Pradaxa®

Boehringer Ingelheim

1. NAME OF THE MEDICINAL PRODUCT

PRADAXA 75 mg hard capsules
PRADAXA 110 mg hard capsules
PRADAXA 150 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 75 mg or 110 mg or 150 mg of dabigatran etexilate (as mesilate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

75 mg capsule: Consist of an imprinted hydroxypropylmethylcellulose (HPMC) capsule with white opaque cap and white opaque body of size 2. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with “R75”. The colour of the imprint is black.
110 mg capsule: Consist of an imprinted hydroxypropylmethylcellulose (HPMC) capsule with light blue opaque cap and light blue opaque body of size 1. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with “R110”. The colour of the imprint is black.
150 mg capsule: Consist of an imprinted hydroxypropylmethylcellulose (HPMC) capsule with light blue opaque cap and white opaque body of size 0. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with “R150”. The colour of the imprint is black.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

75mg capsule:
Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

110mg capsule:
Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

150mg capsule:
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

4.2 Dosage and Administration

Primary prevention of Venous Thromboembolism (VTE) events in adult patients who have undergone elective knee replacement surgery:
The recommended dose of PRADAXA is 220 mg once daily taken as 2 capsules of 110 mg. Treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for a total of 10 days.

Primary prevention of Venous Thromboembolism (VTE) events in adult patients who have undergone elective hip replacement surgery:

The recommended dose of PRADAXA is 220 mg once daily taken as 2 capsules of 110 mg. Treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for a total of 28-35 days.

For both surgeries, if haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules of 110 mg once daily.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:
The recommended daily dose of PRADAXA is 300 mg taken orally as 150 mg hard capsules twice daily.

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

The recommended daily dose of PRADAXA is 300mg taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 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 (eg. recent surgery, trauma, immobilization) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.

SPAF, DVT/PE

For the following groups the recommended daily dose of PRADAXA is 220mg taken as one 110mg capsule twice daily:

- Patients aged 80 years or above
- Patients who receive concomitant verapamil

For the following groups the daily dose of PRADAXA of 300mg or 220mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding:

- Patients between 75-80 years
- Patients with moderate renal impairment
- Patients with gastritis, esophagitis or gastroesophageal reflux
- Other patients at increased risk of bleeding

The recommendation for the use of PRADAXA 220mg taken as one 110mg capsule twice daily is based on pharmacokinetic and pharmacodynamics analyses and has not been studied in this clinical setting.

In case of intolerability to dabigatran, patients should be instructed to immediately consult their treating physician in order to be switched to alternate acceptable treatment options for prevention of stroke and SEE associated with atrial fibrillation or for DVT/PE.

Special patient populations:

Renal impairment:
Renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCl < 30ml/min).There are no data to support use in patients with severe renal impairment (creatinine clearance < 30 ml/min). Given the substantial increase in dabigatran exposure observed in this patient population, treatment in this population with PRADAXA is not recommended (see “Contraindications”).

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

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

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery:
In patients with moderate renal impairment (creatinine clearance 30-50 ml/min), there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg (see sections on Special Warnings & Precautions and Properties).
After knee replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules of 75 mg once daily thereafter for a total of 10 days.

After hip replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules of 75 mg once daily thereafter for a total of 28-35 days.

For both surgeries, if haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules of 75 mg once daily.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation; treatment of DVT and PE, and prevention of recurrent DVT and PE in adults:
Treatment with PRADAXA in patients with severe renal impairment (CrCL<30mL/min) is contraindicated.

No dose adjustment is necessary in patients with mild renal impairment (CrCL 50 -≤80mL/min). For patients with moderate renal impairment (CrCL 30 -50mL/min) the recommended dose of PRADAXA is also 300mg taken as one 150mg capsule twice daily. However for patients with high risk of bleeding a dose reduction of PRADAXA to 220mg taken as one 110mg capsule twice daily should be considered. Close clinical surveillance is recommended in patients with renal impairment.

Elderly:

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery:
As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCl < 30ml/min). The renal function should also be assessed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc).

In elderly patients (> 75 years) there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg (see sections on Special Warnings & Precautions and Properties).
After knee replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 10 days.
After hip replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 28-35 days.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibirillation; treatment of DVT and PE, and prevention of recurrent DVT and PE :
Patients between 75-80 years should be treated with a daily dose of 300mg taken as one 150mg capsule twice daily. A dose of 220mg taken as one 110mg capsule twice daily can be individually considered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high.

Patients aged 80 years or above should be treated with a daily dose of 220mg taken as one 110mg capsule twice daily due to the increased risk of bleeding in this population.

As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCl < 30ml/min). The renal function should also be assessed at least once a year in patients treated with PRADAXA or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc).

Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure in those patients with age-related decline of renal function.
See also dose and administration in renal impairment.

Hepatic impairment:
Patients with elevated liver enzymes > 2 upper limit of normal (ULN) were excluded in clinical trials. No treatment experience is available for this subpopulation of patients, and therefore the use of PRADAXA is not recommended in this population (see sections “Special Warnings & Precautions” and “Pharmacokinetics”). Hepatic impairment or liver disease expected to have any impact on survival is contraindicated.

Weight:
There is very limited clinical experience in patients with a body weight < 50 kg or > 110 kg at the recommended posology. Given the available clinical and kinetic data, no adjustment is necessary (see

section “Pharmacokinetics”) but close clinical surveillance is recommended in patients with a body weight <50kg (see “Special Warnings & Precautions”).

Gender:
Given the available clinical and kinetic data, no dose adjustment is necessary (see section “Pharmacokinetics”).

Post-surgical patients with an increased risk for bleeding:
Patients at risk for bleeding or patients at risk of overexposure, notably patients with moderate renal impairment (creatinine clearance 30 – 50 ml/min), should be treated with caution (see sections on Special Warnings & Precautions and Properties).

Children and adolescents:
Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery; Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:
PRADAXA has not been investigated in patients <18 years of age. Treatment of children with PRADAXA is therefore not recommended.

Treatment of DVT and PE, and prevention of recurrent DVT and PE:
PRADAXA is under investigation in patients < 18 years.
The safety and efficacy in children has not yet been established. Treatment of children with PRADAXA is therefore not recommended.

Concomitant use of PRADAXA with strong P-glycoprotein inhibitors, e.g. Amiodarone, Quinidine or Verapamil:

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery:
Dosing should be reduced to PRADAXA 150 mg taken once daily as 2 capsules of 75 mg in patients who concomitantly receive PRADAXA and amiodarone, quinidine or verapamil (see on “Drug Interactions”).
Treatment initiation with verapamil should be avoided in patients who have undergone major orthopaedic surgery who are already treated with PRADAXA. Simultaneous initiation of treatment with PRADAXA and verapamil should also be avoided.

Treatment with PRADAXA should be initiated orally within 1 - 4 hours of completed surgery with a single capsule of 75 mg and continuing with 2 capsules of 75 mg once daily thereafter for a total of 10 days (following knee replacement surgery) or 28-35 days (following hip replacement surgery).

For both surgeries, if haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules of 75 mg once daily.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation; treatment of DVT and PE, and prevention of recurrent DVT and PE :
No dose adjustment is necessary for concomitant use of amiodarone or quinidine.
Dosing should be reduced to 220mg taken as one 110mg capsule twice daily in patients who receive concomitantly dabigatran etexilate and verapamil. In this situation PRADAXA and verapamil should be taken at the same time.

Patients at risk of bleeding (SPAF/DVT/PE)
Patients with an increased risk of bleeding (see Special Warnings and Precautions, Haemorrhagic risk, Table 1), should be closely monitored clinically (looking for signs of bleeding or anaemia). Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient. A coagulation test may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. When excessive dabigatran exposure is identified in patients at high risk of bleeding, a dose of 220 mg taken as one 110 mg capsule twice daily is recommended. When clinically relevant bleeding occurs, treatment should be interrupted.

For subjects with gastritis, esophagitis, or gastroesophageal reflux, the dose of 220 mg taken as one 110 mg capsule twice daily may be considered due to the elevated risk of major gastro-intestinal bleeding.

Close clinical surveillance (looking for signs of bleeding or anaemia) is recommended throughout the treatment period, especially if risk factors are combined.

Table 1 summarises factors which may increase the haemorraghic risk. Please also refer to contraindications.

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

Pharmacodynamic and kinetic factors	Age ≥ 75 years
Factors increasing dabigatran plasma levels	Major: • Moderate renal impairment (30-50 mL/min CrCL) • Strong P-gp inhibitors • Mild to moderate P-gp inhibitor co-medication (e.g. amiodarone, verapamil, quinidine and ticagrelor; see section "Drug Interactions") Minor: • Low body weight (< 50 kg)
Pharmacodynamic interactions	• ASA and other platelet aggregation inhibitors such as clopidogrel • NSAID • SSRIs or SNRIs • Other medicinal products which may impair haemostasis
Diseases / procedures with special haemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Recent biopsy or major trauma • Bacterial endocarditis • Esophagitis, gastritis or gastroesophageal reflux • Recent intracranial haemorrhage or brain, spinal or ophthalmic surgery

The measurement of dabigatran-related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors.

In patients who are bleeding, an aPTT test may be useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity. An aPTT > 80 sec at trough, i.e., when the next dose is due, is associated with a higher risk of bleeding (see Monitoring and Laboratory Tests).
Should severe bleeding occur, treatment with PRADAXA must be discontinued and the source of bleeding investigated promptly.

Assessment of renal function (SPAF, DVT/PE):

In all patients and especially in the elderly (>75 years), as renal impairment may be frequent in this age group:

- Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with PRADAXA to exclude patients with severe renal impairment (i.e. CrCL < 30 mL/min). PRADAXA is contraindicated in patients with severe renal impairment

- Renal function should also be assessed when a decline in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products)

Additional requirements in patients with mild to moderate renal impairment and in patients aged over 75 years:

- Renal function should be assessed during treatment with PRADAXA at least once a year or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (e.g. hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products)

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

- For creatinine in μmol/L:

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

- For creatinine in mg/dL:

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

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

Switching from PRADAXA treatment to parenteral anticoagulant:
Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery:
It is recommended to wait 24 hours after the last dose before switching from PRADAXA to a parenteral anticoagulant (see section on Drug Interactions).

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation;treatment of DVT and PE, and prevention of recurrent DVT and PE :
It is recommended to wait 12 hours after the last dose before switching from PRADAXA to a parenteral anticoagulant.

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

Switching from Vit. K antagonists to PRADAXA
Prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation; treatment of DVT and PE, and prevention of recurrent DVT and PE:
The Vit. K antagonist should be stopped. PRADAXA can be given as soon as the INR is < 2.0.

Switching from PRADAXA to Vit. K antagonists (VKA)
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE):
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 CrCL as follows:
• CrCL ≥ 50 ml/min, start VKA 3 days before discontinuing dabigatran etexilate.
• CrCL ≥ 30-< 50 ml/min, start VKA 2 days before discontinuing dabigatran etexilate.

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.

Because PRADAXA can impact the International Normalized Ratio (INR), the INR will better reflect VKA's effect only after PRADAXA has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.

Note that when converting a patient from PRADAXA to vitamin K antagonist 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, and not that of PRADAXA, since it is not a valid measure to assess the anticoagulant activity of PRADAXA. The INR is only calibrated and validated for VKA and should not be used for any other anticoagulant, including PRADAXA.

Catheter ablation for atrial fibrillation
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:
Catheter ablation can be conducted in patients on 150 mg twice daily PRADAXA treatment. PRADAXA treatment does not need to be interrupted (see "Pharmacological Properties").

Cardioversion
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:
Patients can stay on PRADAXA while being cardioverted.

Percutaneous coronary intervention (PCI) with stenting
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:
Patients with non valvular atrial fibrillation who undergo a PCI with stenting can be treated with PRADAXA in combination with antiplatelets after haemostasis is achieved (see "Pharmacological Properties")

Missed dose
Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery:
Continue with your remaining daily doses of PRADAXA at the same time of the next day. Do not take a double dose to make up for missed individual doses.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation; treatment of DVT and PE, and prevention of recurrent 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.
Do not take a double dose to make up for missed individual doses.

Method of administration
PRADAXA hard capsules can be taken with or without food. PRADAXA hard capsules should be swallowed as a whole with a glass of water, to facilitate delivery to the stomach. If gastrointestinal symptoms develop it is recommended to take Pradaxa with a meal and/or a proton pump inhibitor such as pantoprazole. Patients should be instructed not to open the capsule as this may increase the risk of bleeding.

Instruction for Use/Handling
When removing a hard 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

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Patients with severe renal impairment (CrCl < 30 ml/min)
- Active clinically significant bleeding
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with the following strong P-gp inhibitors: systemic ketoconazole, cyclosporine, itraconazole and dronedarone (see section on "Drug Interactions")
- Prosthetic heart valve replacement requiring anticoagulant treatment (see section on Pharmacological Properties)
- Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH, except at doses necessary to maintain patency of central venous or arterial catherter or during catheter ablation for aterial fibrillation), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, apixaban, etc.) except under specific circumstances. These are switching anticoagulant therapy (see section "Dosage and Administration") or when UFH is given at doses necessary to maintain an open central venous or arterial catheter or when UFH is given during catheter ablation for atrial fibrillation (see section "Drug Interactions")

4.4 Special warnings and precautions

Hepatic impairment:

Patients with elevated liver enzymes > 2 ULN were excluded in controlled clinical trials investigating the VTE prevention following elective hip or knee replacement surgery. No treatment
experience is available for this subpopulation of patients, and therefore the use of PRADAXA is not recommended in this population. Hepatic impairment or liver disease expected to have any impact on survival is contraindicated (see section “Contraindications”).

Haemorrhagic risk:
As with all anticoagulants, PRADAXA should be used with caution in conditions with an increased risk of bleeding. 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.

For situation of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effects of dabigatran is required, the specific reversal agent (PRAXBIND, idarucizumab) is available (see “Surgery and Interventions”, “Pre-operative Phase” and “Overdose”.)

PRADAXA treatment does not require anticoagulant monitoring. The INR test is unreliable in patients on PRADAXA and false positive INR elevations have been reported. Therefore INR tests should not be performed.

Tests of anticoagulant activity such as thrombin time (TT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) are available to detect excessive dabigatran activity.

Dabigatran related anticoagulation can be assessed by ECT or TT. If ECT or TT is not available, the aPTT test provides an approximation of PRADAXA’s anticoagulant activity

Table 2 shows coagulation test thresholds at trough that may be associated with an increased risk of bleeding.

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

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: In atrial fibrillation patients in RE-LY treated with 150 mg bid an aPTT of greater than 2.0 – 3.0 fold of normal range at trough was associated with an increased risk of bleeding.

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

Patients who develop acute renal failure should discontinue PRADAXA.

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

The concomitant use of PRADAXA with the following treatments has not been studied and may increase the risk of bleeding:desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfinpyrazone, prasugrel, and P-gp inhibitors such as but not limited to , tacrolismus, ritonavir, tipranavir, nelfinavir and saquinavir.

The concomitant use of PRADAXA with the fixed-dose combination of the P-gp inhibitors glecaprevir/pibrentasevir has been shown to increase exposure of dabigatran and may increase the risk of bleeding.

The concomitant use of dronedarone increases exposure of dabigatran and is not recommended (see “PK in specific populations”).

The concomitant use of ticagrelor increases the exposure to dabigatran and may show pharmacodynamic interaction, which may result in an increased risk of bleeding.

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

Use of fibrinolytic agents for the treatment of acute ischemic stroke:
The use of fibrinolytic agents for the treatment of acute ischemic stroke may be considered if the patient presents with a thrombin time (TT), or Ecarin clotting time (ECT), or activated partial thromboplastin time (aPTT) not exceeding the upper limit of normal (ULN) according to the local reference range.

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

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery:
NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with PRADAXA. There is limited evidence regarding the use of regular NSAID medication with half-lives of less than 12 hours during treatment with PRADAXA and this has not suggested additional bleeding risk.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:
Co-administration of anti-platelet (including ASA and clopidogrel) and NSAID therapies increase the risk of bleeding. Specifically, with concomitant intake of antiplatelets or strong P-gp inhibitors in patients aged ≥75 years, the risk of major bleeding, including gastrointestinal bleeding, increases. If bleeding is clinically suspected, appropriate measures such as testing for occult blood in stool, or testing for a drop in hemoglobin is suggested**.**

Interaction with P-gp inducers:
The concomitant use of PRADAXA with the strong P-gp inducer rifampicin reduces dabigatran plasma concentrations. Other P-gp inducers such as St. John`s Wort or carbamazepine are also expected to reduce dabigatran plasma concentrations, and should be co-administered with caution (see section “Drug Interactions” and “PK in specific populations”).

Patients with antiphospholipid syndrome:
Patients with antiphospholipid syndrome Direct acting Oral Anticoagulants (DOACs) including rivaroxaban/apixaban/edoxaban/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 therapy.

Surgery and Interventions:
Patients on PRADAXA who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore surgical interventions may require the temporary discontinuation of PRADAXA (see section on “Pharmacokinetics”).

For SPAF: Patients can stay on PRADAXA while being cardioverted. PRADAXA treatment (150 mg twice daily) does not need to be interrupted in patients undergoing catheter ablation for atrial fibrillation (see “Dosage and administration”).

In case of emergency surgery or urgent procedures when rapid reversal of the anticoagulation effect is required the specific reversal agent (PRAXBIND, idarucizumab) to PRADAXA is available.

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.

Preoperative Phase

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

Emergency Surgery or Urgent Procedure:
The specific reversal agent (PRAXBIND, idarucizumab) of PRADAXA is available for the rapid reversal of the anticoagulation effect (see “Surgery and Interventions”).

Acute Surgery/Intervention:
If an acute intervention is required, PRADAXA should be temporarily discontinued. An acute surgery/ intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed there may be an increase in the risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

Elective Surgery/Intervention:
If possible, PRADAXA should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete hemostasis may be required consider stopping PRADAXA 2-4 days before surgery. Clearance of dabigatran in patients with renal insufficiency may take longer. This should be considered in advance of any procedures (see Table 3 and also section “Pharmacokinetics”).

Table 3 summarizes discontinuation rules before invasive or surgical procedures.

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

*for more details see Table 25 “Pharmacokinetics”

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

Patients at high surgical mortality risk and with intrinsic risk factors for thromboembolic events:
There are limited efficacy and safety data for dabigatran available in these patients and therefore they should be treated with caution.

Spinal anesthesia/ epidural anesthesia/lumbar puncture:
Procedures such as spinal anesthesia may require complete hemostatic function. The risk of spinal or epidural haematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 2 hours should elapse before the administration of the first dose of PRADAXA. These patients require frequent observation for neurological signs and symptoms of spinal or epidural hematoma.

Post Procedural Period:
PRADAXA treatment can be resumed / started after complete haemostasis is achieved.

Hip fracture surgery:
There is no data on the use of PRADAXA in patients undergoing hip fracture surgery. Therefore treatment is not recommended.

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

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

Active Cancer Patients (DVT/PE):
The efficacy and safety have not been established for DVT/PE patients with active cancer.

4.5 Drug Interactions

The concomitant use of PRADAXA with treatments that act on haemostasis or coagulation including Vitamin K antagonists can markedly increase the risk of bleeding. (see “Special warnings and precautions”).

Dabigatran etexilate and dabigatran are not metabolised by the cytochrome P450 system and have no *in vitro* effects on human cytochrome P450 enzymes. Therefore, related medicinal product interactions are notexpected with dabigatran (see “PK in specific Populations”).

NSAIDs:
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. With chronic use in the RE-LY study, NSAIDs increased the risk of bleeding by approximately 50 % on both dabigatran etexilate and warfarin. Therefore, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives >12 hours, close observation for signs of bleeding is recommended.

P-glycoprotein interactions:

P-glycoprotein inhibitors:

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

Concomitant administration of systemic ketoconazole is contraindicated.

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery:
For the concomitant use of P-gp inhibitors and dosing of PRADAXA in the indication, please see “Dosing and administration” and “PK in specific populations”.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE):
For the P-gp inhibitors listed above, no dose adjustments are required for PRADAXA in this indication.

***Amiodarone*:** Amiodarone is an inhibitor of the efflux transporter P-glycoprotein and dabigatran etexilate a substrate of this transporter. Dabigatran exposure in healthy subjects was increased by 1.6 fold (+60 %) in the presence of amiodarone (see “Special Populations”). In view of the long half-life of amiodarone the potential for drug interaction may exist for weeks after discontinuation of amiodarone.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:
In patients in the RE-LY trial concentrations were increased by no more than 14% and no increased risk of bleeding was observed.

***Verapamil*:** When PRADAXA (150mg) was coadministered with oral verapamil, the C_{max} and AUC of dabigatran were increased but the magnitude of this change differs, depending on timing of administration and formulation of verapamil (see “PK in specific populations”).

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: In patients in the RE-LY trial concentrations were increased by no more than 21% and no increased risk of bleeding was observed.

Quinidine: Dabigatran exposure in healthy subjects was increased by 1.5 fold (+53 %) in the presence of quinidine (see “PK in specific populations”).

***Clarithromycin*:** Dabigatan exposure in healthy subjects was increased by about 19% in the presence of clarithromycine without any clinical safety concern (see “PK in specific populations”).

***Ketoconazole*:** Dabigatran exposure was increased by 2.5 fold (+150%) after single and multiple doses of systemic ketoconazole (see " Contraindications" and "PK in specific populations").

***Dronedarone*:** Dabigatran exposure was increased by 2.1 fold (+114%) after single or 2.4 fold (+136%) after multiple doses of dronedarone, respectively (see "PK in specific populations").

Ticagrelor: Dabigatran exposure in healthy subjects was increased by 1.46 fold (+ 46%) in the presence of ticagrelor at steady state or by 1.73 fold (+73%) when a loading dose of ticagrelor was administered simultaneously with a single dose of 75 mg dabigatran etexilate.
Dabigatran steady state exposure in healthy subjects was increased by 1.26 fold (+ 26 %) in the presence of ticagrelor at steady state or by 1.49 fold (+49%) when a loading dose of ticagrelor was administered simultaneously with 110 mg dabigatran etexilate. The increase in exposure was less pronounced when the 180 mg ticagrelor loading dose was given two hours after dabigatran intake (+27%).

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

P-glycoprotein inducers:
After 7 days of treatment with 600 mg rifampicin qd total dabigatran $AUC_{0-\infty}$ and C_{max} were reduced by 67% and 66% compared to the reference treatment, respectively.
The concomitant use with P-gp inducers (e.g., rifampicin, St. John´s wort (Hypericum perforatum), carbamazepine, or phenytoin) reduces exposure to dabigatran and should be avoided (see "Special Warnings and Precautions" and "Special Populations").

4.6 Fertility, pregnancy and lactation

Pregnancy
No clinical data on exposed pregnancies are available. The potential risk for humans is unknown.
Women of child-bearing potential should avoid pregnancy during treatment with PRADAXA and when pregnant, women should not be treated with PRADAXA unless the expected benefit is greater than the risk.

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

Fertility
No clinical data available. Non-clinical reproductive studies did not show any adverse effects on fertility or postnatal development of the neonate.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery:
In the primary VTE prevention trials after elective total hip replacement or total knee replacement surgery, a total of 10,795 patients were treated in 6 controlled studies with at least one dose of dabigatran extexilate (150mg qd, 220mg qd, enoxaparin). 6,684 of the 10,795 patients were treated with 150 mg or 220 mg once daily of dabigatran etexilate. In total, about 9% of patients treated with dabigatran and about 10% of patients treated with enoxaparin for VTE prevention after elective hip or knee surgery (short-term treatment up to 42 days) experienced adverse reactions.

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

In the RELY trial investigating the prevention of stroke and systemic embolism in patients with atrial fibrillation, a total of 12,042 patients were treated with dabigatran etexilate. Of these 6,059 were treated with 150 mg twice daily of dabigatran etexilate, while 5,983 received doses of 110 mg twice daily.
About 22% of patients with atrial fibrillation treated with dabigatran and about 16% of patients treated with warfarin for the prevention of stroke and systemic embolism (long-term treatment for up to 3 years) experienced adverse events considered related to treatment.

Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE):
In the acute DVT/PE treatment trials (RE-COVER, RE-COVER II) a total of 2,553 patients were included in the safety analysis for dabigatran etexilate. All patients were treated with dabigatran etexilate 150 mg bid. 14% of patients treated for acute DVT/PE treatment (long-term treatment up to 6 months) experienced adverse reactions.

Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE):
In the recurrent DVT/PE prevention trials (RE-MEDY, RE-SONATE) a total of 2,114 patients were treated with dabigatran etexilate; 552 of the 2,114 patients were rolled over from the RE-COVER trial (acute DVT/PE treatment) into the RE-MEDY trial and are counted in both the acute and recurrent patient totals. All patients were treated with dabigatran etexilate 150 mg bid and 15% of patients treated for recurrent DVT/PE prevention (long-term treatment up to 36 months) experienced adverse reactions.

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

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

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 Tables 4, 5 and 6 below.

Prevention of VTE after THR or TKR surgery

Table 4: 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 5: 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 6: 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 RECOVER, RECOVER II, REMEDY and RE-SONATE followed the recommendations of the International Society on Thrombosis and Haemostasis. A bleeding event was categorised as an MBE if it fulfilled at least one of the following criteria:
• Fatal bleeding
• Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial, or intramuscular with compartment syndrome. In order for bleeding in a critical area or organ to be classified as an MBE it had to be associated with a symptomatic clinical presentation.
• Bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or red cells.

[#]The definition of Clinically Relevant Bleeding Event (CRBE): In Studies RECOVER II (1160.46), RECOVER (1160.53), and REMEDY (1160.47), 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 are counted from the first intake of dabigatran etexilate or warfarin after the parenteral therapy has been discontinued (oral only treatment period). This includes all bleeding events which occurred during dabigatran therapy. All bleeding events which occurred during warfarin therapy are included except for those during the overlap period between warfarin and parenteral therapy.

Table 7: 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 16
[&] statistically significant

Table 8: 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 RELY trial

In Table 9, 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 9: 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	
Intra-cranial 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 hemorrhagic stroke and subdural and/or subarachnoid haemorrhage.
a Investigator-reported bleeding events

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:
Major bleeding fulfilled one or more of the following criteria:

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

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

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

Subjects randomized to dabigatran etexilate 110 mg twice daily and 150mg twice daily had a significantly lower risk for life-threatening bleeds, haemorrhagic stroke and intracranial bleeding compared to warfarin [$p < 0.05$]. Both dose strengths of dabigatran etexilate had also a statistically significant lower total bleed rate. Subjects randomized to dabigatran etexilate 110mg twice daily had a signficantly lower risk for major bleeds compared with warfarin (hazard ratio 0.81, p=0.0027).

Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE):
The definition of major bleeding events (MBEs) followed the recommendations of the International Society on Thrombosis and Haemostasis. A bleeding event was categorised as an MBE if it fulfilled at least one of the following criteria:

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

In a pooled analysis of the two pivotal trials (RE-COVER, RE-COVER II) in acute DVT/PE treatment, subjects randomized to dabigatran etexilate had lower rates of the following bleeding events, which were statistically significant:

- Major bleeding events (hazard ratio 0.60 (0.36, 0.99))
- Major or clinically relevant bleeding events (CRBEs) (hazard ratio 0.56 (0.45, 0.71))
- Any bleeding events (hazard ratio 0.67 (0.59, 0.77))

All of which were superior vs. warfarin.

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

Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE):
The definition of MBEs followed the recommendations of the International Society on Thrombosis and Haemostasis. A bleeding in RE-MEDY event was categorised as an MBE if it fulfilled at least one of the following criteria:

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

In RE-MEDY, patients randomized to dabigatran etexilate had significantly less bleeds compared to warfarin for the following categories: major bleeding events or clinically relevant bleeding events (hazard ratio 0.55 (0.41, 0.72), p<0.0001) and any bleeding events (hazard ratio 0.71 (0.61, 0.83), p<0.0001).

A bleeding event in RE-SONATE was categorised as an MBE if it fulfilled at least one of the following criteria:

- Fatal bleeding
- Associated with a fall in haemoglobin of 2 g/dL or more
- Led to the transfusion of ≥ 2 units packed cells or whole blood
- Occurred in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal

In RE-SONATE, the rates of MBE were low (2 patients with MBEs (0.3%) for dabigatran etexilate vs. 0 patients with MBE (0%) for placebo. The rate of major bleeding events or clinically relevant bleeding events were higher with dabigatran etexilate compared with placebo (5.3% vs. 2.0%).

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			
Anemia	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)
Anemia 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 (2.1)	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 - RELY trial

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

	Dabigatran etexilate 110 mg N (%)	Dabigatran etexilate 150 mg N (%)	Warfarin N (%)
	5,983 (100)	6,059 (100)	5,998 (100)
Bleeding and anemia*	**599 (10.0)**	**747 (12.3)**	**825 (13.8)**
Anemia	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 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, hemorrhagic gastritis, hemorrhagic erosive gastritis, gastrointestinal ulcer).

Gastrointestinal (GI) haemorrhage occurred at a higher frequency with PRADAXA 150 mg bid, compared to warfarin (see Table 22 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 RELY study, observed abnormalities of liver function tests (LFT) are presented below in Table 13.

Table 13: Liver Function Tests in the RELY trial

	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily 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.

Table 14: Adverse reactions identified from studies and post-marketing data in:

- *Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.*
- *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.*
- *Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.*

Blood and lymphatic system disorders:
Anemia, thrombocytopenia, neutropenia*, agranulocytosis*

Immune system disorders:
Drug hypersensitivity including pruritus, rash and urticaria, bronchospasm*, angioedema*, anaphylactic reaction*.

Nervous system disorders:
Intracranial haemorrhage

Vascular disorders:
Haematoma, haemorrhage

Respiratory, thoracic and mediastinal disorders:

Epistaxis, haemoptysis

Gastrointestinal disorders:
Gastrointestinal haemorrhage, abdominal pain, diarrhoea, dyspepsia, nausea, gastrointestinal ulcer, including oesophageal ulcer, gastrooesophagitis, gastrooesophageal reflux disease, vomiting, dysphagia

Hepatobiliary disorders:
Hepatic function abnormal

Skin and subcutaneous tissue disorders:
Skin haemorrhage, alopecia*

Musculoskeletal, connective tissue and bone disorders:
Haemarthrosis

Renal and urinary disorders:
Urogenital haemorrhage

General disorders and administration site conditions:
Injection site haemorrhage, catheter site haemorrhage

Injury, poisoning and procedural complications:
Traumatic haemorrhage, incision site haemorrhage

* including post-marketing data

Table 15: Additional specific adverse reactions identified per indication

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (pVTEp):

Vascular disorders:
Wound haemorrhage

General disorders and administration site conditions:
Bloody discharge

Injury, poisoning and procedural complications:
Post-procedural haematoma, post-procedural haemorrhage, anaemia post-operative, post-procedural discharge, wound secretion

Surgical and medical procedures:
Wound drainage, post-procedural drainage

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF):
None

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE):
None

4.9 Overdose

Symptoms
Overdose following administration of PRADAXA may lead to haemorrhagic complications due to its pharmacodynamic properties. Doses of PRADAXA beyond those recommended expose the patient to increased risk of bleeding.

Therapy

In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained.

Depending on the clinical situation appropriate standard treatment, e.g. surgical haemostasis as indicated and blood volume replacement, should be undertaken.

For situations when rapid reversal is required the specific reversal agent (PRAXBIND, idarucizumab) antagonising the pharmacodynamics effect of PRADAXA is available (see section “Special warnings & precautions; “Surgery and Interventions”, “Pre-operative Phase”).

In addition, consideration may be given to the use of fresh whole blood or fresh frozen plasma. Coagulation factor concentrations (activated or non-activated) or recombinant Factor VIIa may be taken into account. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatran but their usefulness in clinical settings has not yet been systematically demonstrated. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet drugs have been used. All symptomatic treatment has to be given according to the physician's judgement.

As protein binding is low, dabigatran is dialysable, however, there is limited clinical experience in using dialysis in this setting (see “PK in specific populations”).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

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

There is a close correlation between plasma dabigatran concentrations and degree of anticoagulant effect. Dabigatran prolongs the aPTT, ECT and TT.

Clinical trials in primary VTE prevention following major joint replacement surgery:
In 2 large randomized, parallel group, double-blind, dose–confirmatory trials, patients undergoing elective major orthopaedic surgery (one for knee replacement surgery and one for hip replacement surgery) received dabigatran etexilate 75 mg or 110 mg within 1-4 hours of surgery followed by 150 or 220 mg once daily thereafter, haemostasis having been secured, or enoxaparin 40 mg on the day prior to surgery and once daily thereafter.
In the RE-MODEL trial (knee replacement) treatment was for 6 – 10 days and in the RE-NOVATE trial (hip replacement) for 28 – 35 days. Totals of 2076 patients (knee) and 3494 (hip) were treated respectively.
The results of the knee study (RE-MODEL) with respect to the primary end-point, total including asymptomatic venous thromboembolism (VTE) plus all-cause mortality showed that the antithrombotic effect of both doses of dabigatran etexilate were statistically non-inferior to that of enoxaparin.
Similarly, total including asymptomatic VTE and all-cause mortality constituted the primary end-point for the hip study (RE-NOVATE). Again dabigatran etexilate at both once daily doses was statistically non-inferior to enoxaparin 40 mg daily.

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

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

In RE-MODEL and RE-NOVATE the randomisation to the respective study medication was done pre-surgery, and in the RE-MOBILIZE and the Japanese placebo controlled trial the randomisation to the respective study medication was done post-surgery. This is of note especially in the safety evaluation of these trials. For this reason the trials are grouped in pre- and post surgery randomised trials in Table 16.

Data for the major VTE and VTE-related mortality end-point and adjudicated major bleeding endpoints are shown in the Table 16 below. VTE was defined as the composite incidence of deep vein thrombosis and Pulmonary Embolism.

Table 16: Analysis of major VTE and VTE-related mortality during the treatment period in the RE-MODEL and the RE-NOVATE orthopaedic surgery studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
RE-NOVATE (hip) [1]			
N	909	888	917
Incidences (%)	28 (3.1)	38 (4.3)	36 (3.9)
Risk differences vs. enoxaparin (%)	- 0.8	0.4	
95 % CI	- 2.5, 0.8	- 1.5, 2.2	
Risk ratio over enoxaparin	0.78	1.09	
95% CI	0.48, 1.27	0.70, 1.70	
RE-MODEL (knee) [1]			
N	506	527	511
Incidences (%)	13 (2.6)	20 (3.8)	18 (3.5)
Risk differences vs. enoxaparin (%)	- 1.0	0.3	
95 % CI	- 3.1, 1.2	-2.0, 2.6	
Risk ratio over enoxaparin	0.73	1.08	
95% CI	0.36, 1.47	0.58, 2.01	
RE-MOBILIZE (knee) [2]			Enoxaparin 60 mg
N	618	656	668
Incidences (%)	21 (3.4)	20 (3.0)	15 (2.2)
Risk differences vs. enoxaparin (%)	1.2	0.8	
95 % CI	(-0.7, 3.0)	(-0.9, 2.5)	
Risk ratio over enoxaparin	1.51	1.36	
95% CI	(0.79, 2.91)	(0.70, 2.63)	
Japanese knee study [2]			
			Placebo
N	102	113	104
Incidences (%)	0	2 (1.8)	6 (5.8)
Risk differences vs. placebo (%)	−5.8	−4.0	
95 % CI	(−10.3, −1.3)	(−9.1, 1.1)	

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

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

The clinical evidence for the efficacy of dabigatran etexilate is derived from the RE-LY study (Randomized Evaluation of Long term anticoagulant therapy) a multi-center, multi-national, randomized parallel group study of two blinded doses of dabigatran etexilate (110 mg bid and 150 mg bid) compared to open-label warfarin in patients with atrial fibrillation at moderate to high risk of stroke or systemic embolism. The primary objective in this study was to determine if dabigatran was non-inferior to warfarin in reducing the occurrence of the composite endpoint, stroke and systemic embolic events (SEE).
In the RE-LY study, a total of 18,113 patients were randomized, with a mean age of 71.5 years and a mean $CHADS_2$ score of 2.1. The population had approximately equal proportions of patients with $CHADS_2$ score 1, 2 and ≥3. The patient population was 64% male, 70% Caucasian and 16% