28.5%, agents acting on the renin-angiotensin system 24.7%, lipids lowering agents 19.1%, beta-blockers 14.8%, calcium channel blockers 9.7%, NSAIDs 21.7%, aspirin 9.2%, antiplatelet agents 0.7%, P-gp inhibitors 2.0% (verapamil -1.2% and amiodarone -0.4%).

Two trials in patients presenting with acute DVT and/or PE treated initially for at least 5 days of parenteral therapy, RE-COVER and RE-COVER II, demonstrated that treatment with dabigatran etexilate 150 mg twice daily was non-inferior to the treatment with warfarin (p values for non-inferiority: RE-COVER p<0.0001, RE-COVER II p=0.0002). Refer to Adverse Effects section for information on bleeding events in RE-COVER and RE-COVER II.

Table 10: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the pooled studies RE-COVER and RE-COVER II

	Dabigatran etexilate 150 mg twice daily	Warfarin
Treated patients, n	2,553	2,554
Recurrent symptomatic VTE and VTE-related death (%)	68 (2.7)	62 (2.4)
Hazard ratio vs. warfarin (95% CI)	1.09 (0.77, 1.54)	
Secondary efficacy endpoints		
Recurrent symptomatic VTE and all-cause deaths (%)	109 (4.3)	104 (4.1)
95% CI	3.52, 5.13	3.34, 4.91
Symptomatic DVT (%)	45 (1.8)	39 (1.5)
95% CI	1.29, 2.35	1.09, 2.08
Symptomatic PE (%)	27 (1.1)	26 (1.0)
95% CI	0.70, 1.54	0.67, 1.49
VTE-related deaths (%)	4 (0.2)	3 (0.1)
95% CI	0.04, 0.40	0.02, 0.34
All-cause deaths (%)	51 (2.0)	52 (2.0)
95% CI	1.49, 2.62	1.52, 2.66

Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in adults

Two randomised, parallel group, double-blind studies were performed in patients previously treated with anticoagulation therapy. RE-MEDY, the warfarin controlled study, enrolled patients already treated for 3 to 12 months with the need for further anticoagulant treatment and RE-SONATE, the placebo controlled study, enrolled patients already treated for 6 to 18 months with Vitamin K inhibitors. Patients were to be included in the RE-MEDY or RE-SONATE study if they had objectively confirmed DVT or PE and had prior treatment with an oral anticoagulant for between 3 and 18 months (varied by study). The RE-MEDY study was designed to recruit typical patients at risk of recurrent VTE; RE-SONATE was designed to recruit patients at lower risk who might benefit from extended anticoagulation. Patients were not eligible to participate in any study if they had any of the following at screening: excessive risk of bleeding, CrCL below 30 mL/min, known liver disease expected to have any potential impact on survival or pregnancy, breast feeding, or not using adequate contraceptive methods.

The objective of the RE-MEDY study was to compare the safety and efficacy of oral dabigatran etexilate (150 mg twice daily) to warfarin (target INR 2.0-3.0) for the long-term treatment and prevention of recurrent, symptomatic DVT and/or PE. A total of 2,866 patients were randomised and 2,856 patients were treated. The index events at baseline: DVT - 65.1%, PE - 23.1%, PE and DVT -11.7%. Patients' baseline characteristics: mean age 54.6 years, males 61.0%, Caucasian 90.1%, Asian 7.9%, blacks 2.0%. Co-morbidities included hypertension 38.6%, diabetes mellitus 9.0%, CAD 7.2% and gastric or duodenal ulcer 3.8%. Concomitant medications: agents acting on the renin-angiotensin system 27.9%, vasodilators 26.7, lipid lowering agents 20.6%, NSAIDs 18.3%, beta-blockers 16.3%, calcium channel blockers 11.1%, aspirin 7.7%, P-gp inhibitors 2.7% (verapamil 1.2% and amiodarone 0.7%), antiplatelets 0.9%. Duration of dabigatran exilate treatment ranged from 6 to 36 months (median - 534.0 days). For patients randomised to warfarin, the median time in therapeutic range (INR 2.0-3.0) was 64.9%.

RE-MEDY demonstrated that treatment with dabigatran etexilate 150 mg twice daily was non-inferior to warfarin (p=0.0135 for non-inferiority). Refer to Adverse Effects section for information on bleeding events in RE-MEDY.

As in the pooled RE-COVER/RE-COVER II studies, in RE-MEDY concomitant use of P-gp inhibitors was reported by few patients (2.7%); verapamil (1.2%) and amiodarone (0.7%) were the most frequent. In the pooled acute VTE treatment studies, concomitant use of P-gp inhibitors was reported by few patients (2.0%); most frequent were verapamil (1.2% overall) and amiodarone (0.4% overall).

Table 11 displays details of key results of the RE-MEDY study.

Table 11: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the RE-MEDY study

	Dabigatran etexilate 150 mg twice daily	Warfarin
Treated patients, n	1,430	1,426
Recurrent symptomatic VTE and VTE-related death (%)	26 (1.8)	18 (1.3)
Hazard ratio vs. warfarin (95% CI)	1.44 (0.78, 2.64)	
p-value (non-inferiority)	0.0135	
Patients with event at 18 months	22	17
Cumulative risk at 18 months (%)	1.7	1.4
Risk difference vs. warfarin (%)	0.4	
95% CI	-0.5, 1.2	
p-value (non-inferiority)	<0.0001	
Secondary efficacy endpoints		
Recurrent symptomatic VTE and all-cause deaths (%)	42 (2.9)	36 (2.5)
95% CI	2.12, 3.95	1.77, 3.48
Symptomatic DVT (%)	17 (1.2)	13 (0.9)
95% CI	0.69, 1.90	0.49, 1.55
Symptomatic PE (%)	10 (0.7)	5 (0.4)
95% CI	0.34, 1.28	0.11, 0.82
VTE-related deaths (%)	1 (0.1)	1 (0.1)
95% CI	0.00, 0.39	0.00, 0.39
All-cause deaths (%)	17 (1.2)	19 (1.3)
95% CI	0.69, 1.90	0.80, 2.07

The objective of the RE-SONATE study was to evaluate superiority of dabigatran etexilate versus placebo for the prevention of recurrent symptomatic DVT and/or PE in patients who had already completed 6 to 18 months of treatment with VKA. The intended therapy was 6 months dabigatran etexilate 150 mg twice daily without need for monitoring.

The index events at baseline: DVT 64.5%, PE 27.8%, PE and DVT 7.7%. A total of 1,353 patients were randomized and 1,343 patients treated. Patients' baseline characteristics: mean age 55.8 years, males 55.5%, Caucasian 89.0%, Asian 9.3%, blacks 1.7%. Co-morbidities included hypertension 38.8%, diabetes mellitus 8.0%, CAD 6.0 % and gastric or duodenal ulcer 4.5%. Concomitant medications: agents acting on the renin-angiotensin system 28.7%, vasodilators 19.4%, lipid lowering agents 17.9%, beta-blockers 18.5%, calcium channel blockers 8.9%, NSAIDs 12.1%, aspirin 8.3%, antiplatelets 0.7% and P-gp inhibitors 1.7% (verapamil 1.0% and amiodarone 0.3%).

RE-SONATE demonstrated dabigatran etexilate was superior to placebo for the prevention of recurrent symptomatic DVT/PE events including unexplained deaths, with a risk reduction of 92% (absolute risk reduction 5.2%) during the treatment period (p<0.0001). All secondary and sensitivity analyses of the primary endpoint and all secondary endpoints showed superiority of dabigatran etexilate over placebo. The rates of MBEs and the combination of MBEs/CRBEs were significantly higher in patients receiving dabigatran etexilate as compared with those receiving placebo.

The study included observational follow-up for 12 months after the conclusion of treatment. After discontinuation of study medication the effect was maintained until the end of the follow-up, indicating that the initial treatment effect of dabigatran etexilate was sustained. No rebound effect was observed. At the end of the follow-up VTE events in patients treated with dabigatran

etexilate was 6.9% vs. 10.7% among the placebo group (hazard ratio 0.61 (0.42, 0.88), p=0.0082).

Table 12 displays details of key results of the RE-SONATE study.

Table 12: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the RE-SONATE study

	Dabigatran etexilate 150 mg twice daily	Placebo
Treated patients , n	681	662
Recurrent symptomatic VTE and related deaths (%)	3 (0.4)	37 (5.6)
Hazard ratio (95% CI)	0.08 (0.02, 0.25)	
p-value	<0.0001	
Secondary efficacy endpoints		
Recurrent symptomatic VTE and all-cause deaths	3 (0.4)	37 (5.6)
95% CI	0.09, 1.28	3.97, 7.62
Symptomatic DVT (%)	2 (0.3)	23 (3.5)
95% CI	0.04, 1.06	2.21, 5.17
Symptomatic PE (%)	1 (0.1)	14 (2.1)
95% CI	0.00, 0.82	1.16, 3.52
VTE-related deaths (%)	0 (0)	0 (0)
95% CI	0.00, 0.54	0.00, 0.56
Unexplained deaths (%)	0 (0)	2 (0.3)
95% CI	0.00, 0.54	0.04, 1.09
All-cause deaths (%)	0 (0)	2 (0.3)
95% CI	0.00, 0.54	0.04, 1.09

Other Measures Evaluated

Liver Function Tests

In the active controlled studies RE-COVER, RE-COVER II and RE-MEDY, potential abnormalities of liver function tests (LFT) occurred with a comparable or lower incidence in dabigatran etexilate vs. warfarin treated patients. In RE-SONATE, there was no marked difference between the dabigatran- and placebo groups with regard to possible clinically significant abnormal LFT values.

Prevention of thromboembolism in patients with prosthetic heart valves

A phase II study examined dabigatran etexilate and warfarin in a total of 252 patients with recent mechanical heart valve replacement surgery (i.e. within the current hospital stay) and in patients who received a mechanical heart valve replacement more than three months before. Analysis of the study data revealed more thromboembolic events, including stroke, transient ischaemic events, valve thrombosis and myocardial infarction in the patients assigned to treatment with dabigatran etexilate compared with warfarin. In the early post-operative patients, major bleeding manifested predominantly as haemorrhagic pericardial effusions, specifically in patients who started dabigatran etexilate early (i.e. on Day 3) after heart valve replacement surgery.

INDICATIONS

Prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement). (see Dosage and Administration section for details of treatment duration).

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

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

CONTRAINDICATIONS

- Known hypersensitivity to dabigatran or dabigatran etexilate or to one of the excipients of the product.
- Severe renal impairment (CrCL <30 mL/min).
- Haemorrhagic manifestations, patients with a bleeding diathesis, or patients with spontaneous or pharmacological impairment of haemostasis.
- Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.
- Indwelling spinal or epidural catheter and during the first two hours after removal (see Precautions).
- Hepatic impairment or liver disease expected to have any impact on survival.
- History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding.
- Gastrointestinal haemorrhage within the past year unless the cause has been permanently eliminated, e.g. by surgery.
- Conditions associated with increased risk of bleeding (see Precautions, Haemorrhagic risk, Table 14 Diseases / procedures with special haemorrhagic risks).
- Concomitant treatment with systemic ketoconazole, cyclosporin, itraconazole or dronedarone (see Precautions).
- Simultaneous initiation of treatment with dabigatran etexilate and oral verapamil.
- Treatment initiation with oral verapamil in patients following major orthopaedic surgery who are already treated with dabigatran etexilate.
- Prosthetic heart valve replacement.

