PRODUCT MONOGRAPH

Pr PRADAXA®

Dabigatran Etexilate Capsules

Capsules 75 mg, 110 mg and 150 mg Dabigatran Etexilate, (as Dabigatran Etexilate Mesilate)

Anticoagulant

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Dabigatran Etexilate Capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Capsules: 75 mg, 110 mg and 150 mg	Acacia, carragenan, dimethicone, hydroxypropyl cellulose, hypromellose, indigo carmin, iron oxide black, potassium chloride, potassium hydroxide, propylene glycol, shellac, talc, tartaric acid, titanium dioxide.

INDICATIONS AND CLINICAL USE

PRADAXA (dabigatran etexilate) is indicated for the:

- prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement (THR) or total knee replacement (TKR) surgery
- treatment of venous thromboembolism events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE
- prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate

Geriatrics (>65 years of age): Most older subjects demonstrate an increase in exposure to dabigatran, usually in association with age-related decline of renal function (see WARNINGS AND PRECAUTIONS, Renal, and DOSAGE AND ADMINISTRATION, Renal Impairment).

Pediatrics (<18 years of age): The safety and efficacy of PRADAXA have not been established in children <18 years of age. Therefore, PRADAXA is not indicated in this patient population.

CONTRAINDICATIONS

PRADAXA is contraindicated in:

- Patients with severe renal impairment (eCrCl < 30mL/min)
- Patients with haemorrhagic manifestations, clinically significant active bleeding, including gastrointestinal bleeding, bleeding diathesis, spontaneous or pharmacological impairment of hemostasis

- Patients with lesions at risk of clinically significant bleeding, e.g. extensive cerebral infarction (haemorrhagic or ischemic) within the last 6 months, active peptic ulcer disease with recent bleeding
- Combination with **strong** P-glycoprotein (P-gp) inhibitors, i.e. oral ketoconazole or oral glecaprevir/pibrentasvir (see WARNINGS AND PRECAUTIONS, *P-gp inhibitors* and DRUG INTERACTIONS)
- Combination with any other anticoagulant, including
    - unfractionated heparin (UFH), except at doses used to maintain a patent central venous or arterial catheter, or during catheter ablation for atrial fibrillation,
    - low molecular weight heparins (LMWH), such as enoxaparin and dalteparin,
    - heparin derivatives, such as fondaparinux,
    - anti-thrombin agents, such as bivalirudin, and
    - oral anticoagulants, such as warfarin, rivaroxaban, apixaban, except under circumstances of switching therapy to or from PRADAXA.
- Patients with prosthetic heart valve(s) requiring anticoagulation due to valvular status itself (see WARNINGS AND PRECAUTIONS, *Patients with Valvular Disease*).
- Patients with a known hypersensitivity to dabigatran or dabigatran etexilate or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- Nursing women (see WARNINGS AND PRECAUTIONS, Special Populations, Nursing Women).

WARNINGS AND PRECAUTIONS

PREMATURE DISCONTINUATION OF ANY ORAL ANTICOAGULANT, INCLUDING PRADAXA, INCREASES THE RISK OF THROMBOTIC EVENTS.

To reduce this risk, consider coverage with another anticoagulant if PRADAXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy.

Bleeding

As with all anticoagulants, PRADAXA (dabigatran etexilate) should be used with caution in circumstances associated with an increased risk of bleeding. The possibility of a haemorrhage should be considered in evaluating the condition of any anticoagulated patient. Bleeding can occur at any site during therapy with PRADAXA. An unexplained fall in hemoglobin and/or hematocrit or blood pressure should lead to a search for a bleeding site.

Patients with a known high risk of bleeding should not be prescribed PRADAXA (see CONTRAINDICATIONS).

Should severe bleeding occur, treatment with PRADAXA must be discontinued and the source of bleeding investigated promptly.

For situations of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effects of dabigatran is required, the specific reversal agent, PRAXBIND (idarucizumab), may be used (see Surgery/Procedural Interventions, below, and OVERDOSAGE).

Close clinical surveillance is recommended throughout the treatment period, i.e., looking for signs of bleeding or anaemia, by testing for occult blood in the stool or ruling out a significant drop in serum hemoglobin, especially if risk factors which increase bleeding risk are combined (see Table 1 below) and DRUG INTERACTIONS, Drug-Drug Interactions, Table 14).

Table 1: Factors which increase haemorrhagic risk, as identified in clinical studies

Factors increasing dabigatran plasma levels	Moderate renal impairment (30 - 50 mL/min eCrCl)
	Co-medication with P-glycoprotein inhibitors, including dronedarone, amiodarone, quinidine and verapamil
Pharmacodynamic interactions	NSAID (diclofenac)
	Anti-platelet agents, including ASA, clopidogrel, prasugrel and ticagrelor
	Selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs)
	Thrombolytic agents
Diseases / procedures with special haemorrhagic risks	Congenital or acquired coagulation disorders
	Thrombocytopenia or functional platelet defects
	Active ulcerative gastrointestinal disease
	Recent gastro-intestinal bleeding
	Recent biopsy or major trauma
	Recent intracranial haemorrhage
	Brain, spinal or ophthalmic surgery
	Bacterial endocarditis
Others	Age ≥ 75 years

The measurement of dabigatran-related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Antiplatelet agents:
Prasugrel and ticagrelor: The ADP receptor inhibitors prasugrel and ticagrelor have not been studied with PRADAXA in the prevention of stroke in patients with atrial fibrillation (AF), and are not recommended as concomitant therapy. Note that the concomitant use of ticagrelor increases exposure to dabigatran (see DRUG INTERACTIONS, Table 14, *Ticagrelor*).

NSAIDs, ASA or clopidogrel: Concomitant use of ASA or other antiplatelet agents, such as clopidogrel, based on medical need to prevent myocardial infarction, should be undertaken with caution. Close clinical surveillance is recommended.

In AF patients in the RE-LY trial, concomitant use of ASA or clopidogrel with PRADAXA approximately doubled the risk of major bleed, irrespective of the dose of PRADAXA used. However, there was little improvement in stroke and systemic embolic events. A similar increase in the risk of major bleed was noted with concomitant use with the study comparator, warfarin. Concomitant use of PRADAXA with an antithrombotic is not recommended for prevention of cardiogenic thromboembolic stroke in AF patients.

P-gp Inhibitors: Concomitant treatment with strong P-gp inhibitors, i.e. oral ketoconazole or oral glecaprevir/pibrentasvir is contraindicated (see CONTRAINDICATIONS).

PRADAXA should not be used with dronedarone (see DRUG INTERACTIONS, Drug-Drug Interactions, Table 14).

Thrombolytic agents: Since there is very limited experience with the use of thrombolytic agents in conjunction with PRADAXA, a careful risk-benefit assessment is required before instituting thrombolytics due to potential increased risk of major bleeding. Thrombolytic agents for treatment of acute myocardial infarction or acute ischemic stroke in conjunction with PRADAXA may be considered, if thrombin time (TT), ecarin clotting time (ECT), or activated thromboplastin time (aPTT), not exceeding the upper limit of normal (ULN) have been obtained (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Patients with atrial fibrillation and another cardiovascular condition: In patients with atrial fibrillation and having another cardiovascular condition that warrants single or dual antiplatelet therapy, a careful assessment of the potential risks against potential benefits should be made before combining this therapy with PRADAXA.

Specifically, co-administration of oral antiplatelet drugs, including ASA, clopidogrel or NSAIDs, or P-gp inhibitors in patients aged ≥75 years increases the risk of major bleeding, including gastrointestinal bleeding, by about 2-fold.

Cardiovascular

Acute myocardial infarction (AMI)
Discontinuation of PRADAXA in the setting of AMI should be considered if the MI treatment involves invasive procedures, such as percutaneous coronary revascularization, or coronary artery bypass surgery. Similar consideration should be given if thrombolytic therapy is to be initiated, because bleeding risk may be expected to increase. Patients with AMI should be treated according to current clinical guidelines for that disorder. In this setting, PRADAXA may be resumed for the prevention of stroke and systemic embolism upon completion of these revascularization procedures.

Cardioversion
Patients can be maintained on PRADAXA while being cardioverted (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations, Cardioversion).

Catheter ablation for atrial fibrillation
Catheter ablation can be conducted in patients on 150 mg twice daily PRADAXA treatment. PRADAXA treatment does not need to be interrupted.

Percutaneous coronary intervention (PCI) with stenting
Patients with nonvalvular atrial fibrillation who undergo a PCI with stenting can be treated with PRADAXA in combination with antiplatelets after hemostasis is achieved.

Patients with Valvular Disease
Safety and efficacy of PRADAXA have not been studied in patients with prosthetic heart valves, or those with hemodynamically significant rheumatic heart disease, especially mitral stenosis, with or without atrial fibrillation. Occasional reports of thromboembolism in association with mechanical valves have been received. Therefore, the use of PRADAXA is not recommended in this setting.

A Phase II study examined the effects of dabigatran etexilate and warfarin in a total of 252 patients with recent mechanical valve replacement surgery (i.e. within the current hospital stay), and in patients who received a mechanical valve replacement more than 3 months earlier. More thromboembolic events (mainly strokes and symptomatic prosthetic valve thrombosis) and more bleeding events were observed with dabigatran etexilate than with warfarin (see CONTRAINDICATIONS).

Of note, in the pivotal Phase III RE-LY trial in atrial fibrillation, about 22% of patients had other valvular disease including aortic stenosis, aortic regurgitation, and/or mitral regurgitation. About 17% had mitral regurgitation.

Patients with Antiphospholipid Syndrome
Direct acting Oral Anticoagulants (DOACs) including dabigatran etexilate are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist (VKA) therapy.

Hepatic

No treatment experience is available for patients with severe hepatic impairment (Child-Pugh classification C), acute liver disease or with elevated liver enzymes ≥2 upper limit of normal (ULN). Therefore, the use of PRADAXA is not recommended in these populations.

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 (see DOSAGE AND ADMINISTRATION).

Other Surgery/Procedural Interventions

As with any anticoagulant, patients on PRADAXA who undergo surgery or invasive procedures are at increased risk for bleeding. In these circumstances, temporary discontinuation of PRADAXA may be required (see DOSAGE AND ADMINISTRATION - Cardioversion and catheter ablation for atrial fibrillation).

In case of necessary emergency surgery or urgent procedures, when rapid reversal of the anticoagulation effect is required, the specific reversal agent, PRAXBIND (idarucizumab), may be used.

Pre-Operative Phase
Elective Surgery/Intervention: PRADAXA should be stopped at least 24 hours before the intervention, if possible, based on the clinical judgement of the physician.
Patients at higher risk of bleeding (see DOSAGE AND ADMINISTRATION) or in major surgery where complete hemostasis may be required: Consider stopping PRADAXA 2-4 days before surgery.

Patients with renal insufficiency: Clearance of dabigatran in patients with renal insufficiency may take longer (see DOSAGE AND ADMINISTRATION, Renal Impairment). This should be considered in advance of any procedures, see Table 2 below.

Table 2: Discontinuation rules before invasive or surgical procedures

Renal function (eCrCl 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 but < 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 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Table 20

Patients with acute renal failure: PRADAXA is contraindicated in patients with severe renal dysfunction (eCrCl <30 mL/min) (see CONTRAINDICATIONS). If acute renal failure occurs before surgery is required, PRADAXA should generally be stopped at least 5 days before major surgery.

In cases of acute intervention: If acute intervention is required, PRADAXA should be temporarily discontinued, due to increased risk of bleeding. Acute surgical or procedural interventions should be delayed if possible at least 12 hours after the last dose of PRADAXA, with risk of bleeding weighed against the urgency of the needed intervention (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Peri-Operative Spinal/Epidural Anaesthesia, Lumbar Puncture
Procedures such as spinal anaesthesia may require complete hemostatic function.

In patients treated with PRADAXA for VTE prevention following major orthopedic surgery 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.

In the case of these peri-spinal procedures, administration of the 1st dose of PRADAXA should occur after hemostasis has been obtained and no sooner than 2 hours following puncture or removal of catheters related to these procedures.

The risk of these rare events may be higher with post-operative use of indwelling epidural catheters or the concomitant use of other products affecting hemostasis. Accordingly, the use of PRADAXA is not recommended in patients undergoing anesthesia with post-operative indwelling epidural catheters.

Post-Procedural Period
Resume/start treatment with PRADAXA as soon as complete hemostasis is achieved and the clinical situation allows.

Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. PRADAXA treatment can be re-initiated 24 hours after administration of PRAXBIND (idarucizumab), if the patient is clinically stable and adequate hemostasis has been achieved.

Renal

Determine estimated creatinine clearance (eCrCl) in all patients before instituting PRADAXA, and monitor renal function during PRADAXA treatment, as clinically appropriate (see DOSAGE AND ADMINISTRATION).

PRADAXA is contraindicated in cases of severe renal impairment (eCrCl < 30 mL/min) (see CONTRAINDICATIONS). PRADAXA should be discontinued in patients who develop acute renal failure.

Special Populations

Pregnant Women: There are no studies of PRADAXA in pregnant women and therefore, the potential risk in these patients is unknown. Women should avoid pregnancy during treatment with PRADAXA and when pregnant, should not be treated with PRADAXA unless the expected benefit is greater than the risk.

Animal Data: Dabigatran decreased the number of implantations when male and female rats were treated at dosages about 2.6-3.0x the human exposure at maximum recommended human dose (MRHD) prior to mating and up to implantation (gestation Day 6). Treatment of pregnant rats after implantation at the same dose increased the number of dead offspring and caused

excess vaginal/uterine bleeding close to parturition. Although dabigatran increased the incidence of delayed or irregular ossification of fetal skull bones and vertebrae in the rat, it did not induce major malformations in rats or rabbits.

Labour and Delivery: Safety and effectiveness of PRADAXA during labor and delivery have not been studied in clinical trials. Consider the risks vs the benefits in using PRADAXA in this setting.

Animal Data: Death of offspring and mother rats during labour in association with uterine bleeding occurred during treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with dabigatran at doses about 2.6x the human exposure at MRHD.

Nursing Women: There are no clinical data available on the excretion of dabigatran into breast milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from PRADAXA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother (see CONTRAINDICATIONS).

Geriatrics (> 65 years of age): Most older subjects demonstrate an increase in drug exposure; especially in those patients with age-related decline of renal function (see WARNINGS AND PRECAUTIONS, Renal, and DOSAGE AND ADMINISTRATION, Renal Impairment).

Pediatrics (< 18 years of age): The safety and efficacy of PRADAXA have not been established in children <18 years of age. Therefore, PRADAXA is not indicated in this patient population.

Patients of low body weight (< 50 kg): Use PRADAXA with caution since limited data are available in these patients.

Monitoring and Laboratory Tests

Although there is no need to monitor anticoagulation effect of PRADAXA during routine clinical practice, in certain infrequent situations such as overdosage, acute bleeding, urgent surgery, in cases of suspected non-compliance, or in other unusual circumstances, assessment of the anticoagulant effect of dabigatran may be appropriate.

At recommended doses of PRADAXA, dabigatran prolongs coagulation time as measured by the:

- activated partial thromboplastin time (aPTT),
- thrombin time (TT) and
- ecarin clotting time (ECT).

In patients who are bleeding due to excess activity of dabigatran, these coagulation assays would be expected to be elevated and may be helpful in assessing anticoagulant activity of dabigatran.

The preferred assays are the **calibrated Hemoclot TT assay** and the ECT assay, but if they are not available, the aPTT assay is widely available and provides an approximation of

PRADAXA's anticoagulant activity. The aPTT assay is generally less sensitive to anticoagulant activity than either the TT or ECT assay.

Prothrombin time (PT) (INR) tests should not be performed in patients taking PRADAXA. The PT (INR) assay is unreliable and false-positive INR elevations have been reported.

Assays sensitivity and precision with varying dabigatran plasma concentrations:
aPTT assay: A curvilinear relationship was shown between dabigatran plasma concentrations and aPTT. The aPTT assay shows low sensitivity at dabigatran plasma concentrations >100 ng/mL and well within the range observed following effective oral doses.

TT assay: The TT assay exhibited a linear relationship with plasma concentration. The TT assay shows a high level of sensitivity and may be too sensitive to dabigatran plasma concentrations in the clinically relevant plasma concentration range; for example, at dabigatran concentrations >600 ng/mL, TT frequently exceeded the maximum measurement time of the coagulometer. Therefore, the TT assay may serve as a sensitive method for determining if any dabigatran is present. However, since reagents used for determining TT at different laboratories are not standardised, **the calibrated Hemoclot® thrombin inhibitor assay (a diluted TT assay) with dabigatran standards should be used to calculate dabigatran concentration.**

ECT assay: The ECT assay displayed a linear relationship with drug plasma concentrations in the clinically-relevant drug concentration range and exhibited adequate sensitivity and precision. However, given the lack of uniform standardisation of this assay, the clinical utility of this test remains to be established.

Results of coagulation tests indicating an increased risk of bleeding
TT assay: A TT measure with the calibrated Hemoclot® thrombin inhibitor assay (Hyphen BioMed, Neuvillesur-Oise, France), indicating >200 ng/mL dabigatran plasma concentration (approximately > 65 seconds), taken just prior to the next dose of PRADAXA after 150 mg bid dosing (at trough, i.e., 10-16 hours after the previous dose), is associated with a higher risk of bleeding.

aPTT assay: AF patients treated with PRADAXA 150 mg bid, having an aPTT >2.0 – 3.0-fold of normal range at trough, were seen to have an increased risk of bleeding.

Results of coagulation tests indicating a lack of efficacy
aPTT assay: An aPTT assay in the normal range in patients deemed to have been anticoagulated with PRADAXA, indicates no meaningful ongoing anticoagulant effect so planned surgery entailing high risk of bleeding could then proceed, if required.

ADVERSE REACTIONS

The overall safety of PRADAXA (dabigatran etexilate) was evaluated in 23,393 patients who were treated with PRADAXA in 11 clinical trials.

Prevention of VTE after THR or TKR surgery
Out of the 6,684 patients treated with 150 mg or 220 mg PRADAXA once daily following major elective orthopedic surgery (short-term treatment up to 42 days) in 6 clinical trials, 9% of patients experienced adverse reactions; about 10% of patients treated with enoxaparin experienced adverse reactions.

Treatment of VTE and Prevention of Recurrent DVT and PE
Out of the 2,553 patients treated with PRADAXA 150 mg bid in the acute DVT/PE treatment trials (RE-COVER, RE-COVER II) (long-term treatment of up to 6 months), 14% of patients experienced adverse reactions.

Out of the 2,114 patients treated with PRADAXA 150mg bid in the recurrent DVT/PE prevention trials (RE-MEDY, RE-SONATE) (long-term treatment up to 36 months), 15% of patients experienced adverse reactions. A total of 552 were rolled over from the RE-COVER trial (acute DVT/PE treatment) into the RE-MEDY trial and were counted in both the acute and recurrent patient totals.

Prevention of stroke and systemic embolism in AF patients – RE-LY trial:
Out of the 12,042 patients exposed to PRADAXA in RE-LY, 6,059 were treated with PRADAXA 150 mg bid, while 5,983 received doses of 110 mg bid. About 21% of AF patients treated with PRADAXA and about 16% of patients treated with warfarin (long-term treatment up to 3 years) experienced adverse events (AEs) considered related to treatment.

Bleeding
Bleeding is the most relevant adverse reaction of PRADAXA. 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% 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 trials 19.4% (RE-MEDY) and 10.5% (RE-SONATE) 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.

Since the patient populations treated with PRADAXA for different indications are not interchangeable, a summary description of major and total bleeding is provided by indication and/or trial in Table 3, Table 4, Table 5, Table 6, Table 7 and Table 8.

Prevention of VTE after THR or TKR surgery

Table 3: Number (%) of patients experiencing bleeding events during the treatment period for VTE prevention in the REMODEL and RENOVATE trials, according to dose

	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin 40 mg QD N (%)
Treated	1,866 (100.0)	1,825 (100.0)	1,848 (100.0)
Major Bleeding Events*	24 (1.3)	33 (1.8)	27 (1.5)
Any bleeding	258(13.8)	251(13.8)	247(13.4)

Table 4: Number (%) of patients experiencing bleeding events during the treatment period for VTE prevention in the REMOBILIZE trial, according to dose

	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin 30 mg BID N (%)
Treated	871 (100.0)	857 (100.0)	868 (100.0)
Major Bleeding Events*	5 (0.6)	5 (0.6)	12 (1.4)
Any bleeding	72 (8.3)	74 (8.6)	84 (9.7)

*Major Bleeding Events: Major bleeding was defined as clinically overt bleeding associated with ≥ 20 g/L fall in hemoglobin; clinically overt bleeding leading to transfusion of ≥ 2 units packed cells or whole blood; fatal, retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding warranting treatment cessation or leading to reoperation. Major bleeding included those events occurring at the surgical site.

Treatment of VTE and Prevention of Recurrent DVT and PE

Table 5: Frequency of MBEs*, MBEs or CRBE(s) [#] and any bleeding event(s) in patients with acute DVT/PE in the RE-COVER and RE-COVER II (pooled data)

	Dabigatran etexilate 150 mg bid N (%)	**Warfarin N (%)**	Hazard ratio vs. Warfarin estimate (95% CI)
RE-COVER and RE-COVER II(Pooled)			
Number of patients	2,456 (100.0)	2,462 (100.0)	
MBEs	24 (1.0)	40 (1.6)	0.60 (0.36, 0.99)
p−value for superiority			0.0470[&]
MBEs or CRBEs	109 (4.4)	189 (7.7)	0.56 (0.45, 0.71)
p−value for superiority			<0.0001[&]
Any bleeding event	354 (14.4)	503 (20.4)	0.67 (0.59, 0.77)
p−value for superiority			<0.0001[&]
Intracranial hemorrhage	2 (0.1)	4 (0.2)	0.50 (0.09, 2.74)
Life-threatening bleed	4 (0.2)	6 (0.2)	0.66 (0.19, 2.36)
Fatal bleeding	1 (0.0)	2 (0.1)	0.50 (0.05, 5.54)

*The definition of major bleeding events (MBEs) in RE-COVER, RE-COVER II, RE-MEDY and RE-SONATE followed the recommendations of the International Society on Thrombosis and Hemostasis. A bleeding event was categorised as an MBE if it fulfilled at least 1 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
#the definition of Clinically Relevant Bleeding Event (CRBE): In Studies RE-COVER II, RE-COVER, and RE-MEDY, a minor bleeding event was categorized as a CRBE if it fulfilled at least 1 of the following criteria:
• Spontaneous skin hematoma ≥25 cm^2
• Spontaneous nose bleed >5 minutes duration
• Macroscopic hematuria, either spontaneous or, if associated with an intervention, lasting >24 hours
• Spontaneous rectal bleeding (more than spotting on toilet paper)
• Gingival bleeding >5 minutes
• Bleeding leading to hospitalization and/or requiring surgical treatment
• Bleeding leading to a transfusion of <2 units of whole blood or red cells
• Any other bleeding event considered clinically relevant by the investigator
&Statistically significant, superior vs. warfarin

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

Table 6: Frequency event rate (%) of bleeding events from MBEs*, MBEs or CRBE(s)# and any bleeding event(s) in patients the RE-MEDY study includes events that occurred between first intake of active study drug and 6 days after last intake of study drug:

	Dabigatran etexilate 150 mg bid N (%)	**Warfarin N (%)**	**Hazard ratio vs. Warfarin estimate (95% CI)**
Number of patients	1,430 (100)	1,426 (100)	
MBEs	13 (0.9)	25 (1.8)	0.54 (0.25,1.16)
p−value for superiority			0.1135
MBEs or CRBE	80 (5.6)	145 (10.2)	0.55 (0.41, 0.72)
p−value for superiority			<0.0001&
Any bleeding event	278 (19.4)	373 (26.2)	0.71 (0.61, 0.83)
p−value for superiority			<0.0001&
Fatal Bleeding	0 (0.0)	1 (0.1)	− (−, −)

*#see footnotes under Table 5
&Statistically significant

Table 7: Frequency event rate (%) of bleeding events from MBEs, MBEs or CRBE(s) and any bleeding event(s) in the RE-SONATE study includes events that occurred between first intake of active study drug and 6 days after last intake of study drug

	Dabigatran etexilate 150 mg bid N (%)	**Placebo N (%)**	Hazard ratio vs. placebo Estimate (95% CI)
Number of patients	684	659	
MBEs	2 (0.3)	0	1.0 (0.00–1.00)
p−value for superiority			0.9964
MBEs or CRBE*	36 (5.3)	13 (2.0)	2.69 (1.43, 5.07)
p−value for superiority			0.0022
Any bleeding event	72 (10.5)	40 (6.1)	1.77 (1.20, 2.61)
p−value for superiority			0.0038
Fatal Bleeding	0 (0.0)	0 (0.0)	− (−, −)

*In RE-SONATE, CRBEs were defined as investigator-reported, overt bleeding not meeting the criteria for an MBE, but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment, or associated with discomfort such as pain, or impairment of activities of daily life.

Prevention of stroke and systemic embolism in AF patients - the RE-LY trial

In Table 8, the category of major bleeds includes both life-threatening and non-life threatening bleeds. Intracranial bleeds is 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 8: Frequency and annualized event rate (%) of bleeding events in patients with atrial fibrillation treated for prevention of stroke and systemic embolism in the RE-LY trial

	Dabigatran etexilate 110 mg bid N (%)	**Dabigatran etexilate 150 mg bid N (%)**	**Warfarin** N (%)**
Patients randomised	6,015	6,076	6,022
Patient-years	11,899	12,033	11,794
Major bleeding event (MBE)*	347 (2.9)	409 (3.4)	426 (3.6)
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 MBE	151 (1.3)	183 (1.5)	221 (1.9)
Hazard ratio vs. warfarin (95% CI)	0.68 (0.55, 0.83)	0.81(0.67, 0.99)	
p-value	0.0002	0.0357	
Intracranial haemorrhage (ICH)$^{+}$	27 (0.2)	39 (0.3)	91 (0.8)
Hazard ratio vs. warfarin (95% CI)	0.29 (0.19, 0.45)	0.42 (0.29, 0.61)	
p-value	< 0.0001	< 0.0001	
Fatal bleeding	26 (0.22)	0.30 (0.25)	42 (0.36)
Hazard ratio vs. warfarin (95% CI)	0.61 (0.38, 1.00)	0.70 (0.44, 1.12)	
p-value	0.0491	0.1338	
Any bleeding event[a]	1,759 (14.8)	1,997 (16.6)	2,169 (18.4)
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
**Dose-adjusted warfarin to an INR of 2.0 – 3.0
$^{+}$ICH consists of adjudicated haemorrhagic stroke and subdural and/or subarachnoid haemorrhage
a Investigator-reported bleeding events

Major bleeding fulfilled ≥1 of the following criteria:
•Bleeding associated with a reduction in hemoglobin of ≥20 g/L or leading to a transfusion of ≥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 ≥1 of the following criteria:
•Fatal bleed; symptomatic intracranial bleed; reduction in hemoglobin of ≥50 g/L; transfusion of ≥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.

Patients >75 years of age

AF patients >75 years of age taking an anticoagulant are known to be at increased risk of having a stroke, serious and non-serious bleeding events and death compared to those <75 years of age. This risk is even higher in patients who are also receiving concomitant ASA or an antiplatelet agent compared to those not receiving ASA or an antiplatelet agent
(see Table 9 below).

Table 9: Annualized rates of key safety outcomes in the RE-LY trial in patients > 75 years with or without antiplatelets (AP) or P-glycoprotein inhibitors (Pgp-inh.):

Group	Treatment	No. of patients	Major Bleed (%/y)	Life-Threat Bleed (%/y)	Major GI-bleed (%/y)	ICH (%/y)	Stroke/ SEE (%/y)	Ischemic Stroke (%/y)	Any Death (%/y)
>75 years **with** AP or Pgp-inh.	DE 110*	1356	5.80	2.46	2.42	0.31	2.11	1.81	6.11
	DE 150**	1446	6.67	2.78	3.31	0.50	1.92	1.60	5.85
	Warfarin+	1422	5.20	2.71	1.61	1.13	2.53	1.72	5.53
>75 years **without** AP or Pgp-inh.	DE 110*	993	2.86	1.40	1.10	0.45	1.61	1.25	4.06
	DE 150**	1020	3.25	1.55	1.40	0.30	0.80	0.45	4.09
	Warfarin+	1001	3.46	1.73	1.17	0.86	1.63	1.02	4.13

*Dabigatran etexilate 110 mg bid
** Dabigatran etexilate 150 mg bid
+dose adjusted, INR 2.0 – 3.0
Stroke/SEE and Ischemic Stroke outcomes are provided for comparative purpose only

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Prevention of VTE after THR or TKR surgery

Table 10: Common Adverse Reactions observed in ≥1% of dabigatran-treated patients in active - controlled VTE prevention trials

	Dabigatran etexilate 150 mg N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin[b] N (%)
	2,737 (100)	2,682 (100)	3,108 (100)
Blood and lymphatic system			
Anaemia	110 (4.0)	117 (4.4)	141 (4.5)
Gastrointestinal haemorrhage	33 (1.2)	17 (0.6)	20 (0.6)
Hematoma	38 (1.4)	37 (1.4)	55(1.8)
Hematuria	34 (1.2)	31 (1.2)	25 (0.8)
Wound haemorrhage	35 (1.3)	28 (1.0)	31 (1.0)
Procedural complications			
Wound secretion	130 (4.7)	130 (4.8)	93 (3.0)
Post-procedural hematoma	66 (2.4)	45 (1.7)	78 (2.5)
Post-procedural haemorrhage	28 (1.5)	43 (2.4)	32 (1.7)
Anaemia post-operative	37 (1.4)	54 (2.0)	56 (1.8)
Traumatic hematoma	37 (1.4)	41 (1.5)	51 (1.6)
Post-procedural discharge	31 (1.1)	34 (1.3)	31 (1.0)
Laboratory investigations			
ALT ≥ 3xULN	68 (2.5)	58 (2.2)	95 (3.5)[a]
Hemoglobin decreased	45 (1.6)	35 (1.3)	74 (2.4)

a Based on N = 2,716
b Enoxaparin 40mg QD or 30 mg BID

Treatment of VTE and Prevention of Recurrent DVT and PE

Table 11: Common Adverse Reactions observed in ≥ 1% of dabigatran-treated patients for acute DVT/PE in the RE-COVER and RE-COVER II trials (pooled data) and of dabigatran-treated patients for recurrent DVT/PE prevention in the RE-MEDY and RE-SONATE trials

	RE-COVER and RE-COVER II trials (pooled data)		**RE-MEDY and RE-SONATE**		
System organ class	**Dabigatran etexilate 150 mg N (%)**	**Warfarin N (%)**	**Dabigatran etexilate 150 mg N (%)**	**Warfarin N (%)**	**Placebo N (%)**
Patients	2, 553 (100.0)	2,554 (100.0)	2,114 (100.0)	1,426 (100.0)	659 (100)
Overall frequency	14.2%	18.9%	14.6%	19.6%	6.5%
Vascular disorders					
Haematoma	15 (0.6)	37 (1.4)	21 (1.0)	28 (2.0)	2 (0.3)
Respiratory, thoracic and mediastinal disorders					
Epistaxis	33 (1.3)	81 (3.2)	31 (1.5)	58 (4.1)	3 (0.5)
Gastrointestinal disorders					
Gastrointestinal haemorrhage	60 (2.4)	95 (3.7)	59 (2.8)	57 (4.0)	3 (0.5)
Rectal haemorrhage	*32 (1.3)*	*24 (0.9)*	*25 (1.2)*	*13 (0.9)*	*1 (0.2)*
Dyspepsia	34 (1.3)	8 (0.3)	32 (1.5)	6 (0.4)	3 (0.5)
Abdominal pain	-	-	20 (1.0)	4 (0.3)	7 (1.2)
Skin and subcutaneous tissue disorders					
Skin haemorrhage	32 (1.3)	51 (2.0)	29 (1.4)	41 (2.9)	2 (0.3)
Contusion	*22 (0.9)*	*41 (1.6)*	*25 (1.2)*	*20 (1.4)*	*1 (0.2)*
Renal and urinary disorders					
Urogenital haemorrhage	36 (1.4)	65 (2.5)	25 (1.2)	36 (2.5)	1 (0.2)
Haematuria	*29 (1.1)*	*57 (2.2)*	*22 (1.0)*	*27 (1.9)*	*1(0.2)*

Prevention of stroke and systemic embolism in AF patients – RE-LY trial

Table 12: Common Adverse Reactions observed in ≥1% of dabigatran-treated patients with atrial fibrillation in the active- controlled trial, RE-LY

	Dabigatran etexilate 110 mg N (%)	Dabigatran etexilate 150 mg N (%)	Warfarin N (%)
	5,983 (100)	6,059 (100)	5,998 (100)
Bleeding and anaemia*	**599 (10.0)**	**747 (12.3)**	**825 (13.8)**
Anaemia	73 (1.2)	97 (1.6)	74 (1.2)
Epistaxis	66 (1.1)	67 (1.1)	107 (1.8)
Gastrointestinal haemorrhage	196 (3.3)	277 (4.6)	155 (2.6)
Urogenital haemorrhage	66 (1.1)	84 (1.4)	96 (1.6)
Skin haemorrhage	78 (1.3)	68 (1.1)	144 (2.4)
Gastrointestinal disorders*	**735 (12.3)**	**772 (12.7)**	**220 (3.7)**
Abdominal pain	135 (2.3)	134 (2.2)	15 (0.3)
Diarrhoea	75 (1.3)	71 (1.2)	11 (0.2)
Dyspepsia	250 (4.2)	234 (3.9)	13 (0.2)
Nausea	58 (1.0)	73 (1.2)	12 (0.2)

*Aggregate incidence presented for all adverse reactions within the body system, including those reactions occurring < 1% and not listed in the Table 12 above.

Gastrointestinal adverse reactions occurred more often with dabigatran etexilate than warfarin. These were related to dyspepsia (including upper abdominal pain, abdominal pain, abdominal discomfort, epigastric discomfort), or gastritis-like symptoms (including GERD, esophagitis, erosive gastritis, gastric haemorrhage, haemorrhagic gastritis, haemorrhagic erosive gastritis, gastrointestinal ulcer).

Gastrointestinal (GI) haemorrhage occurred at a higher frequency with PRADAXA 150 mg bid, compared to warfarin (see Table 12 above). GI-adjudicated major bleeds were reported at 1.1%, 1.6%, and 1.1% (annualized rates) in the DE 110 mg, DE 150 mg and warfarin groups, respectively. GI life-threatening bleeds occurred with a frequency of 0.6%, 0.8% and 0.5% in the DE 110 mg, DE 150 mg and warfarin groups, respectively. Any GI bleeds occurred with frequency of 5.4%, 5.7% and 3.9% in the DE 110 mg, DE 150 mg and warfarin groups, respectively. The underlying mechanism of the increased rate of GI bleeding has not been established (see CLINICAL TRIALS, Prevention of stoke and systemic embolism in patients with atrial fibrillation).

Allergic reactions or drug hypersensitivity including angioedema, urticaria, bronchospasm, rash and pruritus have been reported in patients who received dabigatran etexilate. Rare cases of anaphylactic reactions have also been reported.

Liver Function Tests

In the long-term RE-LY study, observed abnormalities of liver function tests (LFTs) are

presented below in Table 13.

Table 13: Liver Function Tests in the RE-LY trial

	Dabigatran etexilate 110 mg bid N (%)	Dabigatran etexilate 150 mg bid N (%)	Warfarin N (%)
Total treated	5,983 (100.0)	6,059 (100.0)	5,998 (100.0)
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)

In the active controlled studies RE-COVER, RE-COVER II and RE-MEDY, potential abnormalities of LFTs 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.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

- Prevention of VTE after THR or TKR surgery (dabigatran 150 mg and 220 mg /day)
  Blood and lymphatic system: thrombocytopenia, neutropenia, agranulocytosis
  Gastrointestinal disorders: haemorrhoidal haemorrhage, rectal haemorrhage
  General: bloody discharge, catheter site haemorrhage
  Hepatobiliary disorders: alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hepatic function abnormal/liver function test abnormal, transaminases increased
  Injury, poisoning and procedural complications: incision site haemorrhage
  Laboratory Investigations: blood urine present, hematocrit decrease, occult blood positive,
  Musculoskeletal and cumulative tissue disorders: hemarthrosis
  Respiratory and thoracic system: epistaxis
  Skin and sub-cutaneous tissue: ecchymosis
  Surgical and medical procedures: post-procedural drainage, wound drainage
  Vascular disorders: haemorrhage

- Treatment of VTE and Prevention of Recurrent DVT and PE (dabigatran 150 mg bid)
  Blood and lymphatic system disorders: anaemia, thrombocytopenia, neutropenia, agranulocytosis
  Vascular disorders: haematoma, haemorrhage
  Gastrointestinal disorders: diarrhoea, dysphagia, gastrointestinal ulcer (including esophageal ulcer), gastro-esophagitis, gastro-esophageal reflux disease, nausea, vomiting
  Hepatobiliary disorders: hepatic function abnormal
  Musculoskeletal and connective tissue and bone disorders: hemarthrosis
  General disorders and administration site conditions: catheter site haemorrhage, injection site haemorrhage

Injury, poisoning and procedural complications: incision site haemorrhage, traumatic haemorrhage
Immune system disorder: anaphylaxis*, angioedema, drug hypersensitivity (bronchospasm*, pruritus, rash, urticaria)
Respiratory disorders: hemoptysis
Nervous system disorders: intracranial haemorrhage
*These side effects were not reported in clinical trials as ADRs (AEs only); therefore, a frequency could not be calculated.

- Prevention of stroke and systemic embolism in AF patients - the RE-LY trial (dabigatran 110 mg bid and 150 mg bid)
  Blood and lymphatic system disorders: thrombocytopenia, neutropenia, agranulocytosis
  Vascular disorders: haematoma, haemorrhage
  Gastrointestinal disorders: dysphagia, gastrointestinal ulcer (including esophageal ulcer), gastro-esophagitis, gastro-esophageal reflux disease, vomiting
  Hepatobiliary disorders: hepatic enzyme increased, hepatic function abnormal / liver function test abnormal
  Musculoskeletal and connective tissue and bone disorders: hemarthrosis
  Renal and urinary disorders: urogenital haemorrhage
  General disorders and administration site conditions: catheter site haemorrhage, injection site haemorrhage
  Injury, poisoning and procedural complications: incision site hematoma, incision site haemorrhage, traumatic haemorrhage, traumatic hematoma
  Immune system disorder: anaphylaxis, drug hypersensitivity (bronchospasm*, pruritus, rash, urticaria)
  Respiratory disorders: hemoptysis
  Nervous system disorders: intracranial haemorrhage
  *These side effects were not reported in clinical trials as ADRs (AEs only)

Long-term experience in AF patients

RELY-ABLE, the open-label extension study of RE-LY (see CLINICAL TRIALS), assessed the long-term safety of two doses of PRADAXA (110 mg bid and 150 mg bid) in patients with AF who had not permanently discontinued study medication at the time of their final RE-LY study visit. Patients enrolled in RELY-ABLE continued to receive the same dose of PRADAXA as assigned in RE-LY for an additional 2.5 years. There were 5,851 patients enrolled in RELY-ABLE, representing 49% of patients originally randomized to receive PRADAXA in RE-LY and 86% of RELY-ABLE-eligible patients. In this open-label study, the investigator-reported rates of outcome events (thromboembolic events, major bleed and other bleeding events) were consistent with event rates observed in RE-LY, including lower frequencies of bleeding events with the 110 mg bid dose compared with the 150 mg bid dose. The results of RELY-ABLE indicated that the long-term safety profile of PRADAXA remained favourable for both test doses. No new safety findings were observed.

Post-Marketing Experience

The following additional adverse reactions have been identified during post-approval use of PRADAXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on ≥1 of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to PRADAXA.

Rare cases of angioedema and anaphylactic reaction have been reported in patients receiving PRADAXA. Occasional reports of haemorrhagic pericardial effusion have been received.

Severe liver injury adverse events including cases of acute liver failure have been reported in patients treated with PRADAXA irrespective of indication. A causal relationship with PRADAXA has not been established.

Cases of alopecia were observed post marketing.

Cases of neutropenia and agranulocytosis have been observed. Neutropenia and agranulocytosis may manifest with symptoms such as frequent infection with fever, sore throat or mouth ulcers.

In addition to the Phase III RE-LY trial, an international, observational study (GLORIA-AF), prospectively collected (in its second phase) safety and effectiveness data in newly diagnosed NVAF patients on dabigatran etexilate in a real-world setting. Outcomes were reported as observed (unadjudicated). The study included 4,859 patients on dabigatran etexilate (dosages according to local clinical practice and local label; 55% treated with 150 mg bid, 43% treated with 110 mg bid, 2% treated with 75 mg bid). Patients were followed-up for 2 years. The mean $CHADS_2$ and HAS-BLED scores were 1.9 and 1.2, respectively, compared to a mean $CHADS_2$ and HAS-BLED score of 2.1 and 1.3 in RE-LY, respectively. Mean on-therapy follow-up time was 18.3 months. Major bleeding occurred in 0.97 per 100 patient-years. Life-threatening bleeding was reported in 0.46 per 100 patient-years, intracranial haemorrhage in 0.17 per 100 patient-years and gastrointestinal bleeding in 0.60 per 100 patient-years. Stroke occurred in 0.65 per 100 patient-years. Furthermore, in an obervational study in more than 134,000 elderly patients (≥65 years) with nonvalvular atrial fibrillation (NVAF) in the United States (contributing more than 37,500 patient-years of follow-up time), patients were treated with either PRADAXA or warfarin, under real-world conditions between October 2010 and December 2012. Dabigatran etexilate (84% patients treated with 150 mg bid, 16% patients treated with 75 mg bid) was associated with a statistically significant reduced risk of ischemic stroke (hazard ratio 0.80, 95% confidence interval [CI] 0.67 – 0.96), intracranial hemorrhage (hazard ratio 0.34, CI 0.26 – 0.46), and mortality (hazard ratio 0.86, CI 0.77 – 0.96) and increased risk of gastrointestinal bleeding (hazard ratio 1.28, CI 1.14 – 1.44) compared to warfarin. No significant difference was found for major bleeding (hazard ratio 0.97, CI 0.88 – 1.07).

In both these studies, the observations in real-world settings were consistent with the established safety and efficacy profile for PRADAXA in this indication.

DRUG INTERACTIONS

Overview

Concomitant use of PRADAXA with other anticoagulants is contraindicated (see CONTRAINDICATIONS). Concomitant use with antiplatelet agents is not recommended (see WARNINGS AND PRECAUTIONS, Bleeding).

CYP P450 System

Based on *in vitro* evaluations, neither dabigatran etexilate nor its active moiety, dabigatran, are metabolised by the human cytochrome P450 system, nor do they exhibit effects on human CYP P450 isozymes.

Transporter interactions

Dabigatran etexilate, but not dabigatran, is a substrate with moderate affinity for the efflux P-glycoprotein (P-gp) transporter. Therefore, potent P-gp inducers or inhibitors may be expected to impact exposure to dabigatran.

P- glycoprotein inhibitors: Concomitant treatment with strong P-gp inhibitors, such oral ketoconazole is contraindicated (see CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS, Bleeding).

For other P-gp inhibitors, such as amiodarone, quinidine and verapamil, see Table 14 below and DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, *Patients taking the P-gp inhibitor verapamil*).

P-gp inhibitors such as but not limited to cyclosporine, itraconazole, nelfinavir, posaconazole, ritonavir, saquinavir, tacrolimus and tipranavir may be expected to increase systemic exposure to dabigatran and should be used with caution.

The concomitant use of PRADAXA with the fixed-dose combination of the P-gp inhibitors glecaprevir/pibrentasvir has been shown a 2.05 and 2.38-fold increase of dabigatran C_{max} and AUC and may increase the risk of bleeding. Concomitant use of dabigatran and strong P-glycoprotein (P-gp) inhibitors, i.e. oral ketoconazole or oral glecaprevir/pibrentasvir is contraindicated (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, P-gp inhibitors).

P- glycoprotein inducers: Potent P-gp inducers such as the anticonvulsants carbamazepine, phenytoin and Saint John's Wort are expected to reduce dabigatran systemic exposure. Co-administration with PRADAXA is not recommended. Caution is advised when co-administering these drug products.

P-glycoprotein substrates: Dabigatran etexilate is not expected to have a clinically meaningful interaction with P-gp substrates that do not also act as inhibitors or inducers of

P-gp.

Drug-Drug Interactions

Table 14: Summary of Pharmacokinetic Drug-Drug Interactions

Proper name	Ref*	Effect	Clinical comment
Acetylsalicylic acid (ASA)	CT	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. In AF patients (RE-LY) treated for the prevention of stroke and systemic embolism, co-administration of ASA increased the risk of bleeding by about 2-fold.	Use with caution. Close observation for signs of bleeding is recommended (see WARNINGS AND PRECAUTIONS, Bleeding, Table 1). AF patients: If necessary, co-administration of low-dose ASA, i.e. ≤100 mg daily, with PRADAXA may be considered for indications other than stroke prevention in AF. Note that in the RE-LY trial; there was no evidence that adding ASA to dabigatran or warfarin improved stroke outcomes (see CLINICAL TRIALS, Stroke Prevention in Atrial Fibrillation).
Amiodarone	CT	A single oral dose of 600mg amiodarone increased dabigatran AUC by 60% and C_{max} by 50%. Orthopedic patients have a higher risk of major and clinically relevant bleeding, which can be further increased by concomitant administration of amiodarone. In AF patients, dabigatran concentrations were increased by ≤14% and no increased risk of bleeding was observed compared to patients on warfarin and amiodarone.	Prevention of VTE after THR or TKR surgery Adjust dosing to 150 mg daily PRADAXA taken as 2 capsules of 75 mg. Caution should be exercised (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Patients taking P-glycoprotein inhibitors). AF patients: No dose adjustment is generally recommended. Use with caution. Occasional testing of aPTT may be considered to rule out excessive anticoagulant effect. Treatment of VTE and Prevention of Recurrent DVT and PE: No dose adjustment is generally recommended. Use with caution.
Antacids (aluminium compounds, sodium bicarbonate, calcium and/or magnesium compounds, or combinations of	CT	In population PK analyses, over the first 24 hours following surgery, dabigatran exposure was reduced by 35%. Thereafter, (> 24 hours after surgery), a reduction of about 11% was observed.	As may be expected for any drug resulting in an increase in gastric pH, diminished clinical effect may occur during PRADAXA administration. PRADAXA should be administered at least 2 hours before taking an antacid (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage

Proper name	Ref*	Effect	Clinical comment
these)			Adjustment, Patients taking antacids). Prevention of VTE after THR or TKR surgery Co-administration with PRADAXA should be avoided within 24 hours after orthopedic surgery.
Atorvastatin	CT	Co-administration of atorvastatin with dabigatran decreased dabigatran concentrations by about 20%.	No dose adjustment is recommended.
Clarithromycin	CT	Co-administration of 500 mg clarithromycin bid with dabigatran etexilate caused no clinically relevant PK-interaction (increased AUC by 19% and C_{max} by 15%).	No dose adjustment is recommended. Caution should be exercised.
Clopidogrel	CT	With a loading dose of 300 or 600 mg clopidogrel, dabigatran AUCt,ss and C_{max},ss were increased by about 30-40%. In AF patients treated for the prevention of stroke and systemic embolism, co-administration of clopidogrel increased the risk of bleeding by about 2-fold.	Use with caution. Close observation for signs of bleeding is recommended (see WARNINGS AND PRECAUTIONS, Bleeding, Table 1) AF patients: Note that in the RE-LY trial, there was no evidence that adding clopidogrel to dabigatran or warfarin improved stroke outcomes (see CLINICAL TRIALS, Stroke Prevention in Atrial Fibrillation).
Diclofenac *(NSAID)*	CT	When dabigatran etexilate was co-administered with diclofenac, pharmacokinetics of both drugs appeared unchanged. 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.	No dose adjustment is recommended. Use with caution due to the risk of haemorrhage, especially GI haemorrhage, notably with NSAIDs with elimination half-lives >12 hours. There is limited evidence with the use of regular NSAID medication with half-lives of <12 hours during treatment with dabigatran etexilate and this has not suggested additional bleeding risk. Close observation for signs of bleeding is recommended (see WARNINGS AND PRECAUTIONS, Bleeding, Table 1).
Digoxin	CT	When dabigatran etexilate was co-administered with digoxin, no PK-interaction was observed.	No dose adjustment is recommended.
Dronedarone	CT	Single and multiple doses of 400 mg dronedarone increased total dabigatran $AUC_{0-\infty}$ by 114-136% and C_{max} by 87-125%. When single and multiple doses of dronedarone were given 2 hours after dabigatran etexilate, dabigatran $AUC_{0-\infty}$	**PRADAXA should not be used with dronedarone** since it may increase the risk of bleeding.

Proper name	Ref*	Effect	Clinical comment
		and C_{max} increased by 30% and 60%, respectively.	
Ketoconazole	CT	Single and multiple oral doses of 400 mg ketoconazole increased total dabigatran $AUC_{0-\infty}$ by 138-153% and C_{max} by 135-149%.	**Co-administration of systemic ketoconazole with PRADAXA is contraindicated** (see CONTRAINDICATIONS).
Glecaprevir/ pibrentasvir	CT	The concomitant use of dabigatran and glecaprevir/pibrentasvir had a 2.05 and 2.38-fold increase of dabigatran C_{max} and AUC, respectively.	The concomitant use of dabigatran and glecaprevir/pibrentasvir is contraindicated (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).
Pantoprazole/Proton Pump Inhibitors (PPIs)	CT	When dabigatran etexilate was co-administered with pantoprazole, a decrease in dabigatran AUC of about 30 % was observed. In RE-LY, PPI co-medication did not result in lower trough levels and on average only slightly reduced post-dose concentrations (- 11 %).	No dose adjustment is recommended. Diminished clinical effect of PRADAXA may occur, as may be expected for any drug resulting in an increase in gastric pH.
Quinidine	CT	Dabigatran exposure in healthy subjects was increased by 53 % (1.5 fold) in the presence of quinidine. Orthopedic patients have a higher risk of major and clinically relevant bleeding, which can be further increased by concomitant administration of quinidine. In AF patients, concomitant administration of quinidine with dabigatran etexilate did not appear to increase the relative risk of bleeding compared to subjects on warfarin and quinidine.	Prevention of VTE after THR or TKR surgery Adjust dosing to 150 mg daily PRADAXA taken as 2 capsules of 75 mg. Caution should be exercised. (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Patients taking P-glycoprotein inhibitors).
			AF patients No dose adjustment is recommended. However, if possible, to minimise potential for interaction, PRADAXA should be given at least two 2 hours before quinidine. Caution should be exercised.
			Treatment of VTE and Prevention of Recurrent DVT and PE: No dose adjustment is recommended. Caution should be exercised.
Rifampicin	CT	After 7 days of treatment with 600 mg rifampicin q.d., total dabigatran $AUC_{0-\infty}$ was reduced by 67% and C_{max} by 66% compared to the reference treatment. Dabigatran exposure returned close to reference after discontinuation of rifampicin for 7 days.	Concomitant use of PRADAXA with rifampicin should be avoided. Concomitant use would be expected to result in substantially diminished anticoagulant effect of PRADAXA.
Selective serotonin re-	CT	SSRI use increased the risk of bleeding in AF patients treated with 110 mg and	Use with caution.

Proper name	Ref*	Effect	Clinical comment
uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs)		150 mg dabigatran etexilate bid and warfarin by about 50-100%. SNRI use increased the risk of bleeding in AF patients treated with 110 mg and 150 mg dabigatran etexilate bid by about 100%.	
Ticagrelor	CT	Concomitant use of ticagrelor with dabigatran etexilate increases exposure to dabigatran. Simultaneous concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg dabigatran etexilate (in steady state, multiple doses, bid) increased dabigatran AUC by 49% and C_{max} by 65%. When a loading dose of 180 mg ticagrelor was given 2 hours after 110 mg dabigatran etexilate bid, dabigatran AUC increased by 27% and C_{max} by 24%. Compared with dabigatran etexilate given alone, concomitant administration of 90 mg ticagrelor bid (maintenance dose) with 110 mg dabigatran etexilate bid increased dabigatran AUC by 26% and C_{max} by 29%.	Concomitant use with PRADAXA is not recommended as it may lead to increased risk of bleeding (see WARNINGS AND PRECAUTIONS, Bleeding).
Verapamil	CT	Co-administration of 150 mg dabigatran etexilate once daily with moderate doses (120mg bid or 240 mg) of oral verapamil resulted in variable increases of dabigatran AUC (20-150%) and C_{max} (10-180%) depending on the timing (1 hour prior, concurrently, 2 hours after, steady state) of administration and the formulation (immediate- or extended-release) of verapamil used. Orthopedic patients have a higher risk of major and clinically relevant bleeding, which can be further increased by concomitant administration of verapamil. In AF patients, co-administration with verapamil at least once increased dabigatran plasma concentrations by ≤ 21% and no increased risk of bleeding was observed. No meaningful interaction is expected with parenteral application of verapamil.	All Patients: Simultaneous initiation of treatment with PRADAXA and verapamil should be avoided at any time. In all cases, to minimize potential interaction, PRADAXA should be given at least 2 hours before verapamil. Caution should be exercised. Close clinical surveillance (looking for signs of bleeding or anaemia) is required. Prevention of VTE after THR or TKR surgery Dosing should be reduced to 150 mg PRADAXA taken as 2 capsules of 75 mg. In patients with moderate renal impairment, a dose reduction of PRADAXA to 75 mg taken once daily should be considered. Treatment initiation with verapamil should be avoided in patients following orthopedic surgery who are already treated

Proper name	Ref*	Effect	Clinical comment
			with PRADAXA. (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Patients taking P-glycoprotein inhibitors).
			AF patients: No dose adjustment is recommended.
			Treatment of VTE and Prevention of Recurrent DVT and PE: No dose adjustment is recommended. Caution should be exercised.

* C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

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

Drug-Herb Interactions

Drug-herb interactions have not been investigated. Potent P-gp inducers such as Saint John's Wort (Hypericum perforatum) may be expected to reduce systemic exposure of dabigatran. Co-administration of these products is not recommended.

Drug-Laboratory Interactions

Drug-laboratory interactions have not been investigated.

Drug-Lifestyle Interactions

Alcohol: No direct interaction between dabigatran etexilate and alcohol was demonstrated in animal models or has been hypothesized.

Ability to drive and use machine: The effect of PRADAXA on the ability to drive, cycle and use machines has not been investigated. However, no such interaction is to be expected.

DOSAGE AND ADMINISTRATION

As for any non-vitamin K antagonist oral anticoagulant (NOAC) drug, before initiating PRADAXA (dabigatran etexilate), ensure that the patient understands and is prepared to accept adherence to NOAC therapy, as directed.

PRADAXA (dabigatran etexilate) should be taken orally with the entire capsule to be swallowed whole. The capsule should not be chewed, broken, or opened.

PRADAXA should be taken regularly, as prescribed, to ensure optimal effectiveness. All temporary discontinuations should be avoided, unless medically indicated.

Monitoring renal function:

Before starting PRADAXA: Determine estimated creatinine clearance (eCrCl) in all patients.

During PRADAXA treatment: Monitor renal function as clinically appropriate.

Determination of renal function by eCrCl should occur at least once per year, and especially during circumstances when renal function may be expected to be compromised, i.e., acute myocardial infarction (AMI), acute decompensated heart failure (AHF), increased use of diuretics, use of certain co-medications, dehydration, hypovolemia, etc. Clinically relevant deterioration of renal function may require dosage adjustment or discontinuation of PRADAXA (see Renal Impairment).

Glomerular filtration rate may be estimated by calculating eCrCl, using the following formula:

eCrCl (mL/min) =

in males: $\frac{(140\text{-age})\ (\text{years}) \times \text{weight (kg)} \times 1.23}{\text{serum creatinine } (\mu\text{mol/L})}$ or, $\frac{(140\text{-age})\ (\text{yrs}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/100 mL)}}$

in females: $\frac{(140\text{-age})\ (\text{years}) \times \text{weight (kg)} \times 1.04}{\text{serum creatinine } (\mu\text{mol/L})}$ or, $\frac{(140\text{-age})\ (\text{yrs}) \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/100mL)}}$

Elderly: As with any anticoagulant, caution is required when prescribing PRADAXA to the elderly (see CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS, Bleeding). Renal impairment may be frequent in the elderly (>75 years of age).

Renal impairment: PRADAXA is contraindicated in patients with severe renal impairment (eCrCl <30 mL/min) (see CONTRAINDICATIONS).

Patients taking the P-glycoprotein (P-gp) inhibitor verapamil (see DRUG INTERACTIONS): Simultaneous initiation of treatment with PRADAXA and verapamil should be avoided at any time. In all cases, to minimize potential interaction, PRADAXA should be given at least 2 hours before verapamil.

Patients at higher risk of bleeding: As for any anticoagulant, PRADAXA is NOT indicated in patients at excessive risk of bleeding (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).**

Patient Body Weight: Population PK modelling showed that patients with a body weight of about 120 kg have about 20% lower drug exposure. Patients with a body weight of about 48 kg have about 25% higher drug exposure compared to patients with average weight. No dose

adjustment is deemed necessary.

Recommended Dose and Dosage Adjustment

VTE prevention following elective hip- or knee-replacement surgery

General: Treatment should normally be initiated within 1-4 hours of completed surgery once hemostasis is secured. If hemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery for whatever reason, then treatment should be initiated with 2 capsules at once.

Table 15: Recommended dose and dosage adjustment for VTE prevention following elective hip - or knee-replacement surgery

<table>
<tr><th>Patient population</th><th>Sub-population</th><th>PRADAXA starting dose (day of surgery)</th><th>PRADAXA maintenance dose</th><th>Dosing schedule and Treatment duration</th></tr>
<tr><td rowspan="2">General</td><td>After elective knee-replacement surgery</td><td rowspan="2">1 capsule of 110 mg</td><td rowspan="2">2 capsules of 110 mg</td><td>Once daily for 10 days</td></tr>
<tr><td>After elective hip-replacement surgery</td><td>Once daily for 28-35 days</td></tr>
<tr><td rowspan="4"></td><td>With moderate renal impairment (eCrCl 30-50 ml/min)</td><td>1 capsule of 75 mg</td><td>2 capsules of 75 mg</td><td rowspan="4">Once daily</td></tr>
<tr><td>Elderly >75 years old</td><td colspan="2" rowspan="2">Consider 2 capsules of 75 mg</td></tr>
<tr><td>Taking P-gp inhibitors, including amiodarone, quinidine and verapamil</td></tr>
<tr><td>With moderate renal impairment and taking P-gp inhibitor verapamil</td><td colspan="2">Consider 1 capsule of 75 mg</td></tr>
</table>

Patients taking the P-gp inhibitor verapamil: Treatment initiation with verapamil should be avoided in patients following orthopedic surgery who are already treated with PRADAXA.

Patients taking antacids, including aluminium compounds, sodium bicarbonate, calcium and/or magnesium compounds, or combinations of these (see DRUG INTERACTIONS)**:**

- Co-administration of an antacid with PRADAXA should be avoided within 24 hours after orthopedic surgery.
- PRADAXA should be administered at least 2 hours before taking an antacid.

Treatment and prevention of DVT and PE

General: Start treatment with PRADAXA following treatment with a parenteral anticoagulant for 5-10 days. The duration of therapy should be individualized after careful assessment of the treatment benefit against the risk of bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. surgery, trauma, immobilisation) and extended duration should be based on permanent risk factors or idiopathic DVT or PE.

Table 16: Recommended dose and dosage adjustment for the treatment and prevention of DVT and PE

Patient population	PRADAXA dose	Dosing schedule
General	1 capsule of 150 mg	Twice daily
Elderly ≥ 80 years	1 capsule of 110 mg	
At higher risk of bleeding, including elderly ≥ 75 years with ≥ 1 risk factor for bleeding		

Elderly: The information of dose adjustment in this patient population has been extrapolated based on the PK/PD analysis of PRADAXA and has not been studied in this clinical setting.

Renal impairment: A dose reduction from 150 mg bid to 110 mg bid in the prevention or treatment of DVT/PE in patients with moderate renal impairment (eCrCl 30-50 mL/min) has not been studied and cannot be recommended. The dose selected should be based on the risk/benefit assessment of a given patient.

Patients at higher risk of bleeding*:* There are limited clinical data available for patients with multiple risk factors for bleeding. In these patients, PRADAXA should only be given if the expected benefit outweighs bleeding risks.

Prevention of stroke and systemic embolism in patients with atrial fibrillation

Table 17: Recommended dose and dosage adjustment for the prevention of stroke and systemic embolism in patients with atrial fibrillation

Patient population	PRADAXA dose	Dosing schedule
General	1 capsule of 150 mg	Twice daily
Elderly ≥ 80 years	1 capsule of 110 mg	
At higher risk of bleeding, including elderly ≥ 75 years with ≥ 1 risk factor for bleeding		

Elderly:

- Patients ≥80 years of age: Alternate dosing may be considered for other geriatric patients (see CLINICAL TRIALS, Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation, Table 38 and Table 39).
- Patients >75 years of age with ≥1 risk factor for bleeding (see WARNINGS AND PRECAUTIONS, Bleeding, Table 1). The dosing may also be considered for patients taking concomitant anti-platelet agents or P-gp inhibitors (see ADVERSE REACTIONS, *Bleeding*, Table 9). The effectiveness of stroke prevention may be expected to be lessened with this dosage regimen, compared to that of the usual 1 capsule of 150 mg PRADAXA twice daily.

Renal impairment: No dose adjustment is generally needed in patients with moderate renal impairment (eCrCl 30-50 mL/min). (see CLINICAL TRIALS, Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation, Table 40 and Table 41).

Switching treatment

Switching from parenteral anticoagulants treatment to PRADAXA: Treatment with PRADAXA should be initiated 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 heparin, (UFH)].

Switching from PRADAXA treatment to parenteral anticoagulant:

- *VTE prevention following hip- or knee-replacement surgery*: Wait **24 hours** after the last dose of PRADAXA before switching to a parenteral anticoagulant.

- *Treatment and prevention of DVT and PE:* wait **12 hours** after the last dose of PRADAXA before switching to a parenteral anticoagulant.

- *Prevention of stroke and systemic embolism in patients with atrial fibrillation*: Wait **12 hours** after the last dose of PRADAXA before switching to a parenteral anticoagulant.

Switching from Vitamin K antagonists (VKAs) to PRADAXA: PRADAXA should only be started after VKAs have been discontinued, and the patient's INR found to be <2.0.

Switching from PRADAXA to VKAs: As with any short-acting anticoagulant, there is a potential for inadequate anticoagulation when transitioning from PRADAXA to a VKA. It is important to maintain an adequate level of anticoagulation when transitioning patients from one anticoagulant to another.

The starting time of the VKA should be adjusted according to the patient's calculated creatinine clearance (eCrCl) as follows:

- eCrCl ≥ 50 mL/min, start VKA 3 days before discontinuing PRADAXA
- eCrCl ≥ 30 to < 50 mL/min, start VKA 2 days before discontinuing PRADAXA

In general, after starting VKA therapy, its clinically relevant anticoagulant effect is not readily apparent for at least 2 days, while the full therapeutic effect is achieved in about 5-7 days.

Note that when converting a patient from PRADAXA to VKA therapy, the INR will not reliably reflect the anticoagulant effect of VKA until at least 2 days after discontinuation of PRADAXA. In switching from PRADAXA to VKA, the INR should only be used to assess the anticoagulant effect of the VKA.

The INR is only calibrated and validated for VKA and should not be used for any other anticoagulant, including PRADAXA.

Cardioversion and catheter ablation for atrial fibrillation

Patients can stay on PRADAXA while being cardioverted (see WARNINGS AND PRECAUTIONS, Cardiovascular, *Cardioversion*).

Catheter ablation can be conducted in patients on 150 mg twice daily PRADAXA treatment. PRADAXA treatment does not need to be interrupted (see WARNINGS AND PRECAUTIONS, Cardiovascular, *Catheter ablation for atrial fibrillation*).

Missed Dose

In all cases, patients should not take a double dose to make up for missed individual doses.

- *Prevention of venous thromboembolism in patients following orthopaedic surgery:* Patients can continue with their remaining daily doses of PRADAXA at the scheduled time of the next day.

- *Treatment and prevention of DVT and PE:* A forgotten 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.

- *Prevention of stroke and systemic embolism in patients with atrial fibrillation:* If the prescribed dose of PRADAXA is not taken at the scheduled time, the dose should be taken as soon as possible on the same day. A forgotten 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. For optimal effect and safety, it is important to take PRADAXA regularly twice a day, at approximately 12 hour intervals.

Administration

PRADAXA should be taken with a full glass of water to facilitate delivery to the stomach. PRADAXA may be taken with food, or on an empty stomach. Patients experiencing dyspepsia should take PRADAXA with meals. Based on clinical judgment, treatment with a proton-pump inhibitor may be considered in patients still experiencing dyspepsia despite taking PRADAXA with or within 30 minutes after meals.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Doses of PRADAXA (dabigatran etexilate) beyond those recommended expose the patient to increased risk of bleeding. Excessive anticoagulation may require discontinuation of PRADAXA.

The use of activated charcoal to reduce absorption in case of PRADAXA overdose may be considered.

In case of complications such as bleeding or need for urgent required surgical procedures, associated with an overdose with PRADAXA, when rapid reversal of the anticoagulation effect is required use of the specific reversal agent, PRAXBIND (idarucizumab), should be considered.

Management of Bleeding

In the event of haemorrhagic complications in a patient receiving PRADAXA, treatment must be discontinued, and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route, adequate diuresis must be maintained. Appropriate standard treatment, e.g. surgical hemostasis as indicated and blood volume replacement, should be undertaken. In addition, consideration may be given to the use of fresh whole blood or the transfusion of fresh frozen plasma.

For a list of assays to assess anticoagulant activity of dabigatran, see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests.

For situations of life-threatening or uncontrolled bleeding in the setting of PRADAXA overdose, when rapid reversal of the anticoagulation effects of dabigatran is required, use of the specific reversal agent, PRAXBIND, should be considered (see WARNINGS AND PRECAUTIONS, Bleeding).

In rare circumstances when mandated clinically, combined or overlapping use of PRAXBIND with one of the following procoagulants may be considered:

- activated prothrombin complex concentrates (aPCC), e.g., FEIBA
- recombinant Factor-VIIa (rFVIIa)
- prothrombin complex concentrate (PCC)

There is some experimental evidence to support the role of these procoagulant agents in reversing the anticoagulant effect of dabigatran but their usefulness in clinical settings has not yet been clearly demonstrated. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet drugs have been used.

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of PRADAXA and should not be used for this specific reason.

Hemodialysis
As protein binding is low, dabigatran can be dialysed, although there is limited clinical experience in using dialysis in this setting.

Clearance of dabigatran by hemodialysis 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 total dabigatran concentrations, respectively, depending on the blood-flow rate. The amount of drug cleared by dialysis was 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

PRADAXA (dabigatran etexilate) is a prodrug which does not exhibit anticoagulant activity itself. Following 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, reversible direct thrombin inhibitor and is the main active principle in plasma. Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

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

Pharmacodynamics

There is a clear correlation between plasma dabigatran concentration and degree of anticoagulant effect. The maximum effect (E_{max}) of dabigatran on pharmacodynamic (PD) parameters occurred at the same time as C_{max}, indicating that thrombin inhibition by dabigatran is a direct effect, linked to the central plasma compartment.

Table 18 below shows peak and trough dabigatran plasma concentrations at steady-state in the RE-LY trial following administration of PRADAXA 110 mg and 150 mg bid in patients with atrial fibrillation, expressed as median values (10^{th} to 90^{th} percentiles):

Table 18:

Dose and Regimen	C2h,ss (ng/mL)	Cpre,ss (ng/mL)
110 mg bid	133 (52–275)	66 (28–155)
150 mg bid	184 (74–383)	93 (40–215)

C2h,ss = dabigatran plasma concentration measured at steady-state 2 hours (deemed peak) after the last dose

Cpre,ss = dabigatran plasma concentration measured at steady-state 10–16 hours (deemed trough) after the last dose

Pharmacokinetics

After oral administration of dabigatran etexilate in healthy volunteers, the pharmacokinetic (PK) profile of dabigatran in plasma is characterised by a rapid increase in plasma concentrations with C_{max} attained 0.5 - 2.0 hours post-administration. After C_{max}, plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of approximately 11 hours in healthy elderly subjects. Following administration of multiple doses, a terminal half-life of about 12-14 hours was observed, with the half-life independent of dose. C_{max} and AUC were dose-proportional.

Half-life is prolonged if renal function is impaired as shown in Table 19.

Table 19: Half-life of total dabigatran in relation to renal function

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

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

Table 20: Summary of PK parameters after single and repeated oral administration in humans

	C_{max}	$t_{½}$ (h)	AUC	Clearance, Excretion	Volume of distribution
Healthy volunteers	0.8 – 1.4 ng/mL/mg	11 hours	6-10 ng*h/mL/mg	Urine (85%) Fecal (6%) Total clearance (IV): about 120 mL/min	Vss = 60-70 L
Patients treated for prevention of VTE after hip- or knee-replacement surgery	C_{max}:1.22 ng/mL/mg T_{max}: 7 – 9 hours following surgery	14-17 hours	9.7 ng*h/mL/mg	n/a (no IV data)	n/a (no IV data)

The oral bioavailability may be increased by 75% (about 1.8 -fold) 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 PRADAXA. 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, Administration).

Absorption: A study evaluating post-operative absorption of PRADAXA, 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- 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 concentration-independent binding of dabigatran to human plasma proteins (about 35%) 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: 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 metabolised in the liver by conjugation with activated glucuronic acid forming pharmacologically active acylglucuronides. Four positional isomers, 1-O, 2-O, 3-O, 4-O-acylglucuronide exist, each accounting for <10% of total dabigatran in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods. CYP 450 metabolic enzymes are not involved in dabigatran metabolism.

Excretion: Metabolism and excretion of dabigatran were studied following a single intravenous (iv) dose of radiolabeled dabigatran in healthy male subjects. After an iv 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.

Hepatic elimination via the bile represents a minor elimination pathway (approximately 20% of the administered 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.

Special Populations

Geriatrics: Elderly subjects showed an increase of 40- 60% (1.4 - 1.6-fold) in the AUC and about 25% (1.3-fold) in C_{max}, compared to young subjects.

Patients >65 years of age: The $AUC_{\tau,ss}$ and $C_{max,ss}$ in elderly females were approximately 1.9-fold and 1.6-fold higher, respectively, than in younger females. In elderly males, the $AUC_{\tau,ss}$ and $C_{max,ss}$ were 2.2-fold and 2.0-fold higher, respectively, than in male subjects aged 18-40 years.

The observed increase of dabigatran exposure correlated with the age-related reduction in creatinine clearance.

Patient ≥75 years
In AF patients in RE-LY, compared to subjects aged 65-75 years, subjects ≥75 years of age showed about 31% (about 1.3-fold) increase in through concentration, while subjects <65 years of age showed about 22% lower through concentration.

Gender: Primary VTE prevention studies: Drug exposure was about 40-50% higher (1.4- 1.5-fold) in female patients than in male patients.

Atrial fibrillation patients: Females had on average 30 % higher (1.3-fold) trough and post-dose concentrations.

Race: The PK of dabigatran were investigated in Caucasian and Japanese volunteers after single and multiple doses. Ethnic origin did not affect the PK of dabigatran in a clinically relevant manner. Only limited PK data in patients from African descent are available.

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

Renal Insufficiency: Following oral dosing with dabigatran etexilate, there is a direct correlation of systemic exposure to dabigatran with degree of renal impairment. Severe renal insufficiency (eCrCl < 30 mL/ min) increased exposure to dabigatran 6-fold (see CONTRAINDICATIONS) while moderate renal impairment (eCrCl 30-50 mL/min) increased exposure 2.7-fold.

In the RE-LY trial, compared to patients without renal impairment (eCrCl ≥80 mL/min), patients with moderate renal impairment (eCrCl 30-50 mL/min) had on average 2.2-fold and 1.8-fold higher pre- and post-dose dabigatran plasma concentrations with 150 mg bid dosing, and 2.4-fold and 1.8-fold-higher pre- and post-dose dabigatran concentrations with 110 mg bid.

In RE-COVER, patients with mild (CrCl >50 mL/min but <80 mL/min) and moderate (CrCl between 30-50 mL/min) renal impairment had on average 1.7-fold and 3.4-fold higher steady state dabigatran trough concentrations compared with patients with CrCl > 80 mL/min.

Hemodialysis: As protein binding is low, dabigatran can be dialysed, although there is limited clinical experience in using dialysis in this setting (see Management of Bleeding).

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

Cardioversion: A total of 1,255 subjects had cardioversions performed during the RE-LY study, 409 (6.8%), 415 (6.8%) and 431 (7.2%) in the dabigatran etexilate 110 mg, dabigatran etexilate 150 mg, and warfarin treatment groups, respectively. The rate of stroke occurring within 30 days of cardioversion was low and similar across all treatment groups, i.e., dabigatran etexilate 110 mg (0.03%), dabigatran etexilate 150 mg (0.03%) and warfarin (0.02%) (see WARNINGS AND PRECAUTIONS, Cardiovascular, Cardioversion).

Catheter Ablation for Atrial Fibrillation:

A prospective, randomized, open-label, multicenter, exploratory study with blinded, centrally adjudicated endpoint evaluation (RE-CIRCUIT) was conducted in patients who were under stable anticoagulant and eligible for dabigatran 150 mg twice daily treatment. The study compared 150 mg twice daily uninterrupted dabigatran etexilate with uninterrupted INR-adjusted warfarin in patients with paroxysmal or persistent atrial fibrillation who underwent catheter ablation. Of the 704 enrolled patients, 635 patients underwent catheter ablation procedure (317 on uninterrupted dabigatran and 318 on uninterrupted warfarin). All patients underwent a Trans-oesophageal Echocardiography (TEE) prior to catheter ablation. The primary outcome , adjudicated major bleeding according to the International Society on Thrombosis and Hemostasis (ISTH) criteria, occurred in 5 (1.6 %) patients in the dabigatran etexilate group and 22 (6.9 %) patients in the warfarin group (risk difference −5.3%; 95% CI −8.4, −2.2; P=0.0009). There was no stroke/systemic embolism/TIA (composite) event in the dabigatran etexilate arm, and one event (TIA) in the warfarin arm from the time of ablation until 8 weeks post-ablation. This study demonstrated that dabigatran etexilate was associated with a significant reduction in major bleeding event (MBE) rate compared with INR-adjusted warfarin, in the setting of ablation.

Patients who underwent Percutaneous coronary intervention (PCI) with stenting:

A prospective, randomized, open-label, blinded endpoint (PROBE) study (Phase IIIb) to evaluate dual-therapy with dabigatran etexilate (110 mg or 150 mg bid) plus clopidogrel or ticagrelor ($P2Y_{12}$ antagonist) vs. triple-therapy with warfarin (adjusted to a INR 2.0 – 3.0) plus clopidogrel or ticagrelor and aspirin was conducted in patients with nonvalvular atrial fibrillation who underwent a PCI with stenting (RE-DUAL PCI). Patients (n=2725) were randomized to dabigatran etexilate 110 mg bid dual-therapy, dabigatran etexilate 150 mg bid dual-therapy or warfarin triple-therapy. In the triple-therapy group, aspirin was discontinued after 1 month in patients in whom a bare metal stent was implanted and after 3 months in patients in whom a drug-eluting stent was implanted. Elderly patients outside of the United States (≥70 years of age for Japan, ≥80 years of age for all other countries) were randomly assigned to the dabigatran etexilate 110 mg dual-therapy group or the warfarin triple-therapy group. The primary endpoint was time to first major or clinically relevant non-major bleeding event, as defined by ISTH.

The incidence of the primary endpoint was 15.4 % (151 patients) in the dabigatran etexilate 110 mg dual-therapy group as compared with 26.9 % (264 patients) in the warfarin triple-therapy group (HR 0.52; 95% CI 0.42, 0.63; P<0.0001 for non-inferiority and P<0.0001 for superiority) and in 20.2 % (154 patients) in the dabigatran etexilate 150 mg dual-therapy group as compared with 25.7 % (196 patients) in the corresponding warfarin triple-therapy group (HR 0.72; 95% CI 0.58, 0.88; P<0.0001 for non-inferiority Both dabigatran etexilate dual-therapy groups had lower rates of intracranial hemorrhage than the corresponding warfarin triple-therapy group: 0.3% (3 patients) in the 110 mg dabigatran etexilate dual-therapy group as compared with 1.0% (10 patients) in the warfarin triple-therapy group (HR 0.30; 95% CI 0.08, 1.07; P=0.064) and 0.1% (1 patient) in the 150 mg dabigatran etexilate dual-therapy group as compared with 1.0% (8 patients) in the corresponding warfarin triple-therapy group (HR 0.12; 95% CI 0.02, 0.98; P=0.047). The incidence of the composite efficacy endpoint of death, thromboembolic events (myocardial infarction, stroke, or systemic embolism) or unplanned revascularization in the two

dabigatran etexilate dual-therapy groups combined was non-inferior to the warfarin triple-therapy group (13.7% vs. 13.4% respectively; HR 1.04; 95% CI: 0.84, 1.29; P=0.0047 for non-inferiority).

This study demonstrated that dual-therapy, with dabigatran etexilate and a $P2Y_{12}$ antagonist, significantly reduced the risk of bleeding vs. warfarin triple-therapy, with non-inferiority for composite of thromboembolic events, in patients with atrial fibrillation who underwent a PCI with stenting.

STORAGE AND STABILITY

Store between 15 -30°C. Store in the original package in order to protect from moisture.

SPECIAL HANDLING INSTRUCTIONS

Store in a safe place out of the reach of children.

When removing a capsule from the blister, please note the following instructions:

- Tear off one individual blister from the blister card along the perforated line
- Peel off the backing foil and remove the capsule
- The capsule should not be pushed through the blister foil

When taking a capsule out of the bottle, please note the following instructions:

- The cap opens by pushing and turning.
- After removing the capsule, place the cap back on the bottle and tightly close the bottle right away after you take your dose.

Store in the original package in order to protect from moisture.

Do not put the capsules in pill boxes or pill organizers, unless capsules can be maintained in the original package.

Any unused product or waste material should be disposed in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

HPMC (hydroxypropylmethylcellulose) Capsules of 75 mg, 110 mg and 150 mg.

75 mg capsule: 86.48 mg of dabigatran etexilate mesilate corresponding to 75 mg of dabigatran etexilate base. Imprinted hydroxypropylmethyl cellulose capsules with white opaque cap and white opaque body of size 2 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with “R75”.

110 mg capsule: 126.83 mg of dabigatran etexilate mesilate corresponding to 110 mg of dabigatran etexilate base. Imprinted hydroxypropylmethyl cellulose capsule with light blue, opaque cap and light blue, opaque body of size 1 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with "R110".

150 mg capsule: 172.95 mg of dabigatran etexilate mesilate corresponding to 150 mg of dabigatran etexilate base. Imprinted hydroxypropylmethyl cellulose capsules with light blue opaque cap and white opaque body of size 0 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with "R150".

Non-medicinal ingredients: Acacia, dimethicone 350, hydroxypropyl cellulose, hypromellose, tartaric acid. HPMC capsule shell contains: Carragenan, hypromellose, Indigo Carmin (132), potassium chloride, purified water, titanium dioxide.

Printing ink contains: Iron oxide black, potassium hydroxide, propylene glycol, shellac.

Packaging: aluminium blister strips contain 10 x 1HPMC capsules.
Cartons containing 1, 3, or 6 blister strips (10 x 1, 30 x 1, or 60 x 1 HPMC capsules).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proprietary name: Dabigatran etexilate (INN).

The pro-drug dabigatran etexilate is used in its salt form dabigatran etexilate mesilate (BIBR 1048 MS).

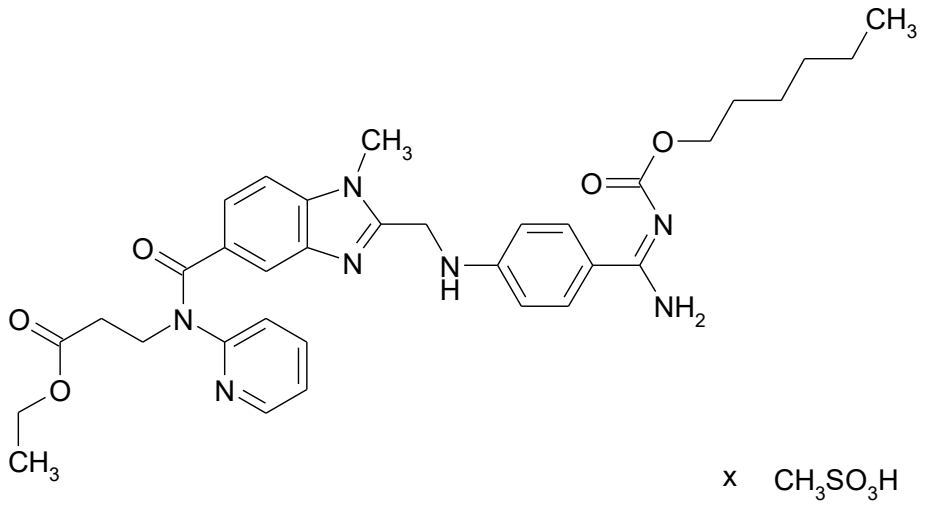
Chemical name: (INN) - Ethyl 3-[[[2-[[[4-[[[(hexyloxy)carbonyl]amino]iminomethyl] phenyl]amino]methyl]-1-methyl-1H- benzimidazol-5-yl]carbonyl](pyridin-2-yl)amino] propanoate.

(IUPAC) - 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.

(CAS name) - beta-Alanine, N-[[2-[[[4-[[[(hexyloxy)carbonyl]amino] iminomethyl]phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-, ethyl ester, methanesulfonate.

Molecular formula and molecular mass: $C_{34}H_{41}N_7O_5$-CH_4SO_3
723.86 g/mol (salt) and 627.75 g/mol (free base)

Structural formula:



Physicochemical properties:

Chirality:	Dabigatran etexilate mesilate has no chiral centres and therefore does not form enantiomers. Geometric isomers (tautomers) are possible.
Physical Appearance:	Yellow-white to yellow powder. The crystals have a rod-like habit
Melting Point:	180 ± 3°C (DSC: 10 K min-1 heating rate)
Dissociation Constants:	pKa1 = 4.0 ± 0.1 pKa2 = 6.7 ± 0.1
Apparent Partition Coefficient:	The partition coefficient of the neutral form (free base) is log P = 3.8
Hygroscopicity:	Non-hygroscopic
pH-Solubility Profile:	Solubility is strongly pH dependent with increased solubility at acidic pH. The solubility in water is 1.8 mg/mL

Table 21: Solubility in Organic Solvents of Dabigatran etexilate mesilate:

Methanol	freely soluble (> 250 mg/mL)
Ethanol	soluble (approx. 50 mg/mL)
Isopropanol	Sparingly soluble (approx. 10 mg/mL)
Acetone	very slightly soluble (approx. 0.3 mg/mL)
ethyl acetate, toluene, n-hexane and diisopropylether	Practically insoluble (< 0.1 mg/mL).

CLINICAL TRIALS

Prevention of VTE after THR or TKR surgery

Table 22: Summary of patient demographics for Phase III clinical trials in primary prevention of VTE following major orthopaedic surgery

Study #	Trial design	Dosage*, route of administration and duration	Study subjects n=number (dose)**	Mean age	Gender
RE-NOVATE	Randomised, double-blind, parallel group, total hip replacement	Dabigatran etexilate 220 mg qd Dabigatran etexilate 150 mg qd Enoxaparin 40 mg qd For 28 – 42 days	N = 1,157 (D220) N = 1,174 (D150) N = 1,162 (E) N = 3,494 (total)	Mean age 64	Female 54% Male 46%
RE-MODEL	Randomised, double-blind, parallel group, total knee replacement	Dabigatran etexilate 220 mg qd Dabigatran etexilate 150 mg qd Enoxaparin 40 mg qd For 6 -10 days	N= 693 (D220) N= 708 (D150) N= 699 (E) N= 2,100 (total)	Mean age 69	Female 65% Male 35%
RE-MOBILIZE	Randomised, double-blind, parallel group, total knee replacement	Dabigatran etexilate 220 mg qd Dabigatran etexilate 150 mg qd Enoxaparin 30 mg bid For 12 -15 days	N= 862 (D220) N = 877 (D150) N = 876 (E) N= 2,615 (total)	Mean age 66	Female 56% Male 44%

* Dabigatran etexilate dose - 220 mg q.d., and 150 mg q.d., each initiated with a half dose on the day of surgery
Enoxaparin dose – 40 mg qd, beginning the night prior to surgery; 30 mg bid beginning 12-24 hours post-operatively
**D220 – Dabigatran etexilate 220 mg
D150 – Dabigatran etexilate 150 mg
E – Enoxaparin

The clinical trials inclusion and exclusion criteria were uniform across the Phase III programme - the mean age was >65 years, about 60% were female, and the mean BMI was >29. Some important patient subgroups excluded by protocol were: patients with known hepatic disease with potential impact on survival or with baseline elevation of liver function tests above 2 x ULN, patients with severe renal insufficiency (eCrCl <30 mL/min), patients who were or had the potential to become pregnant during the study period, and patients under 40 kg.

All the Phase III trials were non-inferiority studies. The pre-specified primary efficacy endpoint was total VTE and all-cause mortality. A pre-specified meta-analysis of the composite endpoint major VTE and VTE-related death including all the 3 Phase III studies showed that there were no clinically relevant differences with regard to this endpoint between any of the 3 treatment regimens tested in this programme.

Table 23: Analysis of total VTE and all-cause mortality during treatment period for FAS* in Phase III orthopaedic surgery studies

Study	Treatment[+]	FAS*	Incidence (%)	Difference % 95% CI (%)[a]	Difference vs. enoxaparin		
					Lower bound of 95% CI placebo-enoxaparin	Enoxaparin effect preserved[b,c] (%)	p-value[a]
RE-NOVATE	DE 220 mg	880	53 (6.0)	-0.7 (-2.9, 1.6)	23.0%	93.0	<0.0001
	DE 150 mg	874	75 (8.6)	1.9 (-0.6, 4.4)	23.0%	81.0	<0.0001
	Enox 40 mg qd	897	60 (6.7)				
RE-MODEL	DE 220 mg	503	183 (36.4)	-1.3 (-7.3, 4.6)	27.7%	83.3	0.0003
	DE 150 mg	526	213 (40.5)	2.8 (-3.1, 8.7)	27.7%	68.5	0.0173
	Enox 40 mg qd	512	193 (37.7)				
RE-MOBILIZE	DE 220 mg	604	188 (31.1)	5.8 (0.8, 10.8)	27.7%	61.1	0.0895
	DE 150 mg	649	219 (33.7)	8.4 (3.4, 13.3)	27.7%	51.8	0.3749
	Enox 30 mg bid	643	163 (25.3)				
RE-NOVATE & RE-MODEL	DE 220 mg	1383	236 (17.1)	-0.7[e] (-2.9, 1.4)			
	DE 150 mg	1400	288 (20.6)	2.0[e] (-0.3, 4.3)			
	Enox 40 mg qd	1409	253 (18.0)				
RE-NOVATE, RE-MODEL, RE-MOBILIZE	DE 220 mg	1987	424 (21.3)	0.2[e] (-1.7, 2.2)			
	DE 150 mg	2049	507 (24.7)	3.1[e] (1.1, 5.2)[d]			
	Enox	2052	416 (20.3)				

[+] DE = Dabigatran Etexilate, Enox = Enoxaparin.
* Full analysis set
a Probability for testing difference vs. enoxaparin > Minimum Important Difference (MID)
b Calculated as [lower bound (placebo-enoxaparin) - upper bound (dabigatran-enoxaparin)] / lower bound (placebo-enoxaparin)
c MID was defined to preserve 2/3 of the enoxaparin effect size based on the lower bound of the 95% confidence interval. MID was 9.2% for RE-MODEL, 7.7% for RE-NOVATE, and 9.2% for RE-MOBILIZE

Pre-specified secondary endpoints of each of the Phase III trials were the composite of major VTE and VTE-related death, as well as each of the individual components of the 2 composite endpoints, total VTE and all-cause mortality, and major VTE and VTE-related mortality.

Table 24: Analysis of major VTE and VTE-related mortality during treatment period in risk ratio scale for FAS-major in Phase III orthopaedic surgery studies and summary of individual components contributing to major VTE and VTE related mortality during treatment period for FAS-major in Phase III orthopaedic surgery studies

Study	Treatment[+]	FAS-major*	Incidence N (%)	Proximal DVT N(%)	PE N(%)	VTE related death [#] N(%)	Risk ratio 95% CI (%)
RE-NOVATE	DE 220 mg	909	28 (3.1)	22 (2.4)	0 (0.0)	0 (0.0)	0.78 (0.48, 1.27)
	DE 150 mg	888	38 (4.3)	35 (3.9)	1 (0.2)	1 (0.2)	1.09 (0.70, 1.70)
	Enox 40 mg qd	917	36 (3.9)	33 (3.6)	3 (0.3)	0 (0.0)	
RE-MODEL	DE 220 mg	506	13 (2.6)	13 (2.6)	0 (0.0)	0 (0.0)	0.73 (0.36, 1.47)
	DE 150 mg	527	20 (3.8)	18 (3.4)	1 (0.2)	1 (0.2)	1.08 (0.58, 2.01)
	Enox 40 mg qd	511	18 (3.5)	17 (3.3)	0 (0.0)	1 (0.2)	
RE-MOBILIZE	DE 220 mg	618	21 (3.4)	14 (2.3)	6 (1.0)	1 (0.2)	1.51 (0.79, 2.91)
	DE 150 mg	656	20 (3.0)	20 (3.0)	0 (0.0)	0 (0.0)	1.36 (0.70, 2.63)
	Enox 30 mg bid	668	15 (2.2)	10 (1.5)	5 (0.7)	0 (0.0)	
RE-NOVATE & RE-MODEL	DE 220 mg	1415	41 (2.9)	35 (2.5)	5 (0.4)	1 (0.1)	0.77 (0.51,1.14)
	DE 150 mg	1415	58 (4.1)	53 (3.7)	1 (0.2)	4 (0.3)	1.09 (0.76,1.56)
	Enox 40 mg qd	1428	54 (3.8)	50 (3.5)	3 (0.2)	1 (0.1)	
RE-NOVATE, RE-MODEL, RE-MOBILIZE	DE 220 mg	2033	62 (3.0)	49 (2.4)	11 (0.5)	2 (0.1)	0.92 (0.66,1.30)
	DE 150 mg	2071	78 (3.8)	73 (3.5)	1 (0.0)	4 (0.2)	1.14 (0.83,1.57)
	Enox	2096	69 (3.3)	60 (2.9)	8 (0.4)	1 (0.0)	

[+] DE = Dabigatran Etexilate, Enox = Enoxaparin

***** Full analysis set – major

#Patients were counted only one in the most severe category in order of death > PE > proximal DVT

Table 25: Major bleeding events (MBE) and any bleeding events by treatment in the Phase III trials (RE-MODEL, RE-NOVATE and RE-MOBILIZE)

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin
RE-NOVATE (hip)			
Treated patients, N	1,146	1,163	1,154 *
Number of MBE, N (%)	23 (2.0)	15 (1.3)	18 (1.6)
RE-MODEL (knee)			
Treated patients, N	679	703	694 *
Number of MBE, N (%)	10 (1.5)	9 (1.3)	9 (1.3)
RE-MOBILIZE (knee)			
Treated patients, N	857	871	868 **
Number of MBE, N (%)	5 (0.6)	5 (0.6)	12 (1.4)

* Enoxaparin dose 40 mg OD
** Enoxaparin dose 30 mg bid

Treatment of VTE and prevention of recurrent DVT and PE

Table 26: Summary of clinical trials in the acute DVT/PE treatment

Study ID	Study Design	Patient Population	Duration of Treatment[2]	Treatment Groups
RE-COVER	Randomised, parallel-group, double-blind, active-controlled	Patients with acute symptomatic DVT and/or acute symptomatic PE eligible for ≥6 months of anticoagulation	6- months	Randomized: 1281 (DE), 1283 (W) Treated[1]: 1274 (DE), 1265 (W)
RE-COVER II	Randomised, parallel-group, double-blind, active-controlled	Patients with acute symptomatic DVT and/or acute symptomatic PE eligible for ≥6 months of anticoagulation	6- months	Randomized: 1293 (DE), 1296 (W) Treated[1]: 1279 (DE), 1289 (W)

[1] Number of patients who took at least 1 dose of any study medication (i.e., patients in the full analysis set [FAS]
[2] Treatment during the acute DVT/PE treatment studies comprised a single-dummy period and an oral only period (double-dummy period)
DE – Dabigatran Etexilate
W – warfarin (target INR 2.0-3.0)

Clinical evidence has demonstrated dabigatran etexilate to be an effective and safe treatment for DVT and/or PE. Two multi-center, randomised, double-blind, parallel-group, replicate studies, RE-COVER and RE-COVER II, compared dabigatran etexilate (150 mg bid) with warfarin (target INR 2.0-3.0) in patients with acute DVT and/or PE. 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.

In the pooled RE-COVER and RE-COVER II studies, a total of 5,153 patients were randomized and 5,107 were treated. Patients were mostly Caucasian (86.1%).

Table 27: Characteristics of the Patients According to Study and Assigned Study Drug

	RE-COVER, RE-COVER II	
	Dabigatran etexilate	Warfarin
Number of patients (double-dummy period)	N=2553(100.0)	N=2554 (100.0)
Age- mean years±SD	54.8±16.0	54.7±16.2
Gender (Female) - N (%)	1033 (40.5)	1033 (40.4)
Estimated creatinine clearance N/(ml/min) ‡	2525/107.0	2533/105.8
Patients with qualifying event [N (%)]		
Symptomatic PE and symptomatic DVT	226 (8.9)	240 (9.4)
Symptomatic PE only	569 (22.3)	567 (22.2)
Symptomatic DVT only	1755 (68.7)	1744 (68.3)
Immobilization - N (%)	366 (14.3)	381 (14.9)
Thrombophilia -N (%)	209 (8.2)	199 (7.8)
Active cancer at any time - N (%)	173 (6.8)	162 (6.3)
Coronary artery disease - N (%)	165 (6.5)	184 (7.2)
Diabetes mellitus - N (%)	238 (9.3)	224 (8.8)
Hypertension - N (%)	921 (36.1)	892 (34.9)

The duration of treatment with fixed dose of dabigatran was 174.0 days without coagulation monitoring. For patients randomized 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%).

RE-COVER and RE-COVER II demonstrated that in patients presenting with acute DVT and/or PE treated initially for ≥5 days of parenteral therapy, 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 $p=0.0002$). Bleeding events (MBEs, MBE or CRBEs and any bleeding) were significantly lower in patients receiving dabigatran etexilate 150 mg twice daily as compared with those receiving warfarin.

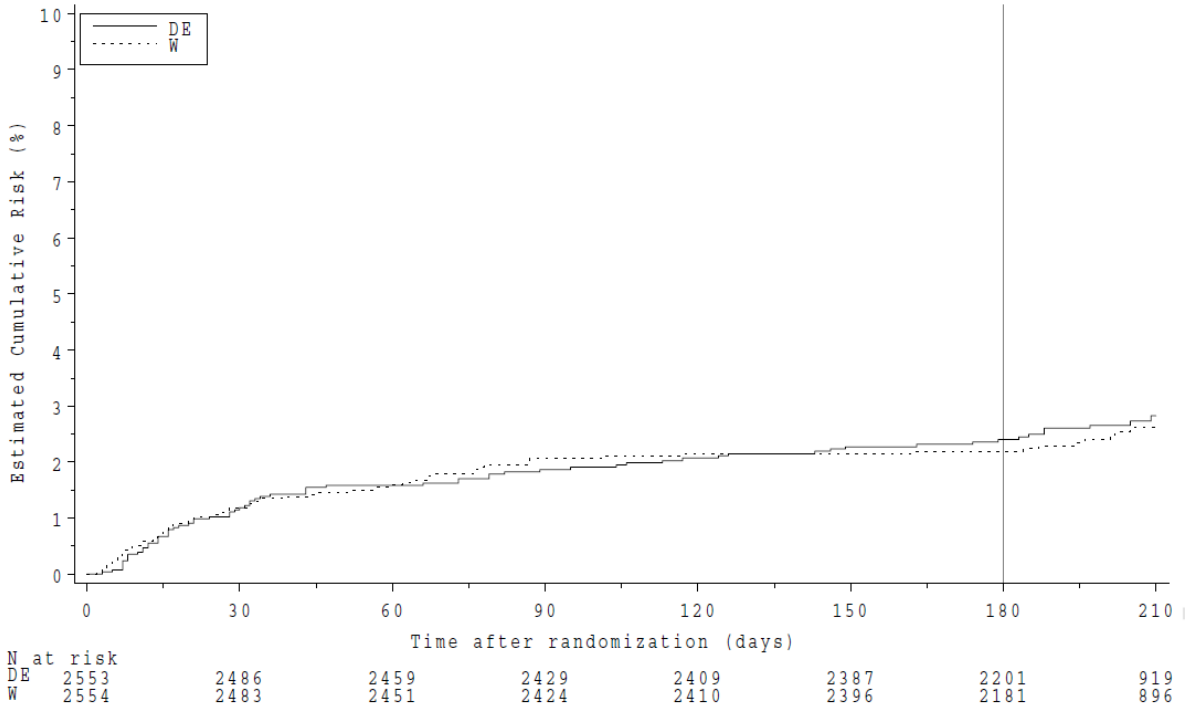


Figure 1 Time to first adjudicated VTE and VTE-related death until the end of post-treatment period for the RE-COVER and RE-COVER II pooled

Table 28: Analysis of the primary and secondary efficacy endpoints for the RE-COVER and RE-COVER II (pooled) [FAS]

	Dabigatran etexilate 150 mg	**Warfarin**
Patients, N (%)	2,553 (100.0)	2,554 (100.0)
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, N (%) [95% CI]		
Recurrent symptomatic VTE and all-cause deaths	109 (4.3) [3.52, 5.13]	104 (4.1) [3.34, 4.91]
Symptomatic DVT	45 (1.8) [1.29, 2.35]	39 (1.5) [1.09, 2.08]
Symptomatic PE	27 (1.1) [0.70, 1.54]	26 (1.0) [0.67, 1.49]
VTE-related deaths	4 (0.2) [0.04, 0.40]	3 (0.1) [0.02, 0.34]
All-cause deaths	51 (2.0) [1.49, 2.62]	52 (2.0) [1.52, 2.66]

*VTE is a composite of DVT and/or PE
Events were taken into account until the end of the post-treatment period

Table 29: Summary of all clinical trials supporting the indication for the prevention of recurrent DVT/PE

Study ID	Study Design	Patient Population	Duration of Treatment	Treatment Groups
RE-MEDY	Randomised, parallel-group, double-blind, active-controlled	DVT of the leg or PE, treated with an approved anticoagulant therapy or participation in RE-COVER	6 - 36 months median treatment duration, oral only treatment period – 534 days	Randomized- 1435 (DE) 1431 (W) Treated[1] -1430 (DE), 1426 (W)
RE-SONATE	Randomised, parallel-group, double-blind, placebo-controlled	Long-term prevention of recurrent symptomatic venous thromboembolism (VTE)	6 - 18 months median treatment duration - 182 days	Randomized - 685 (DE), 668 (P) Treated[1] - 681 (DE), 662 (P)

1 Number of patients who took at least 1 dose of any study medication (i.e., patients in the full analysis set [FAS]
DE – Dabigatran Etexilate
W – warfarin (target INR 2.0-3.0)
P- placebo

Clinical evidence has demonstrated dabigatran etexilate to be an effective and safe treatment for recurrent DVT and/or PE. Two randomized, parallel group, double-blind studies, RE-MEDY and RE-SONATE, were performed in patients previously treated with anticoagulation therapy.

Table 30: Characteristics of the Patients According to Study and Assigned Study Drug

Characteristics	RE-MEDY		RE-SONATE	
	Dabigatran	Warfarin	Dabigatran	Placebo
	(N = 1430)	(N = 1426)	(N = 681)	(N = 662)
Age- mean years±SD	55.4±15.0	53.9±15.3	56.1±15.5	55.5±15.1
Gender (Female) - N (%)	559 (39.1)	555 (38.9)	300 (44.1)	298 (45.0)
Estimated creatinine clearance (ml/min) ±SD ‡	104.2±38.6	106.6±37.9	99.6±35.8	101.2±37.1
Patients with qualifying event [N (%)]				
Symptomatic PE and symptomatic DVT	167 (11.7)	168 (11.8)	59 (8.7)	45 (6.8)
Symptomatic PE only	324 (22.7)	335 (23.5)	192 (28.2)	181 (27.3)
Symptomatic DVT only	938 (65.6)	922 (64.7)	430(63.1)	436 (65.9)
Immobilization - N (%)	94 (6.6)	105 (7.4)	53 (7.8)	36 (5.4)
Thrombophilia -N (%)	262 (18.3)	263 (18.4)	87 (12.8)	68 (10.3)
Active cancer at any time - N (%)	88 (6.2)	105 (7.4)	58 (8.5)	46 (6.9)
Coronary artery disease - N (%)	120 (8.4)	87 (6.1) &	43 (6.3)	38 (5.7)
Diabetes mellitus - N (%)	150 (10.5)	108 (7.6)**	57 (8.4)	50 (7.6)
Hypertension - N (%)	582 (40.7)	520 (36.5) &	281 (41.3)	240 (36.3)

‡ Creatinine clearance was estimated according to the Cockcroft–Gault method
& P = 0.02 for the difference between the dabigatran group and the warfarin group, chi-square test
** P = 0.007 for the difference between the dabigatran group and the warfarin group, chi-square test

RE-MEDY was a warfarin-controlled study, which enrolled patients already treated for 3-12 months with the need for further anticoagulant treatment. The objective of the RE-MEDY study was to compare the safety and efficacy of oral dabigatran etexilate (150 mg bid) 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 randomized and 2,856 patients were treated. Patients were mostly Caucasian (90.1%). 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 etexilate treatment ranged from 6- 36 months (median - 534.0 days). For patients randomized to warfarin, the median time in therapeutic range (INR 2.0-3.0) was 64.9%.

Patients who completed the acute DVT/PE treatment studies (RE-COVER OR RE-COVER II) were also eligible to roll-over into RE-MEDY.

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.

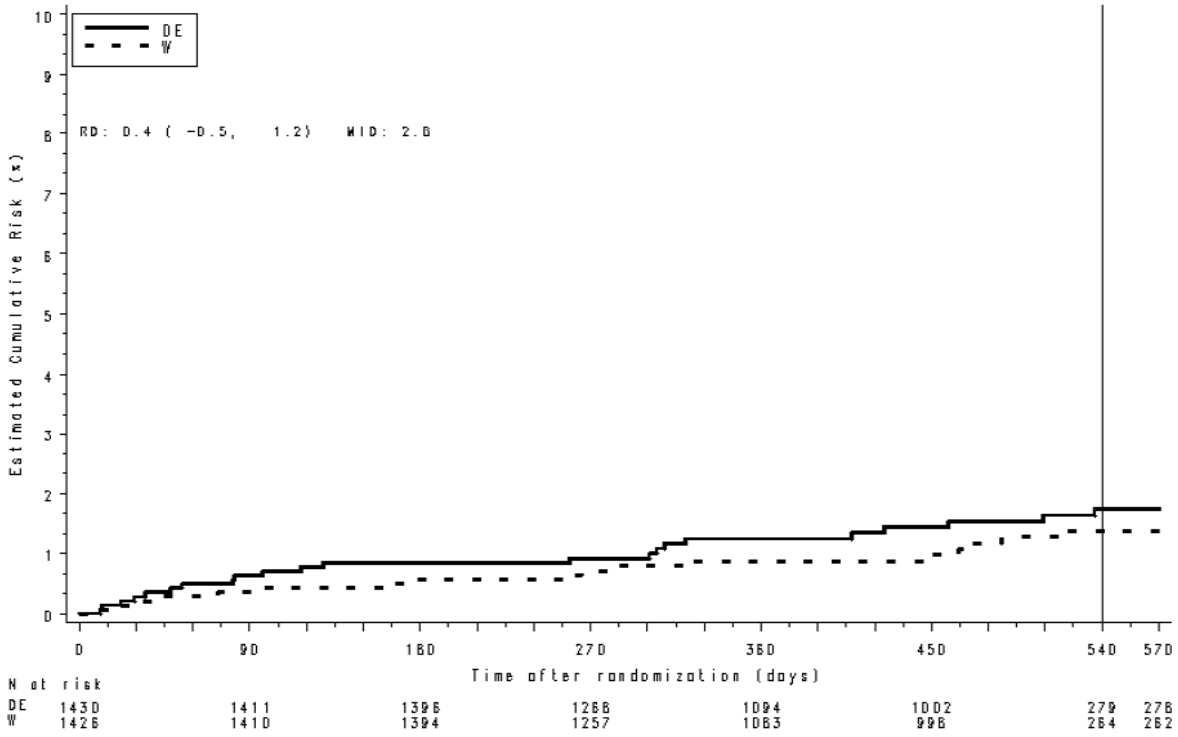


Figure 2: Time to first adjudicated VTE and VTE-related death until the end of the planned treatment period for the RE-MEDY study

RE-MEDY demonstrated that treatment with dabigatran etexilate 150 mg twice daily was non-inferior to warfarin (p=0.0135 for non-inferiority). Bleeding events (MBEs or CRBEs; any bleeding) were significantly lower in patients receiving dabigatran etexilate as compared with those receiving warfarin.

Table 31: Analysis of the primary and secondary efficacy endpoints in RE-MEDY [FAS]:

	Dabigatran etexilate 150 mg	Warfarin
Patients, N (%)	1,430 (100.0)	1,426 (100.0)
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 (%) 95% CI	0.4 (-0.5, 1.2)	
p-value (non-inferiority)	<0.0001	
Secondary efficacy endpoints, N (%) [95% CI]		
Recurrent symptomatic VTE and all-cause deaths	42 (2.9) [2.12, 3.95]	36 (2.5) [1.77, 3.48]
Symptomatic DVT	17 (1.2) [0.69, 1.90]	13 (0.9) [0.49, 1.55]
Symptomatic PE	10 (0.7) [0.34, 1.28]	5 (0.4) [0.11, 0.82]
VTE-related deaths	1 (0.1) [0.00, 0.39]	1 (0.1) [0.00, 0.39]
All-cause deaths	17 (1.2) [0.69, 1.90]	19 (1.3) [0.80, 2.07]

*VTE is a composite of DVT and/or PE
Events were taken into account until the end of the post-treatment period

RE-SONATE was a placebo-controlled study.
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- 18 months of treatment with vitamin K antagonist (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%. 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%).

Patients who had completed the VTE treatment studies were also eligible to roll-over into this study, if the risk and benefit of further anticoagulation therapy were considered at equipoise.

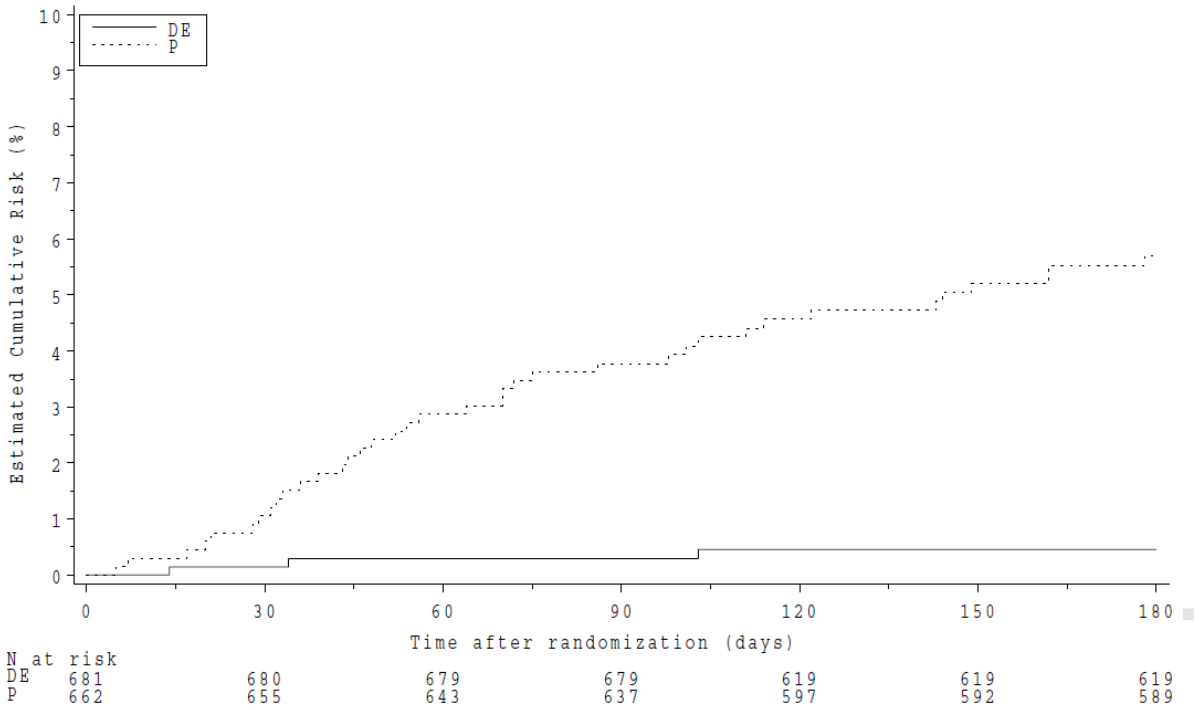


Figure 3: Time to first adjudicated VTE and VTE-related death until the end of the planned treatment period for the RE-SONATE study

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% 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 32: Analysis of the primary and secondary efficacy endpoints for RE-SONATE [FAS]

	Dabigatran etexilate 150 mg	Placebo
Patients , N (%)	681 (100.0)	662 (100.0)
Recurrent symptomatic VTE* and related deaths#	**3 (0.4)**	**37 (5.6)**
Hazard ratio	0.08	
95% CI (p-value for superiority)	0.02, 0.25 (<0.0001)	
Secondary efficacy endpoints, N (%) [95% CI]		
Recurrent symptomatic VTE and all-cause deaths	3 (0.4) [0.09, 1.28]	37 (5.6) [3.97, 7.62]
Symptomatic DVT	2 (0.3) [0.04, 1.06]	23 (3.5) [2.21, 5.17]
Symptomatic PE	1 (0.1) [0.00, 0.82]	14 (2.1) [1.16, 3.52]
VTE-related deaths	0 (0) [0.00, 0.54]	0 (0) [0.00, 0.56]
Unexplained deaths	0 (0) [0.00, 0.54]	2 (0.3) [0.04, 1.09]
All-cause deaths	0 (0) [0.00, 0.54]	2 (0.3) [0.04, 1.09]

*VTE is a composite of DVT and/or PE
#including unexplained deaths
Events were taken into account until the end of the post-treatment period

Myocardial infarction (MI) occurred at a low frequency in all 4 of the VTE studies for all treatment groups. Cardiac death occurred in 1 patient in the warfarin treatment group.

In the 3 active controlled studies, a higher rate of MI was reported in patients who received dabigatran etexilate (20; 0.5%) than in those who received warfarin (5; 0.1%).

In the RE-SONATE study, which compared dabigatran etexilate to placebo, there was 1 MI event in each of the treatment groups, resulting in MI rates with dabigatran equal to MI rates with placebo.

Prevention of stroke and systemic embolism in patients with atrial fibrillation

Table 33: Summary of patient demographics for RE-LY, a Phase III clinical trial in atrial fibrillation

Study #	**Trial design**	**Dosage, route of administration and duration**	**Study subjects n=number (dose)****	**Mean age**	**Gender**
RE-LY	multi-center, multi-national, randomised parallel-group study	two blinded doses of dabigatran: 110 mg bid and 150 mg bid compared to open-label warfarin	N = 18,113 (total) N = 6,015 (DE110) N= 6,076 (DE 150)	71.5	Male 64% Female 36%

**DE110– Dabigatran etexilate 110 mg bid
DE150 – Dabigatran etexilate 150 mg bid

The primary clinical evidence for the effectiveness of dabigatran etexilate in the prevention of stroke and systemic embolism in patients with atrial fibrillation (AF) is derived from the RE-LY study (Randomised Evaluation of Long–term anticoagulant therapy). This was a multi-center, multi-national, randomised parallel-group study of 2 blinded doses of dabigatran (110 mg bid and 150 mg bid), compared to open-label warfarin in AF patients at moderate to high risk of stroke or systemic embolism. The primary objective was to determine if dabigatran was non-inferior to warfarin in reducing the occurrence of the composite endpoint, total 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 (AF) i.e., paroxysmal, persistent or permanent AF, patients had 1 of the following additional risk factors for stroke:

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

Patients with prosthetic heart valves, or those with hemodynamically significant rheumatic heart disease, especially mitral stenosis, were excluded from the RE-LY trial, and thus were not evaluated. The RE-LY trial results do not apply to these patients, with or without atrial fibrillation (see WARNINGS AND PRECAUTIONS, Cardiovascular, Patients with Valvular Disease).

The concomitant diseases of patients in this trial included hypertension (79%), diabetes mellitus (23%), valvular disease (not meeting study exclusion criteria, see paragraph just above) (22%), and CAD (28%). 50% of the patient population was VKA naïve defined as <2 months total lifetime exposure; 32% had never been exposed to a VKA. For those patients randomised to warfarin, the time in therapeutic range (INR 2-3) for the trial was a median of 67%.

Concomitant medications during the study included aspirin (25% of patients used ASA ≥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 (ARBs) (26.1%), oral hypoglycemics (17.5%), insulin (5.2%), digoxin (29.4%), amiodarone (11.3%), diltiazem (8.9%), verapamil (5.4%), and proton pump inhibitors (17.8%).

This study demonstrated that dabigatran etexilate, at a dose of 110 mg bid was non-inferior to warfarin in the prevention of stroke and systemic embolism in AF patients. The dose of 150 mg bid was shown to be superior to warfarin with respect to stroke and systemic embolism. The dose of 110 mg dabigatran demonstrated a significantly lower risk of major bleeding compared to warfarin.

Table 34: Analysis of first occurrence of stroke or systemic embolism (primary endpoint) during the study period in the RE-LY study

	Dabigatran etexilate 110 mg bid	Dabigatran etexilate 150 mg bid	Warfarin[+]
Patients randomised	6,015	6,076	6,022
Total Stroke and/or SEE **			
No. of events (%)*	183 (1.5)	135 (1.1)	203 (1.7)
Hazard ratio over warfarin (95% CI)	0.89 (0.73, 1.09)	0.65 (0.52, 0.81)	
p-value, superiority	p = 0.2721	p = 0.0001	

* % refers to yearly event rate

** SEE: systemic embolic event

[+] dose adjusted, INR 2.0- 3.0

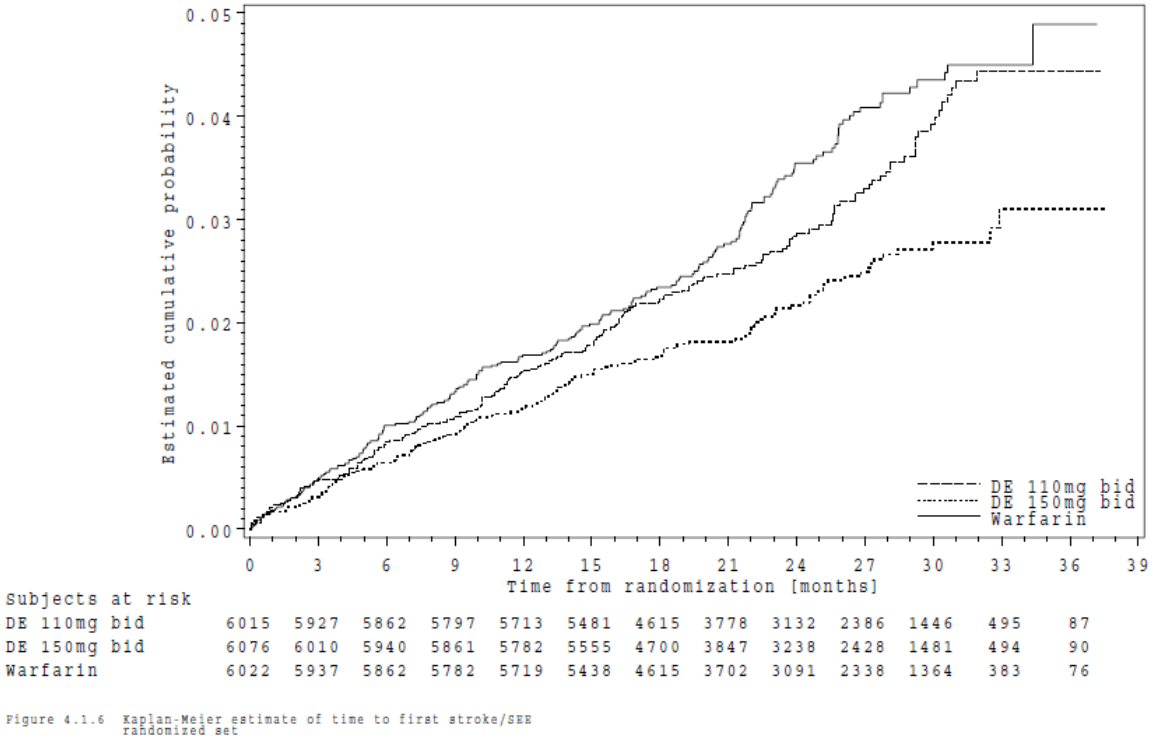


Figure 4: Kaplan-Mayer curve of time to first stroke or systemic embolism in the RE-LY trial

Table 35: Analysis of first occurrence of ischemic or haemorrhagic strokes during the study period in the RE-LY study

	Dabigatran etexilate 110 mg bid	Dabigatran etexilate 150 mg bid	Warfarin+
Patients randomised	6,015	6,076	6,022
Total Stroke			
No. of events (%)	171 (1.4)	123 (1.0)	187 (1.6)
Hazard ratio vs. warfarin (95% CI)	0.91 (0.74, 1.12)	0.64 (0.51, 0.81)	
p-value, superiority	0.3553	0.0001	
SEE			
No. of events (%)	15 (0.1)	13 (0.1)	21 (0.2)
Hazard ratio vs. warfarin (95% CI)	0.71 (0.37, 1.38)	0.61 (0.30, 1.21)	
p-value	0.3099	0.1582	
Ischemic stroke			
No. of events (%)	152 (1.3)	104 (0.9)	134 (1.1)
Hazard ratio vs. warfarin (95% CI)	1.13 (0.89, 1.42)	0.76 (0.59, 0.98)	
p-value	0.3138	0.0351	
Haemorrhagic stroke			
No. of events (%)	14 (0.1)	12 (0.1)	45 (0.4)
Hazard ratio vs. warfarin (95% CI)	0.31 (0.17, 0.56)	0.26 (0.14, 0.49)	
p-value	<0.001	<0.001	

+ dose adjusted, INR 2.0- 3.0
% refers to yearly event rate

Table 36: Analysis of all cause mortality and cardiovascular mortality during the study period in the RE-LY study

	Dabigatran etexilate 110 mg bid	Dabigatran etexilate 150 mg bid	Warfarin+
Patients randomised	6,015	6,076	6,022
All-cause mortality			
No. of events (%)	446 (3.8)	438 (3.6)	487 (4.1)
Hazard ratio vs. warfarin (95% CI)	0.91(0.80, 1.03)	0.88 (0.77, 1.00)	
p-value	0.1308	0.0517	
Vascular mortality *			
No. of events (%)	289 (2.4)	274 (2.3)	317 (2.7)
Hazard ratio vs. warfarin (95% CI)	0.90 (0.77, 1.06)	0.85 (0.72, 0.99)	
p-value	0.2081	0.0430	

+ dose adjusted, INR 2.0- 3.0
% refers to yearly event rate
* vascular mortality: cardiac death (includes sudden and non-sudden cardiac death, e.g. pump failure), and mortality due to stroke, pulmonary embolus, peripheral embolus, aortic dissection/rupture, haemorrhage and deaths of unknown cause

The frequencies of major bleeding events (MBEs) and fatal bleeding were similar between dabigatran etexilate 150 mg bid and warfarin. However, the frequencies of life-threatening

MBEs, intracranial haemorrhage (ICH) and any bleeding event were lower with dabigatran etexilate 150 mg bid than with warfarin. Frequencies for all bleeding events were lower with dabigatran etexilate 110 mg bid than with warfarin (see ADVERSE REACTIONS, *Bleeding*, Table 8).

Abnormalities in liver function tests (LFTs) (ALT or AST >3xULN or >5xULN or >3xULN + Bilirubin >2xULN) were similar among patients treated with dabigatran etexilate 110 mg bid and 150 mg bid, and warfarin (see ADVERSE REACTIONS, *Liver Function Tests*, Table 13).

Table 37: Other Measures Evaluated in the RE-LY study

	Dabigatran etexilate 110 mg bid N (%)	**Dabigatran etexilate 150 mg bid N (%)**	**Warfarin N (%)**
Patients randomised	6,015	6,076	6,022
Myocardial infarction*			
No. of events (%)	98 (0.8)	97 (0.8)	75 (0.6)
Hazard ratio vs. Warfarin (95%CI)	1.29 (0.96, 1.75)	1.27 (0.94, 1.71)	
p-value	0.0929	0.1240	

% refers to yearly event rate
*myocardial infarction including silent MI

For the randomised set, there was an imbalance in adjudicated MI with an increased frequency observed in the dabigatran etexilate (DE) treatment groups compared to the warfarin treatment group. The all-MI hazard ratios for DE110 BID and DE150 BID vs. warfarin were 1.29 (p=0.0929) and 1.27 (p=0.1240), respectively, with confidence intervals that included unity. The increased hazard was not dose-related and did not reach statistical significance. The imbalance could not be explained by differences in baseline risk factors or concomitant treatments. Almost 1/5 (21%) of all MI occurred off study drug. Most of those patients were receiving a non-study drug anticoagulant, either orally or parenterally, at the visit prior to their infarct event. It should be noted that, in the RE-LY trial, treatment with dabigatran etexilate or warfarin in patients that sustained MI, was discontinued as per protocol. Given the different half-life of these drugs, differential anticoagulant effect cannot be ruled out within a period of about 72 hours after discontinuation.

The event rates for efficacy and safety outcomes stratified by age groups are presented in Table 38 and Table 39.

Table 38: Efficacy outcomes by age group in the RE-LY trial during the study period (randomised set)

	DE 110		DE 150		Warfarin		DE 110 vs Warfarin		DE 150 vs. Warfarin	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Stroke/ SEE – first occurrence of stroke or systemic embolic event (primary endpoint)										
All patients	*183 / 6015*	*1.54*	*135 / 6076*	*1.12*	*203 / 6022*	*1.72*	*0.89 (0.73, 1.09)*	*0.2721*	*0.65 (0.52, 0.81)*	*0.0001*
< 65 years	29 / 998	1.47	14 / 1030	0.69	25 / 953	1.35	1.10 (0.64, 1.88)		0.51 (0.26, 0.98)	
65 to 75 years	80 / 2991	1.34	59 / 2901	1.01	84 / 2981	1.42	0.94 (0.69, 1.28)		0.71 (0.51, 0.99)	
> 75 years	74 / 2026	1.87	62 / 2145	1.49	94 / 2088	2.33	0.80 (0.59, 1.09)		0.64 (0.46, 0.88)	
> 80 years	25 / 777	1.69	31 / 860	1.90	43 / 787	2.82	0.59 (0.36, 0.97)		0.67 (0.42, 1.07)	
> 85 years	6 / 154	2.05	9 / 161	2.95	8 / 160	2.77	0.73 (0.25, 2.11)		1.06 (0.41, 2.76)	
Total stroke										
All patients	*171 / 6015*	*1.44*	*123 / 6076*	*1.02*	*187 / 6022*	*1.59*	*0.91 (0.74, 1.12)*	*0.3553*	*0.64 (0.51, 0.81)*	*0.0001*
< 65 years	26 / 998	1.32	13 / 1030	0.64	22 / 953	1.19	1.12 (0.63, 1.97)		0.54 (0.27, 1.07)	
65 to 75 years	74 / 2991	1.24	52 / 2901	0.89	78 / 2981	1.32	0.94 (0.68, 1.29)		0.67 (0.47, 0.96)	
> 75 years	71 / 2026	1.80	58 / 2145	1.39	87 / 2088	2.15	0.83 (0.61, 1.14)		0.64 (0.46, 0.90)	
> 80 years	23 / 777	1.56	29 / 860	1.78	41 / 787	2.69	0.57 (0.34, 0.95)		0.66 (0.41, 1.06)	
SEE										
All patients	*15 / 6015*	*0.13*	*13 / 6076*	*0.11*	*21 / 6022*	*0.18*	*0.71 (0.37,1.38)*	*0.3099*	*0.61 (0.30, 1.21)*	*0.1582*
< 65 years	3 / 998	0.15	1 / 1030	0.05	3 / 953	0.16	0.94 (0.19,4.67)		0.31 (0.03, 2.96)	
65 to 75 years	8 / 2991	0.13	8 / 2901	0.14	8 / 2981	0.14	0.99 (0.37,2.64)		1.02 (0.38, 2.71)	
> 75 years	4 / 2026	0.10	4 / 2145	0.10	10 / 2088	0.25	0.41 (0.13,1.31)		0.39 (0.12, 1.24)	
> 80 years	2 / 777	0.14	2 / 860	0.12	4 / 787	0.26	0.52 (0.09,2.81)		0.47 (0.09, 2.56)	
Ischemic stroke										
All patients	*152 / 6015*	*1.28*	*104 / 6076*	*0.86*	*134 / 6022*	*1.14*	*1.13 (0.89, 1.42)*	*0.3138*	*0.76 (0.59, 0.98)*	*0.0351*
< 65 years	23 / 998	1.17	12 / 1030	0.59	15 / 953	0.81	1.45 (0.76, 2.78)		0.73 (0.34, 1.55)	
65 to 75 years	68 / 2991	1.14	46 / 2901	0.79	57 / 2981	0.97	1.18 (0.83, 1.68)		0.82 (0.55, 1.20)	
> 75 years	61 / 2026	1.55	46 / 2145	1.11	62 / 2088	1.53	1.01 (0.71, 1.43)		0.72 (0.49, 1.05)	
> 80 years	19 / 777	1.28	23 / 860	1.41	28 / 787	1.84	0.69 (0.39, 1.24)		0.77 (0.44, 1.33)	
Haemorrhagic stroke										
All patients	*14 / 6015*	*0.12*	*12 / 6076*	*0.10*	*45 / 6022*	*0.38*	*0.31 (0.17, 0.56)*	*0.0001*	*0.26 (0.14, 0.49)*	*<0.0001*
< 65 years	1 / 998	0.05	1 / 1030	0.05	7 / 953	0.38	0.13 (0.02, 1.09)		0.13 (0.02, 1.06)	
65 to 75 years	6 / 2991	0.10	4 / 2901	0.07	18 / 2981	0.31	0.32 (0.13, 0.82)		0.22 (0.08, 0.66)	
> 75 years	7 / 2026	0.18	7 / 2145	0.17	20 / 2088	0.49	0.36 (0.15, 0.85)		0.34 (0.14, 0.80)	
> 80 years	3 / 777	0.20	3 / 860	0.18	10 / 787	0.66	0.31 (0.09, 1.13)		0.28 (0.08, 1.02)	
Vascular death*										
All patients	*289 / 6015*	*2.43*	*274 / 6076*	*2.28*	*317 / 6022*	*2.69*	*0.90 (0.77, 1.06)*	*0.2081*	*0.85 (0.72, 0.99)*	*0.0430*
< 65 years	49 / 998	2.49	47 / 1030	2.31	62 / 953	3.35	0.75 (0.51, 1.09)		0.69 (0.47, 1.01)	
65 to 75 years	124 / 2991	2.07	87 / 2901	1.49	124 / 2981	2.10	0.98 (0.77, 1.26)		0.71 (0.54, 0.93)	
> 75 years	116 / 2026	2.94	140 / 2145	3.36	131 / 2088	3.24	0.90 (0.70, 1.16)		1.04 (0.82, 1.32)	
> 80 years	58 / 777	3.92	72 / 860	4.42	55 / 787	3.61	1.09 (0.75, 1.58)		1.23 (0.87, 1.75)	
> 85 years	23 / 227	5.33	22 / 249	4.73	21 / 244	4.64	1.13 (0.63, 2.05)		1.01 (0.56, 1.84)	
All cause mortality										
All patients	*446 / 6015*	*3.75*	*438 / 6076*	*3.64*	*487 / 6022*	*4.13*	*0.91 (0.80, 1.03)*	*0.1308*	*0.88 (0.77, 1.00)*	*0.0517*
< 65 years	58 / 998	2.95	60 / 1030	2.95	77 / 953	4.15	0.71 (0.51, 1.00)		0.71 (0.51, 1.00)	
65 to 75 years	177 / 2991	2.96	148 / 2901	2.53	195 / 2981	3.31	0.89 (0.73, 1.09)		0.76 (0.62, 0.95)	
> 75 years	211 / 2026	5.34	230 / 2145	5.53	215 / 2088	5.32	1.00 (0.83, 1.21)		1.04 (0.86, 1.25)	
> 80 years	111 / 777	7.51	127 / 860	7.80	89 / 787	5.84	1.29 (0.98, 1.70)		1.34 (1.03, 1.76)	

n: Number of patients with event; N: total number of patients
Hazard ratio (95% CI) and p-value are from Cox proportional hazard ratio with treatment as a covariate
P-value: two sided for superiority
Warfarin – dose adjusted INR 2.0-3.0
* vascular mortality: cardiac death (includes sudden and non-sudden cardiac death, e.g. pump failure), and mortality due to stroke, pulmonary embolus, peripheral embolus, aortic dissection/rupture, haemorrhage and deaths of unknown cause.

Table 39: Safety outcomes by age group in the RE-LY trial during the study period (randomised set)

	DE 110		DE 150		Warfarin		DE 110 vs Warfarin		DE 150 vs. Warfarin	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Major bleeding events (MBE)[#]										
All patients	*347 / 6015*	*2.92*	*409 / 6076*	*3.40*	*426 / 6022*	*3.61*	*0.81 (0.70, 0.93)*	*0.0027*	*0.94 (0.82, 1.08)*	*0.4070*
< 65 years	16 / 998	0.81	18 / 1030	0.88	46 / 953	2.48	0.32 (0.18, 0.57)		0.35 (0.20, 0.61)	
65 to 75 years	140 / 2991	2.34	16 / 2901	2.74	189 / 2981	3.20	0.73 (0.58, 0.91)		0.86 (0.69, 1.06)	
> 75 years	191 / 2026	4.84	231 / 2145	5.56	191 / 2088	4.73	1.03 (0.84, 1.25)		1.19 (0.98, 1.44)	
> 80 years	84 / 777	5.68	111 / 860	6.82	75 / 787	4.92	1.15 (0.85, 1.58)		1.40 (1.05, 1.88)	
> 85 years	23 / 154	7.87	23 / 161	7.53	18 / 160	6.23	1.27 (0.68, 2.35)		1.21 (0.65, 2.24)	
Life-threatening MBE										
All patients	*151 / 6015*	*1.27*	*183 / 6076*	*1.52*	*221 / 6022*	*1.87*	*0.68 (0.55, 0.83)*	*0.0002*	*0.81 (0.67, 0.99)*	*0.0357*
< 65 years	7 / 998	0.36	7 / 1030	0.34	25 / 953	1.35	0.26 (0.11, 0.61)		0.25 (0.11, 0.59)	
65 to 75 years	60 / 2991	1.00	76 / 2901	1.30	98 / 2981	1.66	0.60 (0.44, 0.83)		0.78 (0.58, 1.05)	
> 75 years	84 / 2026	2.13	100 / 2145	2.40	98 / 2088	2.43	0.88 (0.66, 1.17)		1.00 (0.75, 1.32)	
> 80 years	42 / 777	2.84	54 / 860	3.32	39 / 787	2.56	1.11 (0.72, 1.72)		1.30 (0.86, 1.96)	
Intra-cranial haemorrhage (ICH)[+]										
All patients	*27 / 6015*	*0.23*	*39 / 6076*	*0.32*	*91 / 6022*	*0.77*	*0.29(0.19, 0.45)*	*<0.0001*	*0.42 (0.29, 0.61)*	*<0.0001*
< 65 years	2 / 998	0.10	4 / 1030	0.20	12 / 953	0.65	0.16 (0.04, 0.70)		0.30 (0.10, 0.94)	
65 to 75 years	11 / 2991	0.18	16 / 2901	0.27	35 / 2981	0.59	0.31 (0.16, 0.60)		0.46 (0.25, 0.83)	
> 75 years	14 / 2026	0.35	19 / 2145	0.46	44 / 2088	1.09	0.32 (0.18, 0.59)		0.42 (0.24, 0.72)	
> 80 years	6 / 777	0.41	12 / 860	0.74	19 / 787	1.25	0.32 (0.13, 0.81)		0.59 (0.29, 1.22)	
Fatal bleeding										
All patients	*26 / 6015*	*0.22*	*30 / 6076*	*0.25*	*42/ 6022*	*0.36*	*0.61 (0.38, 1.0)*	*0.0491*	*0.70 (0.44, 1.12)*	*0.1338*
< 65 years	1 / 998	0.05	1 / 1030	0.05	7 / 953	0.38	0.13 (0.02, 1.09)		0.13 (0.02, 1.06)	
65 to 75 years	10 / 2991	0.17	13 / 2901	0.22	17 / 2981	0.29	0.57 (0.26, 1.25)		0.77 (0.37, 1.58)	
> 75 years	15 / 2026	0.38	16 / 2145	0.38	18 / 2088	0.45	0.85 (0.43, 1.68)		0.87 (0.44, 1.70)	
> 80 years	7 / 777	0.47	10 / 860	0.61	5 / 787	0.33	1.45 (0.46, 4.57)		1.89 (0.64, 5.52)	
Any bleeding event [a]										
All patients	*1759/6015*	*14.78*	*1997 / 6076*	*16.6*	*2169 / 6022*	*18.39*	*0.78 (0.73, 0.83)*	*<0.0001*	*0.91 (0.85, 0.96)*	*0.0017*
< 65 years	206 / 998	10.47	208 / 1030	10.22	265 / 953	14.30	0.71 (0.59, 0.85)		0.69 (0.58, 0.83)	
65 to 75 years	850 / 2991	14.20	920 / 2901	15.76	1107 / 2981	18.76	0.73 (0.67, 0.80)		0.84 (0.77, 0.91)	
> 75 years	703 / 2026	17.81	869 / 2145	20.89	797 / 2088	19.72	0.89 (0.81, 0.99)		1.10 (1.00, 1.21)	
> 80 years	286 / 777	19.34	381 / 860	23.41	321 / 787	21.07	0.90 (0.77, 1.06)		1.16 (1.00, 1.35)	

n: Number of patients with event; N: total number of patients
Hazard ratio (95% CI) and p-value are from Cox proportional hazard ratio with treatment as a covariate
P-value: two sided for superiority
adjudicated bleeds
+ICH consists of adjudicated haemorrhagic stroke and subdural and/or subarachnoid haemorrhage.
a Investigator-reported bleeding events

The event rates for efficacy and safety outcomes stratified by renal function are presented in Table 40 and Table 41.

Table 40: Efficacy outcomes by renal function (eCrCL) in the RE-LY trial during the study period (randomised set)

	DE 110		DE 150		Warfarin		DE 110 vs Warfarin		DE 150 vs. Warfarin	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Stroke/ SEE – first occurrence of stroke or systemic embolism (primary endpoint)										
All patients	*183 / 6015*	*1.54*	*135/ 6076*	*1.12*	*203/ 6022*	*1.72*	*0.89 (0.73, 1.09)*	*0.2721*	*0.65 (0.52, 0.81)*	*0.0001*
30-49 mL/min	52 / 1181	2.35	33/ 1198	1.44	55 / 1092	2.68	0.87 (0.59, 1.27)		0.53 (0.34, 0.82)	
50-80 mL/min	94 / 2803	1.69	70 / 2852	1.25	103 / 2898	1.83	0.93 (0.70, 1.23)		0.68 (0.50, 0.92)	
>80 mL/min	35 / 1958	0.88	28 / 1945	0.71	42 / 1941	1.07	0.82 (0.53, 1.29)		0.66 (0.41, 1.06)	
Total stroke										
All patients	*171 / 6015*	*1.44*	*123/ 6076*	*1.02*	*187/ 6022*	*1.59*	*0.91 (0.74, 1.12)*	*0.3553*	*0.64 (0.51, 0.81)*	*0.0001*
30-49 mL/min	50 / 1181	2.26	30/ 1198	1.31	50 / 1092	2.44	0.92 (0.62, 1.36)		0.53 (0.34, 0.83)	
50-80 mL/min	88 / 2803	1.58	64 / 2852	1.14	96 / 2898	1.70	0.93 (0.70, 1.25)		0.67 (0.49, 0.92)	
>80 mL/min	31 / 1958	0.78	26 / 1945	0.66	38/ 1941	0.97	0.81 (0.50, 1.30)		0.68 (0.41, 1.11)	
SEE										
All patients	*15 / 6015*	*0.13*	*13 / 6076*	*0.11*	*21 / 6022*	*0.18*	*0.71 (0.37, 1.38)*	*0.3099*	*0.61 (0.30, 1.21)*	*0.1582*
30-49 mL/min	3 / 1181	0.14	3 / 1198	0.13	8 / 1092	0.39	0.35 (0.09, 1.31)		0.34 (0.09, 1.27)	
50-80 mL/min	7 / 2803	0.13	7 / 2852	0.12	9 / 2898	0.16	0.79 (0.29, 2.12)		0.78 (0.29, 2.10)	
>80 mL/min	5 / 1958	0.13	2 / 1945	0.05	4 / 1941	0.10	1.24 (0.33, 4.60)		0.50 (0.09, 2.71)	
Ischemic stroke										
All patients	*152 / 6015*	*1.28*	*104/ 6076*	*0.86*	*134 / 6022*	*1.14*	*1.13 (0.89, 1.42)*	*0.3138*	*0.76 (0.59, 0.98)*	*0.0351*
30-49 mL/min	44 / 1181	1.99	25 / 1198	1.09	37 / 1092	1.80	1.10 (0.71, 1.70)		0.60 (0.36, 0.99)	
50-80 mL/min	77 / 2803	1.39	55 / 2852	0.98	67 / 2898	1.19	1.17 (0.85, 1.63)		0.83 (0.58, 1.18)	
>80 mL/min	29 / 1958	0.73	23 / 1945	0.58	28 / 1941	0.72	1.02 (0.61, 1.72)		0.81 (0.47, 1.41)	
Haemorrhagic stroke										
All patients	*14 / 6015*	*0.12*	*12 / 6076*	*0.10*	*45 / 6022*	*0.38*	*0.31 (0.17, 0.56)*	*0.0001*	*0.26 (0.14, 0.49)*	*<0.0001*
30-49 mL/min	5 / 1181	0.23	3 / 1198	0.13	12 / 1092	0.58	0.38 (0.14, 1.09)		0.22 (0.06, 0.79)	
50-80 mL/min	7 / 2803	0.13	6 / 2852	0.11	26 / 2898	0.46	0.27 (0.12, 0.63)		0.23 (0.09, 0.56)	
>80 mL/min	2 / 1958	0.05	2 / 1945	0.05	7 / 1941	0.18	0.28 (0.06, 1.36)		0.28 (0.06, 1.36)	
Vascular death*										
All patients	*289 / 6015*	*2.43*	*274 / 6076*	*2.28*	*317 / 6022*	*2.69*	*0.90 (0.77, 1.06)*	*0.2081*	*0.85 (0.72, 0.99)*	*0.0430*
30-49 mL/min	110 / 1181	4.97	88 / 1198	3.84	87 / 1092	4.24	1.17 (0.89, 1.55)		0.90 (0.67, 1.22)	
50-80 mL/min	116 / 2803	2.09	133 / 2852	2.37	161 / 2898	2.85	0.73 (0.57, 0.93)		0.83 (0.66, 1.04)	
>80 mL/min	60 / 1958	1.51	47 / 1945	1.19	63 / 1941	1.61	0.94 (0.66, 1.34)		0.74 (0.51, 1.08)	
All cause mortality										
All patients	*446 / 6015*	*3.75*	*438 / 6076*	*3.64*	*487 / 6022*	*4.13*	*0.91 (0.80, 1.03)*	*0.1308*	*0.88 (0.77, 1.00)*	*0.0517*
30-49 mL/min	176 / 1181	7.95	149 / 1198	6.51	138 / 1092	6.72	1.18 (0.95, 1.48)		0.97 (0.77, 1.22)	
50-80 mL/min	175 / 2803	3.15	198 / 2852	3.53	244 / 2989	4.32	0.72 (0.60, 0.88)		0.81 (0.67, 0.98)	
>80 mL/min	89 / 1958	2.24	81 / 1945	2.04	97 / 1941	2.48	0.90 (0.68, 1.20)		0.82 (0.61, 1.11)	

n: Number of patients with event; N: total number of patients

Hazard ratio (95% CI) and p-value are from Cox proportional hazard ratio with treatment as a covariate

P-value: two sided for superiority

Patients with missing baseline creatinine clearance or baseline creatinine clearance < 30 ml/Min are not included in the analyses.

Warfarin – dose adjusted INR 2.0-3.0

* vascular mortality: cardiac death (includes sudden and non-sudden cardiac death, e.g. pump failure), and mortality due to stroke, pulmonary embolus, peripheral embolus, aortic dissection/rupture, haemorrhage and deaths of unknown cause.

Table 41: Safety outcomes by renal function (eCrCl) in the RE-LY trial during the study period (randomised set)

	DE 110		DE 150		Warfarin		DE 110 vs Warfarin		DE 150 vs. Warfarin	
	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	n/N	Event rate (%/yr)	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Major bleeding events (MBE)[#]										
All patients	*347 / 6015*	*2.92*	*409 / 6076*	*3.40*	*426 / 6022*	*3.61*	*0.81 (0.70, 0.93)*	*0.0027*	*0.94 (0.82, 1.08)*	*0.4070*
30-49 mL/min	125 / 1181	5.65	123 / 1198	5.37	116 / 1092	5.65	1.00 (0.77, 1.28)		0.96 (0.74, 1.23)	
50-80 mL/min	160 / 2803	2.88	194 / 2852	3.45	213 / 2898	3.78	0.76 (0.62, 0.93)		0.92 (0.76, 1.12)	
>80 mL/min	59 / 1958	1.48	84 / 1945	2.12	95 / 1941	2.43	0.61 (0.44, 0.84)		0.87 (0.65, 1.17)	
Life-threatening MBE										
All patients	*151 / 6015*	*1.27*	*183 / 6076*	*1.52*	*221 / 6022*	*1.87*	*0.68(0.55, 0.83)*	*0.0002*	*0.81 (0.67, 0.99)*	*0.0357*
30-49 mL/min	59 / 1181	2.67	56 / 1198	2.45	61 / 1092	2.97	0.89 (0.63, 1.28)		0.82 (0.57, 1.18)	
50-80 mL/min	75 / 2803	1.35	91 / 2852	1.62	109 / 2898	1.93	0.70 (0.52, 0.94)		0.84 (0.63, 1.11)	
>80 mL/min	17 / 1958	0.43	31 / 1945	0.78	50 / 1941	1.28	0.33 (0.19, 0.58)		0.61 (0.39, 0.95)	
Intra-cranial haemorrhage (ICH)[+]										
All patients	*27 / 6015*	*0.23*	*39 / 6076*	*0.32*	*91 / 6022*	*0.77*	*0.29 (0.19, 0.45)*	*<0.0001*	*0.42 (0.29, 0.61)*	*<0.0001*
30-49 mL/min	11 / 1181	0.50	8 / 1198	0.35	26 / 1092	1.27	0.39 (0.19, 0.78)		0.27 (0.12, 0.60)	
50-80 mL/min	14 / 2803	0.25	23 / 2852	0.41	50 / 2898	0.89	0.28 (0.16, 0.51)		0.46 (0.28, 0.75)	
>80 mL/min	2 / 1958	0.05	7 / 1945	0.18	15 / 1941	0.38	0.13 (0.03, 0.57)		0.46 (0.19, 1.13)	
Fatal bleeding										
All patients	*26 / 6015*	*0.22*	*30 / 6076*	*0.25*	*42 / 6022*	*0.36*	*0.61 (0.38, 1.00)*	*0.0491*	*0.70 (0.43, 1.12)*	*0.1338*
30-49 mL/min	12 / 1181	0.54	12 / 1198	0.52	8 / 1092	0.39	1.39 (0.57, 3.40)		1.35 (0.55, 3.29)	
50-80 mL/min	12 / 2803	0.22	11 / 2852	0.20	27 / 2898	0.48	0.48 (0.23, 0.89)		0.41 (0.20, 0.82)	
>80 mL/min	2 / 1958	0.05	5 / 1945	0.13	7 / 1941	0.18	0.28 (0.06, 1.33)		0.70 (0.22, 2.20)	
Any bleeding event [a]										
All patients	*1759 / 6015*	*14.78*	*1997 / 6076*	*16.60*	*2169 / 6022*	*18.39*	*0.78 (0.74, 0.83)*	*<0.0001*	*0.91 (0.85, 0.96)*	*0.0017*
30-49 mL/min	417 / 1181	18.85	475 / 1198	20.75	402 / 1092	19.59	0.96 (0.83, 1.10)		1.12 (0.98, 1.28)	
50-80 mL/min	817 / 2803	14.70	941 / 2852	16.76	1089 / 2898	19.30	0.73 (0.67, 0.80)		0.87 (0.79, 0.94)	
>80 mL/min	503 / 1958	12.66	557 / 1945	14.06	656 / 1941	16.75	0.73 (0.65, 0.82)		0.83 (0.74, 0.92)	

n: Number of patients with event; N: total number of patients
Hazard ratio (95% CI) and p-value are from Cox proportional hazard ratio with treatment as a covariate
P-value: two sided for superiority
Patients with missing baseline creatinine clearance or baseline creatinine clearance < 30 ml/Min are not included in the analyses.
Warfarin – dose adjusted INR 2.0-3.0
P-value: two sided for superiority
adjudicated bleeds
+ICH consists of adjudicated haemorrhagic stroke and subdural and/or subarachnoid haemorrhage.
a Investigator-reported bleeding events

DETAILED PHARMACOLOGY

Intravenous administration of BIBR 953 ZW (dabigatran) and oral administration of BIBR 1048 MS (dabigatran mesilate) result in potent antithrombotic activity in animal models of thrombosis.

BIBR 953 ZW inhibits purified thrombin *in vitro* with a Ki of 4.5 nM. Its selectivity is apparent through the lack of effect on other serine proteases involved in coagulation. It is active in coagulation assays that simulate intrinsic, extrinsic and common pathway activation, not only in human plasma, but in other species as well. Platelet aggregation is not affected by BIBR 953 ZW, unless the aggregation stimulus is thrombin.

Anticoagulant activity *ex vivo* is prolonged in a dose-dependent manner in mice (investigated only in toxicology studies), rats, rabbits and Rhesus monkeys and the aPTT is a particularly sensitive assay. Anticoagulation after oral administration of higher doses of BIBR 1048 could be detected ≤5 hrs p.a. Antithrombotic activity in venous stasis models in both rats and rabbits

showed 50% reduction of thrombus formation with 33 and 66 µg/kg BIBR 953 after i.v. dosing. There was a good correlation between reduction of clot size and increasing aPTT. Similar effects could be shown after oral dosing with BIBR 1048, with maximal thrombus inhibition 30 min and 2 hrs post dosing in rats and rabbits, respectively.

BIBR 953 ZW had no effect on hERG-mediated potassium current at concentrations ≤30 µM. In addition, there was no effect on the action potential configuration in guinea pig papillary muscle at concentrations ≤10 µM. *In vivo* studies were performed in pigs and Rhesus monkeys, with no effect on any ECG parameter. Thus these data suggest that the risk for proarrhythmic events is very low.

Cardiovascular studies in rats, rabbits and Rhesus monkeys, after both i.v. and p.o. routes of administration showed very little effect.

There was no effect on locomotor activity. Further testing in rats at doses ≤300 mg/kg p.o. showed no effect except for a slight reduction in body temperature at the highest dose. At doses >100 mg/kg in mice, there was a dose-dependent increase in the number of deaths due to bleeding.

Effects on the GI tract were minimal. There was no effect on gastrointestinal transit with either i.v. or p.o. routes of administration.

TOXICOLOGY

Acute toxicity

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

Chronic toxicity

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

Reproductive toxicity

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

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

Carcinogenicity / mutagenicity
Comprehensive *in vitro* and *in vivo* studies revealed no evidence of a mutagenic potential of dabigatran etexilate.

Two-year carcinogenicity studies were conducted in male and female mice and rats given oral doses of dabigatran etexilate of 30, 100, and 200 mg/kg/day. In both studies, no evidence for carcinogenic potential of dabigatran etexilate was observed.

PART III: CONSUMER INFORMATION

Pr Pradaxa®

Dabigatran Etexilate Capsules

Read this carefully before you start taking PRADAXA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about PRADAXA.

ABOUT THIS MEDICATION

What the medication is used for:

PRADAXA is a blood thinner (prevents blood clots from forming).

PRADAXA is prescribed:

- After knee or hip replacement surgery to prevent the formation of blood clots in the vein of your leg(s) or in your lung(s);
- To treat blood clots and prevent them from re-occurring in the veins of your legs and/or lungs. If blood clots form in the veins of your legs you are at risk of a blood clot dislodging and traveling to the lungs causing serious health risks;
- To people who have irregular heartbeats (atrial fibrillation) to prevent a stroke (damage to part of the brain caused by an interruption of its blood supply), or sudden blocking of a blood vessel by a blood clot. People with atrial fibrillation have a part of their heart that does not beat the way it should. This can lead to formation of blood clots which increases the risk of stroke.

What it does:

PRADAXA helps prevent the formation of blood clots by blocking the activity of a protein called thrombin.

When it should not be used:

Do not take PRADAXA if you:

- Have severely reduced kidney function or your kidneys do not function;
- Have active bleeding or bleed excessively;
- Have a disease that increases your chances of bleeding, or bleeding in the brain (stroke) within the last 6 months or recent bleeding of a stomach ulcer;
- Have an epidural or spinal catheter in place or within the first two hours after its removal. Your doctor will know what precautionary measures are required. PRADAXA is not recommended for patients receiving epidural pain control after surgery;
- Are taking oral ketoconazole, used to treat fungus infection;
- Are taking oral glecaprevir/pibrentasvir, used to treat chronic hepatitis C virus infection;
- Are already taking another blood thinner, including apixaban (ELIQUIS), bivalirudin, dalteparin, enoxaparin, fondaparinux, rivaroxaban (XARELTO), unfractionated heparin, warfarin (COUMADIN), unless your physician has decided to switch you to or from PRADAXA;
- Have an artificial heart valve;
- Are breastfeeding. It is possible that PRADAXA passes into breast milk;
- Are allergic to dabigatran etexilate, dabigatran, or any other ingredient in the formulation.

What the medicinal ingredient is:

Dabigatran etexilate, as dabigatran etexilate mesilate.

What the non-medicinal ingredients are:

acacia, carragenan, dimethicone, hydroxypropyl cellulose, hypromellose, indigocarmin (150 mg, 110 mg only), iron oxide black, potassium chloride, potassium hydroxide, propylene glycol, shellac, talc, tartaric acid, titanium dioxide.

What dosage forms it comes in:

Capsules: 75 mg, 110 mg and 150 mg.

WARNINGS AND PRECAUTIONS

Stopping early any blood thinner, including PRADAXA, increases the risk of having a sudden blocking of a blood vessel by a blood clot. This can lead to death or severe injury. If you need to stop PRADAXA, your doctor may give you another blood thinner.

You may bleed very seriously or severely in any part of your body while you are taking PRADAXA.

In order to help prevent serious bleeding with PRADAXA, it is important to take PRADAXA exactly as prescribed by your doctor.

In rare occasions, where you need emergency surgery or other urgent procedure or have obvious or hidden uncontrolled bleeding, you may have to discontinue taking PRADAXA. In these situations, PRAXBIND (idarucizumab), a specific antidote for reversing the effect of PRADAXA, can be used to immediately and completely reverse the blood-thinning effect of PRADAXA.

Your doctor will tell you when it is appropriate for you to resume taking PRADAXA.

BEFORE you use PRADAXA talk to your doctor, nurse, or pharmacist if you:

- Have moderately reduced kidney function;
- Are dehydrated;
- Have a disease or have had an operation recently that increases your risk of bleeding. Examples are a blood clotting disease, a stomach ulcer, a biopsy, a very serious injury, or an inflammation of parts of your heart caused by bacteria;
- Are older than 75 years old;
- Have severe or life-threatening liver disease, or high liver enzymes;
- Are going to have a surgery, including a surgery on your

brain, back, eye or other invasive or dental procedure. Your doctor may ask you to stop PRADAXA temporarily for a few days before the surgery;
- Are pregnant or plan to become pregnant. The effects of PRADAXA on pregnancy and the unborn child are not known;
- Are about to give birth;
- Are less than 18 years old;
- Weigh less than 50 kg;
- Know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk in blood clots).

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all the drugs you take. This includes prescription and non-prescription drugs, vitamins, and herbal supplements. PRADAXA may interact with other medications. This may cause serious side effects.

Know the medicines you take. Keep a list of your drugs and show it to your doctor and/or pharmacist each time you get a new drug.

The following may interact with PRADAXA:
- Antacids, used to treat heartburns. If you need to take an antacid, take it at least two hours after taking PRADAXA;
- Antibiotics, including rifampicin and clarithromycin;
- Antidepressants, in particular selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs);
- Antifungal drugs, including oral itraconazole and posaconazole;
- Antiretroviral drugs, used to treat HIV, including nelfinavir, ritonavir, saquinavir, and tipranavir;
- Blood thinners, including clopidogrel, prasugrel (EFFIENT) or ticagrelor (BRILINTA);
- Drugs used to prevent organ rejection after transplantation, including cyclosporine and tacrolimus;
- Drugs used to treat epilepsy, including carbamazepine;
- Drugs used to treat irregular heartbeats, including amiodarone (CORDARONE), dronedarone (MULTAQ) and quinidine;
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include aspirin (ASA), diclofenac, ibuprofen and naproxen;
- Proton pump inhibitors, used to treat heartburns;
- St. John's Wort, a herbal medicine;
- Verapamil, used to lower blood pressure.

PROPER USE OF THIS MEDICATION

Before you start taking PRADAXA and regularly after, your doctor will test your kidney function.

Take PRADAXA exactly as prescribed.

PRADAXA should be taken with a full glass of water and can be taken with or without food. If PRADAXA upsets your stomach, take it with meals or within 30 minutes after meals. If PRADAXA still upsets your stomach, consult your doctor or pharmacist. It is important to continue taking PRADAXA as prescribed.

Swallow the capsule(s) whole. Do not chew or open the capsule. Do not sprinkle the pellets on food or mix with liquids.

Usual Adult Dose:

If your doctor has given you PRADAXA to take **twice a day**, it is important to take it regularly at the same time each day at approximately 12 hour intervals.

- **After knee or hip replacement surgery:** 220 mg once daily, taken as two (2) capsules of 110 mg at the same time.

Depending on your kidney function or other drugs you may be taking, your doctor may prescribe a lower dose of 150 mg once daily (taken as two capsules of 75 mg at the same time).

Take PRADAXA for as long as the doctor tells you.

- **To treat blood clots and prevent them from re-occurring in the veins of your leg(s) or in your lung(s):** 300 mg a day, taken as one (1) capsule of 150 mg twice daily.

You will start taking PRADAXA following 5 to 10 days treatment with an injectable blood thinner.

The doctor will determine how long you should take PRADAXA so take it until your doctor tells you to stop.

If you are 80 years and older and/or the doctor thinks you are more likely to bleed: 220 mg a day, taken as one (1) capsule of 110 mg, twice daily.

- **For patients who have irregular heartbeats (atrial fibrillation):** 300 mg a day, taken as one (1) capsule of 150 mg, twice daily.

If you are 80 years and older and/or the doctor thinks you are more likely to bleed: 220 mg a day, taken as one (1) capsule of 110 mg, twice daily.

Switching to PRADAXA:
If you are currently taking the blood thinner warfarin or receive a blood thinner given by injection, and your doctor has decided PRADAXA is appropriate for you, make sure you ask your doctor when and how best to switch and start taking PRADAXA.

Overdose:

If you think you have taken too much PRADAXA, contact your healthcare professional, hospital emergency department or

regional Poison Control Centre immediately, even if there are no symptoms.

If you take more than the recommended dose of PRADAXA, you may have an increased risk of bleeding. Your doctor can perform a blood test to assess the risk of bleeding.

For situations when rapid reversal of the blood-thinning effect of PRADAXA is required, PRAXBIND (idarucizumab), a specific antidote for reversing the effect of PRADAXA, can be available in hospitals and emergency rooms.

Missed Dose:

For all treatments, if you forget to take PRADAXA, do not take a double dose to make up for the missed dose.

- **After knee or hip replacement surgery:** Take your next dose at the same time next day.
- **To treat blood clots and prevent them from re-occurring in the veins of your leg(s) or in your lung(s):** Take it as soon as you remember, but if it is almost time for your next dose (less than 6 hours before your next dose), take your next dose when you are supposed to.
- **For patients who have irregular heartbeats (atrial fibrillation):** Take it as soon as you remember, but if it is almost time for your next dose (less than 6 hours before your next dose), take your next dose when you are supposed to.

If you had knee or hip replacement surgery or are receiving treatment for prevention of blood clots in the veins of your legs and lungs and stop taking PRADAXA before your doctor told you to, you are at risk of developing a blood clot in a vein of your leg or in the lungs, which can be life-threatening.

If you have atrial fibrillation and stop taking PRADAXA without talking to your doctor, you are at risk of suffering from a stroke or other complications due to blood clot formation, which can be fatal or lead to severe disability.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You should be aware that prescription medicines carry some risks and that all possible risks may not be known at this stage.

As PRADAXA acts on the blood clotting system, most side effects are related to signs of bruising or bleeding.

Although rare, PRADAXA can cause very serious or severe bleeding that can occur in any part of your body. These bleedings may reduce your physical abilities or even lead to death.

If you fall or injure yourself while taking PRADAXA, especially if you hit your head, please seek urgent medical attention. You may need to be checked by a doctor, as you may be at increased risk of bleeding.

Patients treated with PRADAXA may experience the following side effects:

- abdominal pain, diarrhea, heartburn, nausea, reflux of gastric juice, upset stomach, vomiting;
- difficulty swallowing;
- bruising;
- hives, itching, rash;
- hair loss;
- decrease in the number or even lack of white blood cells (which help to fight infections).

PRADAXA can cause abnormal blood test results for kidney and liver function, number of platelets and number of red blood cells (anemia). Your doctor will ask for blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Common	**Anemia:** feeling tired and weak, pale skin, cold hands and feet		✓	
	Bleeding from penis/vagina		✓	
	Blood in the urine that stains it pink or red		✓	
	Bleeding in the stomach or bowel: darker stool (like tar), bright red blood in your toilet or toilet tissue, vomiting blood		✓	
	Bruising or bleeding due to injury or after operation	✓		
	After surgery: severe bleeding from the surgical wound, an injury or other procedures			✓
	After surgery: liquid oozing from the surgical wound		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
	Nose bleed	✓		
	Bleeding under the skin	✓		
Uncommon	**Allergic reaction, including angioedema:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
	Decreased platelets: bruising, bleeding, fatigue and weakness		✓	
	Coughing blood or blood stained sputum		✓	
	Bleeding into a joint: pain, swelling at a single spot on the knee, ankle or shoulder		✓	
	Bleeding into the rectum or from haemorrhoids		✓	
	Bleeding from site of catheter entry into vein	✓		
	Bleeding into the brain: headache, difficulty seeing or speaking, lack of balance and coordination, weakness on one side, numbness			✓
	Inflammation of the stomach, esophagus (food pipe): difficult and/or painful swallowing, heartburn, mouth sores, feeling of something being stuck in the throat, nausea, vomiting		✓	
	Liver disorder: nausea, vomiting, loss of appetite combined with itching, yellowing of the skin or eyes, dark urine			✓
Unknown	**Agranulocytosis and neutropenia** (decrease in the number or lack of white blood cells) which may manifest with symptoms such as frequent infection with fever, sore throat or mouth ulcers		✓	

This is not a complete list of side effects. For any unexpected effects while taking PRADAXA, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children and pets. Do not use PRADAXA after the expiry date printed on the carton or blister.

Store between 15-30°C. Store in the original package to protect from moisture.

When removing a capsule from the blister, please note the following instructions:

- Tear off one individual blister from the blister card along the perforated line;
- Peel off the backing foil and remove the capsule;
- The capsule should not be pushed through the blister foil;
- Do not peel the blister foil until a capsule is required.

Do not put the capsules in pill boxes or pill organizers, unless capsules can be maintained in the original package.

Any unused product or waste material should be disposed in

accordance with local requirements.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about PRADAXA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://healthproducts.canada.ca/dpd-bdpp/index-eng.jsp), the manufacturer's website (https://www.boehringer-ingelheim.ca), or by calling the manufacturer, Boehringer Ingelheim (Canada) Ltd., at: 1-800-263-5103, extension 84633.

This leaflet was prepared by Boehringer Ingelheim (Canada) Ltd. The information in this leaflet is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

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