PRECAUTIONS

Haemorrhagic risk

Dabigatran etexilate increases the risk of bleeding and can cause significant and sometimes fatal bleeding. 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.

In the case of haemorrhagic complications treatment must be discontinued and the source of bleeding investigated.

A specific antidote antagonising the pharmacodynamic effect of dabigatran etexilate is not currently available. Careful clinical monitoring including renal function testing is required for all patients (see Dosage and Administration, Special patient populations).

PRADAXA does not in general require routine anticoagulation monitoring. However, the measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. Coagulation testing should also be considered to assist with the management of patients in the perioperative setting, suspected overdose and emergency situations.

The INR test is unreliable in patients on PRADAXA and false positive INR elevations have been reported. Therefore INR tests should not be performed. Tests of anticoagulant activity such as Thrombin Time (TT), diluted Thrombin Time (dTT), Ecarin Clotting Time (ECT) and activated Partial Thromboplastin Time (aPTT) are available to detect excessive dabigatran activity. Dabigatran related anticoagulation can be assessed by ECT or TT. If ECT, dTT or TT are not available, the aPTT test provides an approximation of PRADAXA's anticoagulant activity (see Effect on laboratory tests).

Table 13: Coagulation test thresholds at trough that may be associated with an increased risk of bleeding* #

Test (trough value)	Indication	
	pVTEp orthopaedic surgery	SPAF and DVT/PE
dTT calibrated for dabigatran [total active dabigatran concentration in plasma in ng/mL]	>67	>200
ECT [x-fold upper limit of normal]	No data	>3
aPTT [x-fold upper limit of normal]	>1.3	>2
INR	Should not be performed	Should not be performed

* dTT, ECT and aPTT tests are not standardised and results should be interpreted with caution

Data are derived from the 90th percentile of measured dabigatran steady state trough concentrations in RENOVATE II (pVTEp, orthopaedic surgery) and RE-LY (SPAF)

In atrial fibrillation patients in RE-LY treated with 150 mg twice daily an aPTT of greater than 2.0–3.0 fold of normal range at trough was associated with an increased 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 (30–50 mL/min CrCL), age ≥75 years or P-glycoprotein (P-gp) inhibitor co-medication are associated with increased dabigatran plasma

levels (see Table 14). The presence of one or more of these factors may increase the risk of bleeding, especially if combined (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, tacrolimus, cyclosporin, ritonavir, tipranavir, nelfinavir and saquinavir (see Interactions with other medicines, Anticoagulants and platelet aggregation agents).

The concomitant use of dronedarone increases exposure of dabigatran and is not recommended (see Interactions with other medicines).

The concomitant use of ticagrelor increases the exposure to dabigatran and may show pharmacodynamic interaction, which may result in an increased risk of bleeding (see Effect on laboratory tests and Interactions with other medicines, Co-medication with P-glycoprotein inhibitors).

Bleeding risk may be increased in patients concomitantly treated with selective serotonin re-uptake inhibitors (SSRI) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs).

The concomitant use of PRADAXA with fibrinolytic treatments has not been studied and may increase the risk of bleeding. The use of fibrinolytic agents for the treatment of acute ischemic stroke may be considered if the patient presents with a thrombin time (TT), or Ecarin clotting time (ECT), or activated partial thromboplastin time (aPTT) not exceeding the upper limit of normal (ULN) according to the local reference range.

Close clinical surveillance (looking for signs of bleeding or anaemia) is recommended throughout the treatment period, especially if risk factors (as summarised in Table 14) are combined. Specifically, with concomitant intake of antiplatelets or strong P-gp inhibitors in patients aged ≥75 years, the risk of major bleeding, including gastrointestinal bleeding, increases. If bleeding is clinically suspected, appropriate measures such as testing for occult blood in stool, or testing for a drop in haemoglobin is suggested.

Table 14: Factors which may increase haemorrhagic risk

Pharmacodynamic and kinetic factors	• Age ≥ 75 years
Factors increasing dabigatran plasma levels	• Moderate renal impairment (30-50 mL/min CrCL) • P-glycoprotein (P-gp) inhibitor co-medication (some P-gp inhibitors are contraindicated – see Contraindications section)
Pharmacodynamic interactions	• Antiplatelet agents, including acetylsalicylic acid (ASA), clopidogrel, prasugrel and ticagrelor • Non steroidal antiinflammatory drugs (NSAIDs) • Selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs) • Thrombolytic agents
Diseases / procedures with special haemorrhagic risks (note these are CONTRAINDICATIONS – see Contraindications section)	• 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

Patients ≥ 75 years of age should not be treated with PRADAXA 150 mg twice a day (see Dosage and Administration, Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation).

NSAIDs (half-lives <12 hours) given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. For the 220 mg dose of dabigatran etexilate, the bleeding incidence associated with NSAIDs is 1.5% compared to 1.4% for all patients. Concomitant use of NSAIDs with half-lives greater than 12 hours should be undertaken with caution.

The increase in yearly event rates of major bleeds by concomitant medications in the RE-LY study are shown in Table 15.

Table 15: Analysis of increase in major bleeding events by concomitant medications in RE-LY

Concomitant Medication	Dabigatran etexilate 110 mg twice daily	Dabigatran etexilate 150 mg twice daily	Warfarin
	Fold Increase in Yearly Event Rates of Major Bleeding		
Acetylsalicylic Acid (ASA)	1.91	1.95	1.93
Clopidogrel	2.06	1.92	2.02
COX-2 Inhibitors	1.63	1.60	1.81
Non Steriodal Antiinflammatory Drugs (NSAIDs)	1.53	1.36	1.49
Proton Pump Inhibitors	2.57	3.45	2.72
Verapamil	1.10	1.33	1.06
H2 blockers	2.59	2.30	2.35
Amiodarone	1.59	1.20	1.28

The results for "Fold Increase in Yearly Event Rates of Major Bleeding" are based on the rates without respective concomitant medication ("never") versus with respective concomitant medication ("at least one time").

Patients taking dabigatran etexilate with PPIs or H2-blockers may be at increased risk of gastrointestinal bleeding due to the associated gastrointestinal conditions for which these drugs are prescribed.

Gastrointestinal bleeds

Gastrointestinal (GI) haemorrhage occurred at a higher frequency with dabigatran etexilate compared to warfarin (see Adverse Effects, Table 22). The underlying mechanism of the increased rate of GI bleeding has not been established. Patients with an increased risk of bleeding (e.g. recent gastrointestinal bleeding), should be closely monitored clinically (looking for signs of bleeding or anaemia). In such patients, a dose of 220 mg, given as 110 mg twice daily may be considered. A coagulation test, such as aPTT (see Precautions, Effect on laboratory tests), may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure.

Achlorhydria

See Interactions with other medicines, Co-medication with gastric pH-elevating agents, Pantoprazole for effect of elevated gastric pH on dabigatran bioavailability.

Myocardial Infarction

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

In the phase III study RE-LY the overall rate of myocardial infarction (MI) was 0.82, 0.81, and 0.64 % / year for dabigatran etexilate 110 mg twice daily, dabigatran etexilate 150 mg twice daily and warfarin, respectively, an increase in relative risk for dabigatran of 29 % and 27 % compared to warfarin. Irrespective of therapy, the highest absolute risk of MI was seen in the following subgroups, with similar relative risk: patients with previous MI, patients ≥ 65 years with either diabetes or coronary artery disease, patients with left ventricular ejection fraction < 40 %, and patients with moderate renal dysfunction. Furthermore a higher risk of MI was seen in patients concomitantly taking ASA plus clopidogrel or clopidogrel alone.

Treatment or, and prevention of recurrent, deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in adults

In the three active controlled studies, a higher rate of MI was reported in patients who received dabigatran etexilate than in those who received warfarin: 0.4% vs. 0.2% in the short-term RE-COVER and RE-COVER II studies; and 0.8% vs. 0.1% in the long-term RE-MEDY trial. The increase was statistically significant in this study (p=0.022).

In the RE-SONATE study, which compared dabigatran etexilate to placebo, the rate of MI was 0.1% for patients who received dabigatran etexilate and 0.2% for patients who received placebo.

Active Cancer Patients

The efficacy and safety have not been established for DVT/PE patients with active cancer.

Interaction with P-glycoprotein 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 generally be avoided (see Precautions, Interactions with other medicines).

Interaction with P-glycoprotein inhibitors

Coadministration of dabigatran etexilate with strong P-gp inhibitors (amiodarone, clarithromycin, nelfinavir, ritonavir, saquinavir, and verapamil) should be used with caution and close clinical

surveillance (looking for signs of active bleeding or anaemia) is required, due to a potential risk of higher plasma levels of dabigatran and consequent potentially exaggerated pharmacodynamic effect of dabigatran etexilate (notably bleeding risk) (see Precautions, Interactions with other medicines). The concomitant use of dabigatran etexilate with tacrolimus is not recommended. Concomitant use of dabigatran etexilate with cyclosporin, itraconazole, ketoconazole or dronedarone is contraindicated.

Hepatic Impairment

Patients with 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 contraindicated in this population. A liver function test is recommended prior to initiating treatment.

Renal Impairment

Pharmacokinetic studies demonstrated up to a 3 fold increase in drug exposure in patients with reduced renal function including age-related decline of renal function (see Pharmacokinetics).

In patients with mild renal impairment increases in dabigatran concentration were observed (see Pharmacokinetics, Special Populations, Renal Impairment, Table 2).

In patients with moderate renal impairment in RE-LY, the observed major bleeding rate was comparable between dabigatran 110 mg and 150 mg (dabigatran 110 mg 5.65%/year versus dabigatran 150 mg 5.27%/year versus warfarin 5.68%/year). Based on theoretical considerations of drug exposure a reduced dose may be considered in these patients (see Dosage and Administration).

The presence of one or more factors known to increase haemorrhagic risk (see Table 14) may increase the risk of bleeding. Caution should be exercised. Close clinical surveillance is recommended.

Dabigatran etexilate is contraindicated in cases of severe renal impairment (CrCL <30 mL/min).

Patients who develop acute renal failure should discontinue dabigatran etexilate.

Pulmonary

Acute Pulmonary Embolus in haemodynamically unstable patients, or in those requiring thrombolysis or pulmonary embolectomy

Safety and efficacy of PRADAXA have not been established for the treatment of VTE in patients with pulmonary embolus who are haemodynamically unstable, or who may receive thrombolysis or pulmonary embolectomy. In these patients the initial anticoagulation therapy should exclude the use of PRADAXA.

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.

Caution should be exercised when treatment is temporarily discontinued for interventions and anticoagulant monitoring is warranted. Clearance of dabigatran in patients with renal insufficiency may take longer (see Pharmacokinetics, Tables 1 and 2). This should be considered in advance of any procedures. In such cases a coagulation test (see Pharmacology

and Precautions, Haemorrhagic risk and Precautions, Effect on laboratory tests) may help to determine whether haemostasis is still impaired.

Preoperative Phase

Due to an increased risk of bleeding dabigatran etexilate may be stopped temporarily in advance of invasive or surgical procedures.

Elective Surgery/Intervention

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 haemostasis 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 (see Table 16 below).

Table 16: Discontinuation rules before invasive or surgical procedures

Renal function (CrCL in mL/min)	Estimated half-life (hours)	Stop dabigatran before elective surgery	
		High risk of bleeding or major surgery	Standard risk
≥80	~13*	2 days before	24 hours before
≥50-<80	~15*	2-3 days before	1-2 days before
≥30-<50	~18*	4 days before	2-3 days before (>48 hours)

*for more details see Pharmacokinetics, Absorption, Table 1

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.

Acute Surgery/Intervention

Dabigatran etexilate should be temporarily discontinued. An acute 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 against the urgency of intervention (for cardioversion see Dosage and Administration, Special patient populations).

Spinal Anaesthesia/Epidural Anaesthesia/Lumbar Puncture

Procedures such as spinal anaesthesia may require complete haemostatic function. In patients treated with dabigatran etexilate and who undergo spinal or epidural anaesthesia, or in whom lumbar puncture is performed in follow-up to surgery, the formation of spinal or epidural haematomas that may result in long-term or permanent paralysis cannot be excluded.

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 2 hours should elapse before the administration of the first dose of dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms.

Post Procedural Period

Resume treatment after complete haemostasis is achieved.

Hip fracture surgery

There is no data on the use of dabigatran etexilate in patients undergoing hip fracture surgery.

Therefore treatment is not recommended.

Effects on fertility

Rat fertility was unaffected by treatment with dabigatran etexilate at oral doses of up to 200 mg/kg/day (approximately 4-5 times clinical exposure, based on AUC). There was a significant decrease in the number of implantations at 70 and 200 mg/kg/day (3 and 4 times clinical exposure, respectively based on AUC), which was associated with an increase in pre-implantation loss. The effect on human fertility is unknown.

Use in pregnancy (Category C)

Anticoagulants and thrombolytic agents can produce placental haemorrhage and subsequent prematurity and foetal loss. There are no adequate and well-controlled studies in pregnant women. It is not known whether dabigatran etexilate can cause foetal harm when administered to pregnant women. Dabigatran etexilate should not be used during pregnancy.

Studies in rats have shown that small amounts of dabigatran and/or its metabolites cross the placenta.

Embryofoetal development studies with oral dabigatran etexilate showed delayed ossification and general disturbances in foetal development of rats at 15 and 70 mg/kg/day (1 to 4 fold anticipated human exposure based on AUC). The delayed ossification, however, was transient, since offspring of rats treated with 15, 30 and 70 mg/kg/day during gestation and lactation showed normal body weights, normal body weight development, normal survival after birth and normal physical postnatal development. Morphogenic effects such as cleft thoracal vertebral body (rats) and dilated cerebral ventricles (rabbits) were seen at a maternotoxic dose of 200 mg/kg/day (relative exposure of 8 and 13, respectively). Maternal toxicity in rats at >70 mg/kg/day was associated with an increased rate of resorptions, and a significant decrease in viable foetuses was seen at 200 mg/kg/day. In rats allowed to deliver, mortality due to excessive vaginal bleeding was seen at 70 mg/kg/day and in one dam at 15 mg/kg/day. An increase in post-implantation loss was seen at 70 mg/kg/day in these animals.

Use in lactation

Dabigatran and/or its metabolites were present in the milk of lactating rats given oral doses of dabigatran etexilate. The ratio of the dabigatran concentration in rat milk to that in the plasma of the mothers was 0.4. No clinical data are available. As a precaution, use of dabigatran etexilate is not recommended in women who are breast-feeding.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

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. Patients should be treated with the dose of dabigatran etexilate as recommended in the Dosage and Administration section. Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure in those patients with age-related decline of renal function (see Precautions, Renal Impairment). The risk of stroke is higher in the elderly, however the risk of bleeding

increases with increasing age (see Table 9). Careful clinical observation is advised and a dosage adjustment is recommended in elderly patients (≥75 years) due in part to age-related impairment of renal function (see Table 14). These patients should be treated with caution (see Dosage and Administration), particularly if they are also taking a drug which is a P-glycoprotein inhibitor (see Precautions, Interaction with P-glycoprotein inhibitors).

Trauma

Patients who are at increased risk of trauma accidents or surgery may have a higher risk of traumatic bleeding.

Body Weight

Limited data in patients <50 kg are available (see Pharmacokinetics, Special populations, Body weight).

Carcinogenicity

Carcinogenicity studies were performed with dabigatran etexilate in mice and rats for up to 2 years. An increased incidence of granulosa cell tumours without increased incidence of preneoplastic precursor lesions was seen in the ovaries of rats treated at 100 and 200 mg/kg/day (3 and 8 times clinical exposure, respectively based on AUC). 10 adverse event reports referring to ovarian masses or adnexal masses were observed during the RE-LY trial. The mechanism for the ovarian effects in animals is unclear and the long term effects for humans are unknown, although dabigatran etexilate is not expected to pose a carcinogenic risk to humans. No tumours were seen in rats at 30 mg/kg/day (similar to clinical exposure at the maximum recommended dose) or in studies in mice.

Genotoxicity

Dabigatran etexilate and its active moiety, dabigatran, were not mutagenic in a bacterial reverse mutation assay (Ames test) and did not induce mutations or chromosome damage in mouse lymphoma cells. Dabigatran etexilate was negative at doses of up to 2000 mg/kg in rats in the mammalian erythrocyte micronucleus test.

Excipients

The product contains the excipient sunset yellow FCF CI15985, which may cause allergic reactions.

Effect on laboratory tests

The aPTT test may be useful in determining an excess of anticoagulant activity. Dabigatran concentration exceeding 450 – 500 ng/mL would result in an aPTT of greater than 2.5 times control. An aPTT greater than 2.5 times control is suggestive of excess anticoagulation (see Pharmacology and Precautions, Haemorrhagic risk).

INTERACTIONS WITH OTHER MEDICINES

Interaction studies have only been performed in adults.

Anticoagulants and platelet aggregation agents

The following treatments are not recommended concomitantly with dabigatran etexilate: unfractionated heparins and heparin derivatives, low molecular weight heparins (LMWH), and

heparin derivatives (fondaparinux, desirudin), thrombolytic medicinal products, and vitamin K antagonists, rivaroxaban, apixaban or other oral anticoagulants, and platelet aggregation medicinal products such as GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, prasugrel, ticagrelor, dextran, and sulfinpyrazone.

From the limited data collected in the phase III study RE LY in patients with atrial fibrillation it was observed that the concomitant use of other oral or parenteral anticoagulants increases major bleeding rates with both dabigatran etexilate and warfarin by approximately 2.5-fold, mainly related to situations when switching from one anticoagulant to another.

Unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter (see Dosage and Administration and Precautions, Haemorrhagic risk).

Enoxaparin: The switch from enoxaparin to dabigatran has been clinically tested in a phase I study. After 3 days treatment of once daily 40 mg enoxaparin s.c., dabigatran exposure was slightly lower 24 hours following the last dose of enoxaparin than after administration of dabigatran etexilate (single dose of 220 mg) alone. A higher anti-FXa/FIIa activity was observed after dabigatran administration with enoxaparin pre-treatment compared to that after treatment with dabigatran alone, which was considered to be due to the carry-over effect of enoxaparin treatment. The other dabigatran-related anti-coagulation tests, i.e., aPTT, ECT and TT, were mainly not affected after a 24 hour washout of enoxaparin.

Interactions linked to dabigatran etexilate and dabigatran metabolic profile

Dabigatran etexilate and dabigatran are not metabolised by the cytochrome P450 system and had no *in vitro* effects on human cytochrome P450 enzymes. This has been confirmed by *in vivo* studies with healthy volunteers, who did not show any interaction between this treatment and the following drugs: atorvastatin (CYP3A4) and diclofenac (CYP2C9). Therefore, related medicinal product interactions are not expected with dabigatran.

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

Diclofenac: When dabigatran etexilate 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. However, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives >12 hours, close observation for signs of bleeding is recommended (see Precautions, Haemorrhagic risk).

P-glycoprotein inhibitors/inducers

The pro-drug dabigatran etexilate but not dabigatran is a substrate of the efflux transporter P-gp. Therefore, co-administration of dabigatran etexilate and a P-gp inhibitor or inducer may alter the plasma dabigatran concentration. Co-medications with P-gp transporter inhibitors and inducers have been investigated.

<u>Co-medication with P-glycoprotein inhibitors</u>

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors (such as amiodarone, verapamil, quinidine, systemic ketoconazole, dronedarone, ticagrelor and clarithromycin) is expected to result in increased dabigatran plasma concentrations.

Amiodarone: When dabigatran etexilate was coadministered with a single 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 1.6-fold and 1.5-fold (+60% and 50%), respectively. In the population pharmacokinetics study from RE-LY, no important changes in dabigatran trough levels were observed in patients who received amiodarone.

In patients in the RE-LY study concentrations were increased by no more than 14%.

The mechanism of the interaction has not been completely clarified. In view of the long half-life of amiodarone the potential for drug interaction may exist for weeks after discontinuation of amiodarone.

Dronedarone: When dabigatran etexilate and dronedarone were given at the same time total dabigatran $AUC_{0-\infty}$ and C_{max} values increased by about 2.4-fold and 2.3-fold (+136 % and 125%), respectively, after multiple dosing of 400 mg dronedarone bid, and about 2.1-fold and 1.9-fold (+114% and 87%), respectively, after a single dose of 400 mg. The terminal half-life and renal clearance of dabigatran were not affected by dronedarone. When single and multiple doses of dronedarone were given 2 hours after dabigatran etexilate, the increases in dabigatran $AUC_{0-\infty}$ were 1.3-fold and 1.6 fold, 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 2.8-fold (+180%) and AUC by about 2.5-fold (+150%)). The effect was progressively decreased with administration of an extended release formulation (increase of C_{max} by about 1.9-fold (+90%) and AUC by about 1.7-fold (+70%)) or administration of multiple doses of verapamil (increase of C_{max} by about 1.6-fold (+60%) and AUC by about 1.5-fold (+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.

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

In the RE-LY study, patients treated concomitantly with verapamil had on average a 16% higher trough dabigatran plasma concentration and a 20% higher 2 hours post-dose dabigatran plasma concentration only, compared to patients who were not on concomitant verapamil. Accordingly, the annualised bleeding rates in patients who had used verapamil at least once together with warfarin, dabigatran etexilate 110 mg twice daily or 150 mg twice daily were 3.33%, 3.09% and 3.92%, respectively.

In the population pharmacokinetics study from RE-LY, no important changes in dabigatran trough levels were observed in patients who received verapamil.

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

Ketoconazole: Systemic ketoconazole increased total dabigatran $AUC_{0-\infty}$ and C_{max} values by about 2.4-fold (+138% and 135%), respectively, after a single dose of 400 mg, and about 2.5-fold (+153% and 149%), respectively, after multiple dosing of 400 mg ketoconazole once daily.

The time to peak, terminal half-life and mean residence time were not affected by ketoconazole. Concomitant administration of systemic ketoconazole is contraindicated.

Quinidine: Quinidine was given as 200 mg dose every 2nd hour up to a dose of 1000 mg. Dabigatran etexilate was given twice daily over 3 consecutive days, on the 3rd day with or without quinidine. Dabigatran $AUC_{\tau,ss}$ and C_{max},ss were increased on average by about 1.5-fold (+53% and 56%), respectively with concomitant quinidine.

Ticagrelor: When a single dose of 75 mg dabigatran etexilate was coadministered simultaneously with a loading dose of 180 mg ticagrelor, the total dabigatran AUC and C_{max} were increased by 1.73-fold and 1.95-fold (+73% and 95%), respectively. After multiple doses of ticagrelor 90 mg twice daily, and following a single dose of 75 mg dabigatran etexilate, the increase of total dabigatran exposure was reduced to 1.56-fold and 1.46-fold (+56% and 46%) for C_{max} and AUC, respectively.

Concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg dabigatran etexilate (in steady state) increased the dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ by 1.49-fold and 1.65-fold (+49% and 65%), respectively, compared with dabigatran etexilate given alone. When a loading dose of 180 mg ticagrelor was given 2 hours after 110 mg dabigatran etexilate (in steady state), the increase of dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ was reduced to 1.27-fold and 1.23-fold (+27% and 23%), respectively, compared with dabigatran etexilate given alone. This staggered intake is the recommended administration for start of ticagrelor with a loading dose. Concomitant administration of 90 mg ticagrelor BID (maintenance dose) with 110 mg dabigatran etexilate increased the adjusted dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ 1.26-fold and 1.29-fold, respectively, compared with dabigatran etexilate given alone.

Co-medication with P-glycoprotein inducers

Rifampicin: Pre-dosing of the probe inducer rifampicin at a dose of 600 mg once daily 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.

The concomitant use of PRADAXA with P-gp inducers (e.g. rifampicin) reduces exposure to dabigatran and should generally be avoided.

Co-medication with P-glycoprotein substrates

Digoxin: When dabigatran etexilate was coadministered with digoxin, no changes to digoxin plasma levels and no clinically relevant changes to dabigatran exposure have been observed.

Co-medication with platelet inhibitors

Acetylsalicylic acid (ASA, aspirin): 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 randomised 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 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, however, also observed for warfarin (see Precautions, Haemorrhagic risk, Table 15).

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.

NSAIDs increased the risk of bleeding in RE-LY in all treatment groups.

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 $AUC_{\tau,ss}$ 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 monotreatments. With a loading dose of 300 or 600 mg clopidogrel, dabigatran $AUC_{t,ss}$ and $C_{max,ss}$ were increased by about 1.3- to 1.4-fold (+30% to 40%) (see ASA section above).

Antiplatelets or other anticoagulants: The concomitant use of dabigatran etexilate and antiplatelets or other anticoagulants may increase the risk of bleeding. See ASA and Clopidogrel sections above.

Co-medication with selective serotonin re-uptake inhibitors (SSRIs)

SSRIs increased the risk of bleeding in RE-LY in all treatment groups.

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 (PPIs) 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 was 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 not be associated with a higher incidence of stroke or systemic embolism, especially in comparison with warfarin, and hence, the reduced bioavailability by pantoprazole co-administration seemed to be of no clinical relevance. An increased risk of bleeding with PPIs and H2 antagonists was observed for both the dabigatran and warfarin treatment groups (see Precautions, Haemorrhagic risk, Table 15). Patients taking PPIs or H2-blockers may be at increased risk of gastrointestinal bleeding due to the associated gastrointestinal conditions for which these drugs are prescribed.

ADVERSE EFFECTS

The safety of PRADAXA has been evaluated overall in 38,141 patients treated in 11 clinical trials; thereof 23,393 PRADAXA patients were investigated.

In the primary VTE prevention trials after major orthopaedic surgery a total of 10,795 patients were treated in 6 controlled studies with at least one dose of dabigatran etexilate (150 mg qd, 220 mg qd) or enoxaparin. 6,684 of the 10,795 patients were treated with 150 or 220 mg once daily of dabigatran etexilate.

In the RE-LY trial investigating the prevention of stroke and systemic embolism in patients with atrial fibrillation a total of 12,042 patients were treated with dabigatran etexilate. Of these 6,059 were treated with 150 mg twice daily of dabigatran etexilate, while 5,983 received doses of 110 mg twice daily.

In the acute DVT/PE treatment trials (RE-COVER, RE-COVER II) a total of 2,553 patients were included in the safety analysis for dabigatran etexilate. All patients were treated with dabigatran etexilate 150 mg twice daily.

In the recurrent DVT/PE prevention trials (RE-MEDY, RE-SONATE) a total of 2,114 patients were treated with dabigatran etexilate. Of these, 552 were rolled over from the RE-COVER trial (acute DVT/PE treatment) into the RE-MEDY trial and are counted in both the acute and recurrent patient totals. All patients were treated with dabigatran etexilate 150 mg twice daily.

In total, about 9% of patients treated for elective hip or knee surgery (short-term treatment for up to 42 days), 22% of patients with atrial fibrillation treated for the prevention of stroke and systemic embolism (long-term treatment for up to 3 years), 14% of patients treated for acute DVT/PE treatment (long-term treatment up to 6 months) and 15% of patients treated for recurrent DVT/PE prevention (long-term treatment up to 36 months) experienced adverse reactions.

Bleeding

Bleeding is the most relevant side effect of PRADAXA. Depending on the indication treated, bleeding of any type or severity occurred in approximately 14% of patients treated short-term for elective hip or knee replacement surgery, in 16.6% yearly of AF patients treated long-term for the prevention of stroke and systemic embolism and in 14.4% of patients with acute DVT and/or PE. In the recurrent DVT/PE trial RE-MEDY 19.4% and in the RE-SONATE trial 10.5% of patients experienced any bleeding.

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.

Prevention of venous thromboembolic events (VTE) in adult patients who have undergone major orthopaedic surgery

A total of 10,795 patients were treated in 6 controlled VTE prevention trials with at least one dose of dabigatran etexilate (150 mg qd, 220 mg qd) or enoxaparin. 6,684 of the 10,795 patients were treated with 150 or 220 mg daily of dabigatran etexilate.

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 International Society on Thrombosis and Haemostasis (ISTH) 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 17 below.

Table 17 shows the number (%) of patients experiencing major and total bleeding event rates during the treatment period in the VTE prevention randomised clinical trials, according to dose.

Table 17: Bleeding broken down to randomisation procedure, severity and dosage of dabigatran etexilate and enoxaparin

Pre-operative randomisation trials			
	DE 150 mg qd N (%)	DE 220 mg qd N (%)	Enoxaparin 40 mg N (%)
Pooled data BISTRO II, RE-MODEL, RE-NOVATE, RE_NOVATE II trials (1160.19, 1160.25, 1160.48, 1160.64)			
Treated	1866 (100.0)	2835 (100.0)	3243 (100.0)
Major Bleeding	24 (1.3)	47 (1.7)	44 (1.4)
Any bleeding	258 (13.8)	349 (12.3)	373 (11.5)
Pooled data from hip and knee studies, RE-MODEL and RE-NOVATE trials (1160.25, 1160.48)			
Treated	1866 (100.0)	1825 (100.0)	1848 (100.0)
Major Bleeding	24 (1.3)	33 (1.8)	27 (1.5)
Any bleeding	258 (13.8)	251 (13.8)	247 (13.4)
Post-operative randomised trials			
RE-MOBILIZE trial (1160.24)			
	DE 150 mg qd N (%)	DE 220 mg qd N (%)	Enoxaparin 60 mg N (%)
Treated	871 (100.0)	857 (100.0)	868 (100.0)
Major Bleeding	5 (0.6)	5 (0.6)	12 (1.4)
Any bleeding	72 (8.3)	74 (8.6)	84 (9.7)
Japanese knee study (1160.50)			
	150 mg qd N (%)	220 mg qd N (%)	Placebo N (%)
Treated	126 (100.0)	129 (100.0)	124 (100.0)
Major Bleeding	0 (0.0)	3 (2.3)	1 (0.8)
Any bleeding	13 (10.3)	14 (10.9)	10 (8.1)
Pooled data RE-MOBILIZE and Japanese knee study (1160.24, and 1160.50)			
	150 mg qd N (%)	220 mg qd N (%)	Enoxaparin 60 mg* N (%)
Treated	997 (100.0)	986 (100.0)	868 (100.0)
Major Bleeding	5 (0.5)	8 (0.8)	12 (1.4)
Any bleeding	85 (8.5)	88 (8.9)	84 (9.7)

*Bleeding data for Enoxaparin 60 mg is from RE-MOBILIZE study (1160.24)

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

Adverse events classified by System Organ Class (SOC) and preferred terms reported ≥1% from any treatment group of all 6 controlled VTE prevention studies are shown in the table below.

Table 18: Adverse events reported in at least 2% of subjects in dabigatran etexilate arms

System Organ Class / Preferred Term.	Dabigatran etexilate 150 mg qd N (%)	Dabigatran etexilate 220 mg qd N (%)	Enoxaparin N (%)
Numbers of subjects	2863 (100.0)	3821 (100.0)	4111 (100.0)
Blood and lymphatic system disorders			
Anaemia	113 (4.0)	153 (4.0)	172 (4.2)
Gastrointestinal disorders			
Constipation	482 (16.8)	559 (14.6)	608 (14.8)
Diarrhoea	131 (4.6)	137 (3.6)	131 (3.2)
Dyspepsia	64 (2.2)	85 (2.2)	84 (2.0)
Nausea	602 (21.0)	736 (19.3)	930 (22.6)
Vomiting	411 (14.4)	526 (13.8)	571 (13.9)
General disorders and administration site conditions			
Oedema peripheral	419 (14.6)	390 (10.2)	421 (10.2)
Pyrexia	368 (12.9)	399 (10.4)	504 (12.3)
Infections and infestations			
Urinary tract infection	65 (2.3)	77 (2.0)	95 (2.3)
Injury, poisoning and procedural complications			
Anaemia post-operative	99 (3.5)	103 (2.7)	139 (3.4)
Post-procedural haematoma	66 (2.3)	47 (1.2)	83 (2.0)
Post procedural oedema	79 (2.8)	76 (2.0)	67 (1.6)
Procedural pain	162 (5.7)	162 (4.2)	157 (3.8)
Wound complication	69 (2.4)	77 (2.0)	80 (2.0)
Wound secretion	132 (4.6)	157 (4.1)	103 (2.5)
Investigations			
Body temperature increased	100 (3.5)	113 (3.0)	109 (2.7)
Haemoglobin decreased	45 (1.6)	94 (2.5)	136 (3.3)
Metabolism and nutrition disorders			
Hypokalaemia	69 (2.4)	86 (2.3)	75 (1.8)
Musculoskeletal and connective tissue disorders			
Arthralgia	79 (2.8)	66 (1.7)	93 (2.3)
Muscle spasms	67 (2.3)	58 (1.5)	79 (1.9)
Pain in extremity	103 (3.6)	118 (3.1)	141 (3.4)
Nervous system disorders			
Dizziness	118 (4.1)	163 (4.3)	198 (4.8)
Headache	102 (3.6)	128 (3.4)	123 (3.0)
Psychiatric disorders			
Insomnia	272 (9.5)	297 (7.8)	352 (8. 6)
Renal and urinary disorders			
Urinary retention	123 (4.3)	173 (4.5)	173 (4.2)
Skin and subcutaneous tissue disorders			
Blister	111 (3.9)	113 (3.0)	103 (2.5)
Erythema	76 (2.7)	73 (1.9)	69 (1.7)
Pruritus	65 (2.3)	94 (2.5)	112 (2.7)
Rash	67 (2.3)	66 (1.7)	72 (1.8)
Vascular disorders			
Deep vein thrombosis	287 (10.0)	246 (6.4)	272 (6.6)
Hypotension	140 (4.9)	180 (4.7)	216 (5.3)

Adverse reactions observed with exposure to dabigatran etexilate 150 mg daily and 220 mg daily from all 6 controlled VTE prevention studies are listed below by system organ class and frequency according to the following categories:

Common ≥1% and <10%, Uncommon ≥0.1% and <1%, Rare ≥0.01% and <0.1%

Blood and lymphatic system disorders

Uncommon: anaemia

Rare: thrombocytopenia

Immune system disorders

Uncommon: drug hypersensitivity (including drug hypersensitivity, pruritus, rash, urticaria, bronchospasm)

Rare: angioedema

Not known: anaphylactic reaction

Nervous system disorders

Rare: intracranial haemorrhage

Vascular disorders

Uncommon: haematoma, wound haemorrhage

Rare: haemorrhage, bloody discharge

Respiratory, thoracic and mediastinal disorders

Uncommon: epistaxis

Rare: haemoptysis

Gastrointestinal disorders

Uncommon: gastrointestinal haemorrhage, diarrhoea, nausea, vomiting

Rare: abdominal pain, dyspepsia, dysphagia, gastrointestinal ulcer, gastrooesophagitis, gastrooesophageal reflux disease

Hepatobiliary disorders

Common: hepatic function abnormal

Skin and subcutaneous tissue disorders

Uncommon: skin haemorrhage

Musculoskeletal, connective tissue and bone disorders

Uncommon: haemarthrosis

Renal and urinary disorders

Uncommon: urogenital haemorrhage, haematuria

General disorders and administration site conditions

Rare: injection site haemorrhage, catheter site haemorrhage

Injury, poisoning and procedural complications

Uncommon: traumatic haemorrhage, post procedural haematoma, post procedural haemorrhage, wound secretion

Rare: incision site haemorrhage, anaemia postoperative, post procedural discharge

Surgical and medical procedures

Rare: wound drainage, post procedural drainage

Table 19: Beyond the reported ALT findings the following laboratory chemistry data had been measured in phase III controlled VTE prevention studies.

	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Numbers of patients	2737 (100)	2682 (100)	3108 (100)
Alaninine aminotransferase increased 3 x ULN	68 (2.5)	58 (2.2)	95 (3.5)

The pattern of adverse events for RE-NOVATE II (1160.64) was similar to RE-NOVATE (1160.48).

For RE-NOVATE II (1160.64), the incidence of MBEs was 1.4% for patients in the dabigatran etexilate 220 mg group and 0.9% for patients in the enoxaparin 40 mg group (p=0.4022). For any bleeding event the incidence was 9.7% for patients in the dabigatran group compared with 8.3% for patients in the enoxaparin group (p=0.2626). In both treatment groups most elevated LFTs occurred in the immediate post-operative period, during the first 10 days of treatment with trial medication, and most were transient. The estimated cumulative incidence of an ALT value >3 x ULN from surgery up to Day 10 was 3.1% for dabigatran patients and to the end of the trial it was 3.6%. Corresponding figures for enoxaparin showed a slightly higher cumulative incidence: 5.0% to Day 10 and 5.4% to the end of the trial. ALT elevations >10 x ULN were higher for dabigatran patients (0.4%) than enoxaparin patients (0.1%). Three patients (all dabigatran group) had alanine transaminase (ALT) elevations above 3 x the upper limit of the normal range (ULN) in combination with elevated bilirubin values above 2 x ULN. In two of these three patients alternative explanations (viral hepatitis) were reported.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

Two doses (110 mg and 150 mg twice daily) of dabigatran etexilate were compared to warfarin in the RE-LY study (Randomised Evaluation of Long - term anticoagulant therapy), the Phase III trial in the prevention of thromboembolic stroke and systemic embolism for safety in more than 18,000 atrial fibrillation patients with a median duration of 20 months.

Drug Discontinuation

Over the course of the trial, the total number of patients with adverse events leading to treatment discontinuation was 19% for dabigatran etexilate 110 mg, 20.5% for dabigatran etexilate 150 mg and 15.6% for warfarin. The most frequent adverse events leading to discontinuation were gastrointestinal events.

Bleeding Definitions

In the RE-LY study, bleeding was classified as major using the following guidelines.

Major bleeding fulfilled one or more of the following criteria:

- Bleeding associated with a reduction in haemoglobin of at least 20 grams per litre 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 haemoglobin of at least 50 grams per litre; 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.

Bleeding

Table 20 shows the number of patients experiencing major and total bleeding event rates during the treatment period in the RE-LY study, with the yearly bleeding rate in (%). Both dabigatran etexilate doses were associated with a lower yearly event rate for life-threatening bleeds, intracranial haemorrhage and any bleeds as compared with warfarin treatment. Subjects randomised to dabigatran etexilate 110 mg twice daily had a significantly lower risk for major bleeds compared with warfarin (hazard ratio 0.81 [p=0.0027]).

In Table 20, the category of major bleeds includes both life-threatening and non-life threatening bleeds. Within life-threatening, intracranial bleeds are a subcategory of life-threatening bleeds. Intracranial bleeds include intracerebral (haemorrhagic stroke), subarachnoid and subdural bleeds. For this reason, these events may be counted in multiple categories.

Table 20: Frequency and yearly event rate (%) of major and other bleeding events in RE-LY.

	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Number of subjects	6015	6076	6022
Subject-years	11899	12033	11794
Major bleeds*	347 (2.92)	409 (3.40)	426 (3.61)
Hazard ratio vs. warfarin (95% CI)	0.81 (0.70, 0.93)	0.94 (0.82, 1.08)	
p-value	0.0027	0.4070	
Life threatening MBEs	151 (1.27)	183 (1.52)	221 (1.87)
Hazard ratio vs. warfarin (95% CI)	0.68 (0.55, 0.83)	0.81 (0.67, 0.99)	
p-value	0.0002	0.0357	
ICH+	27 (0.23)	39 (0.32)	91 (0.77)
Hazard ratio vs. warfarin (95% CI)	0.29 (0.19, 0.45)	0.42 (0.29, 0.61)	
p-value	<0.0001	<0.0001	
Any bleeds#	1759 (14.78)	1997 (16.60)	2169 (18.39)
Hazard ratio vs. warfarin (95% CI)	0.78 (0.74, 0.83)	0.91 (0.85, 0.96)	
p-value	<0.0001	0.0017	

*Adjudicated Bleeds
+ICH consists of adjudicated haemorrhagic stroke and subdural and/or subarachnoid haemorrhage.
Investigator-reported bleeding events

Table 21: Frequency and yearly event rate (%) of major, life-threatening and any gastrointestinal bleeding in RE-LY.

	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Number of subjects	6015	6076	6022
Major GI bleeds	134 (1.13)	192 (1.60)	128 (1.09)
Hazard ratio vs. warfarin (95% CI)	1.04 (0.82, 1.33)	1.48 (1.19, 1.86)	
GI life-threatening bleeds	67 (0.56)	97 (0.81)	58 (0.49)
Hazard ratio vs. warfarin (95% CI)	1.15 (0.81, 1.63)	1.65 (1.19, 2.28)	
Any GI bleeds	600 (5.04)	684 (5.68)	454 (3.85)
Hazard ratio vs. warfarin (95% CI)	1.34 (1.19, 1.52)	1.52 (1.35, 1.72)	

The risk of major bleeding with dabigatran etexilate 110 mg and 150 mg was consistent across all major subgroups of baseline characteristics with the exception of age. There was a higher risk of bleeding with dabigatran etexilate 150 mg in patients ≥75 years of age (hazard ratio vs. warfarin (95% CI) 1.19 (0.99, 1.43)).

GI/dyspepsia

Dabigatran etexilate subjects had the highest incidence of GI AEs (34.6%, 34.5%, and 24.0% for dabigatran etexilate 110 mg, dabigatran etexilate 150 mg, and warfarin, respectively). Additional GI events that were reported more frequently with dabigatran etexilate treatment included upper abdominal pain, gastritis, abdominal discomfort, gastroesophageal reflux disease, dysphagia, and flatulence (Table 22). There was no consistent dose-response relationship with respect to GI AEs.

Table 22: Number (%) of subjects with dyspepsia and gastritis-like symptoms (safety set) in RE-LY.

Preferred term/investigator term	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Number of subjects	5983	6059	5998
Total with dyspepsia/gastritis	983 (16.4)	940 (15.5)	470 (7.8)
Dyspepsia*	761 (12.7)	738 (12.2)	354 (5.9)
Gastritis-like symptoms#**	297 (5.0)	257 (4.2)	142 (2.4)

Percentages were calculated using total number of subjects per treatment as the denominator.
*Dyspepsia includes dyspepsia, abdominal pain upper, abdominal pain, abdominal discomfort, epigastric discomfort
**Gastritis-like symptoms includes gastritis, GERD, oesophagitis, gastritis erosive, gastric haemorrhage, gastritis haemorrhagic, haemorrhagic erosive gastritis
Represents a composite of sponsor-identified AEs (preferred terms) that were similar and likely reporting the same subject.

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 (Table 23).

Table 23: Summary of abnormal liver function tests, Number (%) of subjects (safety set) in RE-LY.

	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Total treated	5983	6059	5998
ALT or AST > 3xULN	118 (2.0)	106 (1.7)	125 (2.1)
ALT or AST > 5xULN	36 (0.6)	45 (0.7)	50 (0.8)
ALT or AST > 3xULN + Bilirubin >2xULN	11 (0.2)	14 (0.2)	21 (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.

Myocardial Infarction

There was an increased frequency in myocardial infarction events in subjects treated with dabigatran etexilate compared to warfarin treated subjects which was not statistically significant (yearly event rate: 150 mg twice daily 0.81%, 110 mg twice daily 0.82%, warfarin 0.64%) (see Precautions).

Overview of adverse events from RE-LY

The incidence of AEs was similar between subjects treated with dabigatran etexilate 110 mg twice daily and dabigatran etexilate 150 mg twice daily (78.6% and 78.3%, respectively) versus 75.9% of subjects treated with warfarin. The incidence of SAEs was similar across treatment groups. However, dabigatran etexilate subjects had a lower incidence of fatal AEs, life-threatening AEs, and events that required hospitalisation as compared to warfarin subjects.

Adverse events classified by system organ class and preferred terms reported ≥2% from any treatment group of the RE-LY study are shown in Table 24 below. Diarrhoea, dyspepsia, and nausea were the most frequently reported GI AEs, all of which were reported at a higher frequency with dabigatran etexilate 110 mg and dabigatran etexilate 150 mg treatment, particularly for dyspepsia (6.2%, 5.7%, and 1.4% for dabigatran etexilate 110 mg, dabigatran etexilate 150 mg, and warfarin, respectively).

Table 24: Adverse events reported in at least 2.0% of subjects in dabigatran etexilate arms (safety set).

System organ class/ Preferred term	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Number of subjects	5983 (100.0)	6059 (100.0)	5998 (100.0)
Infections and infestations			
Nasopharyngitis	315 (5.3)	309 (5.1)	327 (5.5)
Urinary tract infection	242 (4.0)	252 (4.2)	316 (5.3)
Upper respiratory tract infection	266 (4.4)	262 (4.3)	297 (5.0)
Bronchitis	262 (4.4)	277 (4.6)	285 (4.8)
Pneumonia	226 (3.8)	219 (3.6)	236 (3.9)
Influenza	138 (2.3)	144 (2.4)	132 (2.2)
Sinusitis	80 (1.3)	98 (1.6)	120 (2.0)
Blood and lymphatic system disorders			
Anaemia	181 (3.0)	207 (3.4)	165 (2.8)
Metabolism and nutrition disorders			
Gout	125 (2.1)	116 (1.9)	162 (2.7)
Nervous system disorders			
Dizziness	457 (7.6)	458 (7.6)	554 (9.2)
Headache	253 (4.2)	236 (3.9)	242 (4.0)
Syncope	155 (2.6)	150 (2.5)	155 (2.6)
Cardiac disorders			
Atrial fibrillation	303 (5.1)	313 (5.2)	327 (5.5)
Cardiac failure congestive	196 (3.3)	187 (3.1)	210 (3.5)
Cardiac failure	169 (2.8)	171 (2.8)	201 (3.4)
Palpitations	141 (2.4)	138 (2.3)	162 (2.7)
Angina pectoris	124 (2.1)	113 (1.9)	125 (2.1)
Vascular disorders			
Hypertension	253 (4.2)	234 (3.9)	266 (4.4)
Hypotension	120 (2.0)	127 (2.1)	130 (2.2)
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	498 (8.3)	526 (8.7)	551 (9.2)
Cough	320 (5.3)	310 (5.1)	346 (5.8)
Epistaxis	109 (1.8)	127 (2.1)	178 (3.0)
Dyspnoea exertional	110 (1.8)	120 (2.0)	116 (1.9)
Gastrointestinal disorders			
Dyspepsia	368 (6.2)	345 (5.7)	83 (1.4)
Diarrhoea	355 (5.9)	367 (6.1)	328 (5.5)
Nausea	245 (4.1)	259 (4.3)	208 (3.5)
Constipation	188 (3.1)	177 (2.9)	167 (2.8)
Abdominal pain upper	177 (3.0)	170 (2.8)	80 (1.3)
Gastritis	147 (2.5)	127 (2.1)	87 (1.5)
Abdominal pain	130 (2.2)	137 (2.3)	141 (2.4)
Vomiting	132 (2.2)	124 (2.0)	117 (2.0)
Abdominal discomfort	119 (2.0)	112 (1.8)	64 (1.1)
Gastrooesophageal reflux disease	117 (2.0)	99 (1.6)	46 (0.8)
Skin and subcutaneous tissue disorders			
Rash	114 (1.9)	142 (2.3)	159 (2.7)

System organ class/ Preferred term	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Musculoskeletal and connective tissue disorders			
Arthralgia	248 (4.1)	313 (5.2)	329 (5.5)
Back pain	295 (4.9)	289 (4.8)	331 (5.5)
Pain in extremity	227 (3.8)	228 (3.8)	212 (3.5)
Osteoarthritis	129 (2.2)	140 (2.3)	142 (2.4)
Musculoskeletal pain	120 (2.0)	121 (2.0)	116 (1.9)
General disorders and administration site conditions			
Oedema peripheral	446 (7.5)	442 (7.3)	453 (7.6)
Fatigue	370 (6.2)	367 (6.1)	353 (5.9)
Chest pain	287 (4.8)	355 (5.9)	342 (5.7)
Asthenia	165 (2.8)	157 (2.6)	161 (2.7)
Chest discomfort	129 (2.2)	110 (1.8)	88 (1.5)
Injury, poisoning and procedural complications			
Fall	183 (3.1)	178 (2.9)	234 (3.9)
Contusion	149 (2.5)	152 (2.5)	197 (3.3)

Percentages were calculated using total number of subjects per treatment as the denominator.

Adverse reactions observed with exposure to dabigatran 110 mg twice daily and 150 mg twice daily during the RELY trial are listed below by system organ class and frequency according to the following categories:

Common ≥1% and <10%, Uncommon ≥0.1% and <1%, Rare ≥0.01% and <0.1%

Blood and lymphatic system disorders

Common: anaemia

Uncommon: thrombocytopenia

Immune system disorders

Uncommon: drug hypersensitivity (including drug hypersensitivity, pruritus, rash, urticaria, bronchospasm)

Rare: angioedema

Not known: anaphylactic reaction

Nervous system disorders

Uncommon: intracranial haemorrhage

Vascular disorders

Uncommon: haematoma, haemorrhage

Respiratory, thoracic and mediastinal disorders

Common: epistaxis

Uncommon: haemoptysis

Gastrointestinal disorders

Common: gastrointestinal haemorrhage, abdominal pain, diarrhoea, dyspepsia, nausea

Uncommon: dysphagia, gastrointestinal ulcer, gastrooesophagitis, gastrooesophageal reflux disease, vomiting

Hepatobiliary disorders

Uncommon: hepatic function abnormal

Skin and subcutaneous tissue disorders

Common: skin haemorrhage

Musculoskeletal and connective tissue disorders

Rare: haemarthrosis

Renal and urinary disorders

Common: urogenital haemorrhage, haematuria

General disorders and administration site conditions

Rare: catheter site haemorrhage, injection site haemorrhage

Injury, poisoning and procedural complications

Rare: traumatic haemorrhage, incision site haemorrhage

Treatment of, and prevention of recurrent, deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in adults

Bleeding

Table 25 shows bleeding events in the pooled pivotal studies RE-COVER and RE-COVER II testing the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Table 25: Frequency and yearly event rate (%) of bleeding events in the pooled pivotal studies RE-COVER and RE-COVER II

	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)	Hazard ratio vs. warfarin (95% CI)
Patients included in safety analysis	2,456	2,462	
Major bleeding events	24 (1.0 %)	40 (1.6 %)	0.60 (0.36, 0.99)
Intracranial Bleeding	2 (0.1 %)	4 (0.2 %)	0.50 (0.09, 2.74)
Major GI bleeding	10 (0.4 %)	12 (0.5 %)	0.83 (0.36, 1.93)
Life-threatening bleed	4 (0.2 %)	6 (0.2 %)	0.66 (0.19, 2.36)
Major bleeding event/clinically relevant bleeds	109 (4.4 %)	189 (7.7 %)	0.56 (0.45, 0.71)
Any bleeding	354 (14.4 %)	503 (20.4 %)	0.67 (0.59, 0.77)
Any GI bleeding	70 (2.9 %)	55 (2.2 %)	1.27 (0.90, 1.82)

Bleeding events for both treatments are counted from the first intake of dabigatran etexilate or warfarin after the parenteral therapy has been discontinued (oral only treatment period). This includes all bleeding events which occurred during dabigatran therapy. All bleeding events which occurred during warfarin therapy are included except for those during the overlap period between warfarin and parenteral therapy.

The definition of major bleeding events (MBEs) followed the recommendations of the International Society on Thrombosis and Haemostasis. A bleeding event was categorised as an MBE if it fulfilled at least one of the following criteria:

- Fatal bleeding.

- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial, or intramuscular with compartment syndrome. In order for bleeding in a critical area or organ to be classified as an MBE it had to be associated with a symptomatic clinical presentation.
- Bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or red cells.

Table 26 shows bleeding events in pivotal study RE-MEDY testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Table 26: Frequency and yearly event rate (%) of bleeding events in pivotal study RE-MEDY

	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)	Hazard ratio vs. warfarin (95% CI)
Treated patients	1,430	1,426	
Major bleeding events	13 (0.9 %)	25 (1.8 %)	0.54 (0.25, 1.16)
Intracranial Bleeding	2 (0.1 %)	4 (0.3 %)	Not calculable*
Major GI bleeding	4 (0.3%)	8 (0.5%)	Not calculable*
Life-threatening bleed	1 (0.1 %)	3 (0.2 %))	Not calculable*
Major bleeding event/clinically relevant bleeds	80 (5.6 %)	145 (10.2 %)	0.55 (0.41, 0.72)
Any bleeding	278 (19.4 %)	373 (26.2 %)	0.71 (0.61, 0.83)
Any GI bleeding	45 (3.1%)	32 (2.2%)	1.39 (0.87, 2.20)

*HR not estimable as there is no event in either one cohort/treatment

The definition of MBEs followed the recommendations of the International Society on Thrombosis and Haemostasis as described under RE-COVER and RE-COVER II.

Table 27 shows bleeding events in pivotal study RE-SONATE testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE). The rate of the combination of MBEs/CRBEs and the rate of any bleeding was significantly lower at a nominal alpha level of 5 % in patients receiving placebo as compared with those receiving dabigatran etexilate.

Table 27: Frequency and yearly event rate (%) of bleeding events in pivotal study RE-SONATE

	Dabigatran etexilate 150 mg twice daily N (%)	Placebo N (%)	Hazard ratio vs. placebo (95% CI)
Treated patients	684	659	
Major bleeding events	2 (0.3 %)	0	Not calculable*
Intracranial Bleeding	0	0	Not calculable*
Major GI bleeding	2 (0.3%)	0	Not calculable*
Life-threatening bleed	0	0	Not calculable*
Major bleeding event/clinically relevant bleeds	36 (5.3 %)	13 (2.0 %)	2.69 (1.43, 5.07)
Any bleeding	72 (10.5 %)	40 (6.1 %)	1.77 (1.20, 2.61)
Any GI bleeding	5 (0.7%)	2 (0.3%)	2.38 (0.46, 12.27)

*HR not estimable as there is no event in either one cohort/treatment

The definition of MBEs followed the recommendations of the International Society on Thrombosis and Haemostasis as described under RE-COVER and RE-COVER II.

Liver Function Tests

There were no important differences in median ALT, AST, total bilirubin, and alkalinephosphatase (ALP) values in the dabigatran etexilate group compared with the warfarin or placebo groups.

Table 28: Summary of abnormal liver function tests, Number (%) of subjects (safety set) in RE-COVER and RE-COVER II

	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Numbers of patients	2552	2554
ALT or AST increased 3 x ULN	90 (3.53)	94 (3.68)

Table 29: Summary of abnormal liver function tests, Number (%) of subjects (safety set) in RE-MEDY and RE-SONATE

	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)	Placebo N (%)
Numbers of patients	2114	1426	659
ALT or AST increased 3 x ULN	34 (1.61)	31 (2.17)	5 (0.76)

Myocardial Infarction

In the three active controlled studies, a higher rate of MI was reported in patients who received dabigatran etexilate than in those who received warfarin: 0.4% vs. 0.2% in the short-term RECOVER and RECOVER II studies; and 0.8% vs. 0.1% in the long-term RE-MEDY trial. The increase was statistically significant in this study (p=0.022).

In the RE-SONATE study, which compared dabigatran etexilate to placebo, the rate of MI was 0.1 % for patients who received dabigatran etexilate and 0.2 % for patients who received placebo (see Precautions).

Overview of adverse events from RE-COVER and RE-COVER II

In well controlled clinical trials the incidences of adverse events of PRADAXA vs. warfarin were: RE-COVER 66 vs. 68%, RE-COVER-II 67 vs. 71 %. Adverse events classified by SOC and preferred terms reported ≥2% from any treatment group of the RE-COVER trials are shown in Table 30 below.

Table 30: Frequency of patients with treatment emergent AEs with incidence ≥2% by treatment, primary SOC and preferred term for acute VTE treatment studies - (oral only treatment)

System organ class/ Preferred term	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Number of subjects	2456 (100.0)	2462 (100.0)
Infections and infestations		
Nasopharyngitis	87 (3.5)	95 (3.9)
Urinary tract infection	48 (2.0)	53 (2.2)
Nervous system disorders		
Headache	96 (3.9)	114 (4.6)
Dizziness	63 (2.6)	61 (2.5)
Vascular disorders		
Hypertension	45 (1.8)	56 (2.3)
Haematoma	30 (1.2)	52 (2.1)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	58 (2.4)	122 (5.0)
Dyspnoea	60 (2.4)	87 (3.5)
Cough	52 (2.1)	42 (1.7)
Gastrointestinal disorders		
Diarrhoea	82 (3.3)	69 (2.8)
Nausea	76 (3.1)	78 (3.2)
Dyspepsia	71 (2.9)	16 (0.6)
Rectal haemorrhage	63 (2.6)	33 (1.3)
Constipation	26 (1.1)	53 (2.2)
Vomiting	40 (1.6)	52 (2.1)
Gingival bleeding	23 (0.9)	49 (2.0)
Skin and subcutaneous tissue disorders		
Rash	44 (1.8)	54 (2.2)
Musculoskeletal and connective tissue disorders		
Pain in extremity	133 (5.4)	129 (5.2)
Back pain	82 (3.3)	90 (3.7)
Arthralgia	86 (3.5)	66 (2.7)
Renal and urinary disorders		
Haematuria	36 (1.5)	77 (3.1)
General disorders and administration site conditions		
Oedema peripheral	91 (3.7)	82 (3.3)
Chest pain	69 (2.8)	71 (2.9)
Fatigue	43 (1.8)	53 (2.2)
Injury, poisoning and procedural complications		
Contusion	45 (1.8)	72 (2.9)

The overall frequency of adverse reactions in patients receiving PRADAXA for acute DVT/PE treatment was lower for PRADAXA compared to warfarin (14.2% vs. 18.9%).

Adverse reactions (<2%) observed with exposure to dabigatran 150 mg twice daily during the RE-COVER trials are listed below by system organ class and frequency according to the following categories:

Common ≥1% and <10%, Uncommon ≥0.1% and <1%, Rare ≥0.01% and <0.1%

<u>Blood and lymphatic system disorders</u>

Uncommon: anaemia

Rare: thrombocytopenia

Immune system disorders

Uncommon: drug hypersensitivity (including drug hypersensitivity, pruritus, rash, urticaria, bronchospasm)

Rare: angioedema

Nervous system disorders

Rare: intracranial haemorrhage

Vascular disorders

Uncommon: haematoma, haemorrhage

Respiratory, thoracic and mediastinal disorders

Uncommon: haemoptysis

Gastrointestinal disorders

Common: gastrointestinal haemorrhage

Uncommon: abdominal pain, gastrointestinal ulcer, gastrooesophagitis, gastrooesophageal reflux disease

Rare: dysphagia

Hepatobiliary disorders

Uncommon: hepatic function abnormal

Skin and subcutaneous tissue disorders

Common: skin haemorrhage

Musculoskeletal and connective tissue disorders

Uncommon: haemarthrosis

Renal and urinary disorders

Common: urogenital haemorrhage

General disorders and administration site conditions

Rare: injection site haemorrhage, catheter site haemorrhage

Injury, poisoning and procedural complications

Uncommon: traumatic haemorrhage

Rare: incision site haemorrhage

Overview of adverse events from RE-MEDY and RE-SONATE

In well controlled clinical trials the incidences of adverse events of PRADAXA vs. warfarin were: RE-SONATE 51 vs. 49%, RE-MEDY 72 vs. 71 %. Adverse events classified by SOC and preferred terms reported ≥2% from any treatment group of the RE-MEDY and RE-SONATE trials are shown in Table 31 below.

Table 31: Frequency of patients with treatment emergent AEs with incidence ≥2% by treatment, primary SOC and preferred term for secondary VTE prevention studies - treated set

System organ class/ Preferred term	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)	Placebo N (%)
Number of subjects	2114 (100.0)	1426 (100.0)	659 (100.0)
Infections and infestations			
Nasopharyngitis	129 (6.1)	127 (8.9)	18 (2.7)
Influenza	86 (4.1)	67 (4.7)	5 (0.8)
Bronchitis	58 (2.7)	62 (4.3)	7 (1.1)
Upper respiratory tract infection	47 (2.2)	50 (3.5)	13 (2.0)
Urinary tract infection	45 (2.1)	41 (2.9)	8 (1.2)
Sinusitis	34 (1.6)	31 (2.2)	3 (0.5)
Psychiatric disorders			
Insomnia	23 (1.1)	28 (2.0)	4 (0.6)
Nervous system disorders			
Headache	107 (5.1)	101 (7.1)	20 (3.0)
Dizziness	46 (2.2)	50 (3.5)	9 (1.4)
Vascular disorders			
Deep vein thrombosis	19 (0.9)	19 (1.3)	35 (5.3)
Haematoma	35 (1.7)	50 (3.5)	3 (0.5)
Hypertension	75 (3.5)	46 (3.2)	15 (2.3)
Respiratory, thoracic and mediastinal disorders			
Epistaxis	56 (2.6)	95 (6.7)	6 (0.9)
Cough	60 (2.8)	54 (3.8)	6 (0.9)
Pulmonary embolism	11 (0.5)	3 (0.2)	21 (3.2)
Dyspnoea	56 (2.6)	42 (2.9)	11 (1.7)
Gastrointestinal disorders			
Diarrhoea	88 (4.2)	53 (3.7)	9 (1.4)
Dyspepsia	86 (4.1)	27 (1.9)	8 (1.2)
Nausea	48 (2.3)	48 (3.4)	10 (1.5)
Gingival bleeding	30 (1.4)	42 (2.9)	3 (0.5)
Abdominal pain	29 (1.4)	34 (2.4)	2 (0.3)
Rectal haemorrhage	49 (2.3)	22 (1.5)	2 (0.3)
Abdominal pain upper	44 (2.1)	20 (1.4)	8 (1.2)
Skin and subcutaneous tissue disorders			
Rash	32 (1.5)	30 (2.1)	8 (1.2)
Musculoskeletal and connective tissue disorders			
Pain in extremity	133 (6.3)	111 (7.8)	24 (3.6)
Back pain	89 (4.2)	71 (5.0)	10 (1.5)
Arthralgia	79 (3.7)	68 (4.8)	11 (1.7)
Muscle spasms	54 (2.6)	48 (3.4)	7 (1.1)
Musculoskeletal pain	31 (1.5)	33 (2.3)	4 (0.6)
Renal and urinary disorders			
Haematuria	38 (1.8)	49 (3.4)	3 (0.5)
General disorders and administration site conditions			
Oedema peripheral	93 (4.4)	72 (5.0)	14 (2.1)
Chest pain	54 (2.6)	48 (3.4)	11 (1.7)
Fatigue	39 (1.8)	42 (2.9)	7 (1.1)
Investigations			
International normalised ratio	4 (0.2)	41 (2.9)	0 (0.0)

System organ class/ Preferred term	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)	Placebo N (%)
increased			
Injury, poisoning and procedural complications			
Contusion	62 (2.9)	71 (5.0)	3 (0.5)
Fall	35 (1.7)	31 (2.2)	6 (0.9)

The overall frequency of adverse reactions in patients treated for recurrent DVT/PE prevention was lower for PRADAXA compared to warfarin (14.6% vs. 19.6%); compared to placebo the frequency was higher (14.6% vs. 6.5%).

Adverse reactions (<2%) observed with exposure to dabigatran 150 mg twice daily during the RE-MEDY and RE-SONATE trials are listed below by system organ class and frequency according to the following categories:

Common ≥1% and <10%, Uncommon ≥0.1% and <1%, Rare ≥0.01% and <0.1%

Blood and lymphatic system disorders

Rare: anaemia, thrombocytopenia

Immune system disorders

Uncommon: drug hypersensitivity (including drug hypersensitivity, pruritus, rash, urticaria, bronchospasm)

Rare: angioedema

Nervous system disorders

Rare: intracranial haemorrhage

Vascular disorders

Uncommon: haematoma, haemorrhage

Respiratory, thoracic and mediastinal disorders

Uncommon: haemoptysis

Gastrointestinal disorders

Common: gastrointestinal haemorrhage

Uncommon: abdominal pain, gastrooesophagitis, gastrooesophageal reflux disease, vomiting

Rare: dysphagia, gastrointestinal ulcer

Hepatobiliary disorders

Uncommon: hepatic function abnormal

Skin and subcutaneous tissue disorders

Common: skin haemorrhage

Musculoskeletal and connective tissue disorders

Rare: haemarthrosis

Renal and urinary disorders

Common: urogenital haemorrhage

General disorders and administration site conditions

Rare: injection site haemorrhage, catheter site haemorrhage

Injury, poisoning and procedural complications

Rare: traumatic haemorrhage, incision site haemorrhage

Postmarketing surveillance

In addition, the following events have been reported with the use of PRADAXA in clinical practice:

Immune system disorders

Rare: angioedema, anaphylactic reactions

DOSAGE AND ADMINISTRATION

PRADAXA capsules can be taken with or without food. PRADAXA should be swallowed whole with a full glass of water, to facilitate delivery to the stomach.

The capsule should not be chewed, broken, or opened as this may increase the risk of bleeding (see Pharmacokinetics, Absorption).

In case of intolerability to dabigatran, patients should be instructed to immediately consult their treating physician in order to be switched to alternate acceptable treatment options.

Prevention of Venous Thromboembolism (VTE) following major orthopaedic surgery of the lower limb (elective total hip or knee replacement)

The recommended dose of PRADAXA is 220 mg taken orally as two 110 mg capsules once daily.

Patients with moderate renal impairment (30–50 mL/min CrCL) have an increased risk for bleeding. For those patients the recommended dose of PRADAXA is 150 mg given as two 75 mg capsules once daily.

Treatment of PRADAXA 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 for a total of 10 days.

VTE prevention following hip replacement surgery: Treatment for a total of 28–35 days.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

The recommended daily dose of PRADAXA is 300 mg taken orally as one 150 mg capsule twice daily.

In patients with moderate renal impairment (30–50 mL/min CrCL) a reduced dose of 220 mg given as one 110 mg capsule twice daily may be considered.

Patients aged 75 years and above should be treated with a daily dose of 220 mg taken orally as one 110 mg capsule twice daily.

For patients with a potentially higher risk of major bleeding (see Precautions, Haemorrhagic risk, Table 14) a reduced dose of 220 mg given as 110 mg twice daily may be considered.

Treatment should be continued life-long.

Treatment of, and prevention of recurrent, deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in adults

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

In patients with moderate renal impairment (30–50 mL/min CrCL) a reduced dose of 220 mg given as one 110 mg capsule twice daily may be considered.

Patients aged 75 years and above should be treated with a daily dose of 220 mg taken orally as one 110 mg capsule twice daily.

For patients with a potentially higher risk of major bleeding (see Precautions, Haemorrhagic risk, Table 14) a reduced dose of 220 mg given as 110 mg twice daily may be considered. Limited clinical data are available for patients with multiple risk factors. In these patients, PRADAXA should only be given if the expected benefit outweighs bleeding risks.

For DVT/PE the recommendation for the use of PRADAXA 220 mg taken as one 110 mg capsule twice daily is based on pharmacokinetic and pharmacodynamic analyses and has not been studied in this clinical setting for efficacy and safety.

Special patient populations

Patients at risk of bleeding

Patients with an increased bleeding risk (see Precautions, Haemorrhagic risk, Table 14) should be closely monitored clinically (looking for signs of bleeding or anaemia). Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient (refer to dosage adjustment in Dosage and Administration, *Prevention of Venous Thromboembolism (VTE) following major orthopaedic surgery of the lower limb (elective total hip or knee replacement)*, *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation* and *Treatment of, and prevention of recurrent, deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in adults* sections above). A coagulation test may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. When clinically relevant bleeding occurs, treatment should be interrupted.

Hepatic impairment

Patients with 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 PRADAXA is not recommended in this population.

Renal impairment

Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCL <30 mL/min). Treatment with PRADAXA in patients with severe renal impairment (CrCL <30 mL/min) is not recommended (see Contraindications). There are no data to support use in this population.

While on treatment renal function should be assessed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications).

- *Prevention of Venous Thromboembolism (VTE) following major orthopaedic surgery of the lower limb (elective total hip or knee replacement):*

  After i.v. application 85% of dabigatran in plasma is cleared through the kidneys. Patients with moderate renal impairment (CrCL 30–50 mL/min) appear to be at higher risk of bleeding. Dosing should be reduced to 150 mg PRADAXA taken once daily as 2 capsules of 75 mg in patients with moderate renal impairment.

- *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and Treatment of, and prevention of recurrent, deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in adults:*

  In patients with moderate renal impairment (CrCL 30–50 mL/min) a reduced dose of 220 mg given as one 110 mg capsule twice daily may be considered and renal function should be assessed at least once a year.

The method used to estimate renal function (CrCL in mL/min) during the clinical development of PRADAXA was the Cockcroft-Gault method. The formula is as follows:

- For creatinine in µmol/L:

$$\frac{1.23 \times (140\text{-age [years]}) \times \text{weight [kg]} \; (\times 0.85 \text{ if female})}{\text{serum creatinine [µmol/L]}}$$

- For creatinine in mg/dL:

$$\frac{(140\text{-age [years]}) \times \text{weight [kg]} \; (\times 0.85 \text{ if female})}{72 \times \text{serum creatinine [mg/dL]}}$$

This method is recommended when assessing patients' CrCL prior to and during dabigatran treatment.

The formula for estimated glomerular filtration rate (eGFR) from the Modification of Diet in Renal Disease (MDRD) Study is as follows:

- eGFR (mL/min/1.73m^2) = 175 x (Scr, std)$^{-1.154}$ x (age)$^{-0.203}$ (x 0.742 if female) (x 1.212 if African American)
  Scr, std: serum creatinine measured with a standardised assay

Table 32: Classification of Renal Function Based on Estimated GFR (eGFR) or Estimated Creatinine Clearance (CrCL)

Stage	Description[a]	eGFR[b] (mL/min/1.73m^2)	CrCL[c] (mL/min)	*PRADAXA development program description*	*CrCL[c] (mL/min)*
1	Control (normal) GFR	≥ 90	≥ 90	*Normal renal function*	*≥ 80*
2	Mild decrease in GFR	60-89	60-89	*Mild renal impairment*	*50-80*
3	Moderate decrease in GFR	30-59	30-59	*Moderate renal impairment*	*30-50*
4	Severe decrease in GFR	15-29	15-29	*Severe renal impairment*	*15-29*
5	End Stage Renal Disease (ESRD)	<15 not on dialysis/requiring dialysis	<15 not on dialysis/requiring dialysis	*End Stage Renal Disease (ESRD)*	*Requiring dialysis*

[a]Stages of renal impairment are based on *K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease (CKD) from the National Kidney Foundation* in 2002

GFR: glomerular filtration rate

[b] eGFR: estimate of GFR based on an MDRD equation

[c] CrCL: estimated creatinine clearance based on the C-G equation

Elderly

Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure in those patients with age-related decline of renal function. As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCL <30 mL/min). The renal function should also be assessed at least once a year in patients treated with PRADAXA or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications).

See also Dosage and Administration, Renal impairment section above.

- *Prevention of Venous Thromboembolism (VTE) following major orthopaedic surgery of the lower limb (elective total hip or knee replacement):*

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

- *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and Treatment of, and prevention of recurrent, deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in adults:*

  Patients aged 75 years and above should be treated with a daily dose of 220 mg taken orally as one 110 mg capsule twice daily.

Weight

No dose adjustment is necessary.

Post-surgical patients with an increased risk for bleeding

Patients at risk for bleeding or patients at risk of overexposure, notably patients with moderate renal impairment (creatinine clearance 30–50 mL/min), should be treated with caution (see Precautions and Pharmacology).

Children and adolescents

There is no experience in children and adolescents. PRADAXA is not recommended for use in patients below 18 years due to lack of data on safety and efficacy.

Concomitant use of Pradaxa with strong P-glycoprotein inhibitors e.g. amiodarone, quinidine or oral verapamil

Simultaneous initiation of treatment with PRADAXA and oral verapamil should be avoided (see Contraindications).

- *Prevention of Venous Thromboembolism (VTE) following major orthopaedic surgery of the lower limb (elective total hip or knee replacement):*

  Dosing should be reduced to PRADAXA 150 mg taken once daily as 2 capsules of 75 mg in patients who receive concomitant PRADAXA and amiodarone or quinidine (see Precautions, Interaction with other medicines).

  Dosing should be reduced to PRADAXA 150 mg taken once daily as 2 capsules of 75 mg and maintained on that dose when patients are commenced on PRADAXA whilst

receiving existing oral verapamil treatment (see Contraindications, Precautions, Interaction with other medicines).

Treatment initiation with oral verapamil should be avoided in patients following major orthopaedic surgery who are already treated with PRADAXA.

- *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and Treatment of, and prevention of recurrent, deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in adults:*

  P-gp inhibitors verapamil, amiodarone and quinidine do not require dose adjustments (see Precautions, Interactions with other medicines), but co-administration of PRADAXA with strong P-gp inhibitors should be used with caution. Patients should be treated with a daily dose of 300 mg taken orally as a 150 mg capsule twice daily.

  The effect of individual P-gp inhibitors vary and results should not be extrapolated to other P-gp inhibitors.

  When verapamil needs to be initiated on stable dabigatran etexilate therapy or dabigatran etexilate and verapamil need to be initiated concurrently, dabigatran etexilate should be given at least 2 hours before verapamil for the first three days.

  Concomitant treatment with dronedarone or systemic ketoconazole is contraindicated.

<u>Switching from Pradaxa treatment to parenteral anticoagulant</u>

- *Prevention of Venous Thromboembolism (VTE) following major orthopaedic surgery of the lower limb (elective total hip or knee replacement):*

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

- *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and Treatment of, and prevention of recurrent, deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in adults:*

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

Switching from parenteral anticoagulants treatment to Pradaxa

PRADAXA 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 unfractionated heparins).

Switching from Vitamin K antagonists to Pradaxa

The vitamin K antagonist should be stopped. PRADAXA can be given as soon as the INR is <2.0.

Switching from Pradaxa to Warfarin

When converting from PRADAXA to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:

- For CrCL >50 mL/min, start warfarin 3 days before discontinuing PRADAXA.
- For CrCL 31-50 mL/min, start warfarin 2 days before discontinuing PRADAXA.
- For CrCL 15-30 mL/min, start warfarin 1 day before discontinuing PRADAXA.
- For CrCL <15 mL/min, no recommendations can be made.

Because PRADAXA can contribute to an elevated INR, the INR will better reflect warfarin's effect after PRADAXA has been stopped for at least 2 days.

Cardioversion

Patients can stay on PRADAXA while being cardioverted.

Missed dose

- *Prevention of venous thromboembolic events in adult patients who have undergone major orthopaedic surgery:*

  The patient should continue with their remaining daily doses of PRADAXA at the same time the next day. Do not take a double dose to make up for missed individual doses.

- *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and Treatment of, and prevention of recurrent, deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in adults:*

  A missed PRADAXA 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.

OVERDOSAGE

For information on the management of overdose contact the Poisons Information Centre on 13 11 26 (Australia).

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 currently available. Coagulation tests can help to determine a potential bleeding risk in this setting.

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. Depending on the clinical situation, appropriate standard treatment including patient monitoring, resuscitation and haemostasis is essential. Management should be guided by local protocols.

As protein binding is low dabigatran is dialysable, however there is limited clinical experience in using dialysis in this setting (see Pharmacokinetics, Special Populations, Renal Impairment).

In cases of severe bleeding, prothrombin factor complexes may be considered. There is some experimental evidence to support the role of activated prothrombin complex concentrates and recombinant factor VIIa in reversing the anticoagulant effect of dabigatran but their usefulness in clinical settings has not yet been systematically demonstrated and their use may cause an excessive risk of thrombosis when the effects of dabigatran have waned. 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.

PRESENTATION AND STORAGE CONDITIONS

Capsules 75 mg:	Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 2 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with R75. Blister packs: 10, 30*, 60 capsules. Bottle: 60* capsules.
Capsules 110mg:	Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 1 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with R110. Blister packs: 10, 30*, 60 capsules. Bottle: 60* capsules.
Capsules 150 mg:	Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 0 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body

with R150.
Blister packs: 10 (sample), 60 capsules.
Bottle: 60* capsules.

*Not distributed in Australia.

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 4 months. Keep the bottle tightly closed.

NAME AND ADDRESS OF THE SPONSOR

Boehringer Ingelheim Pty Limited

ABN 52 000 452 308

78 Waterloo Road

North Ryde NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE ARTG: 24 November 2008

DATE OF MOST RECENT AMENDMENT: 24 August 2015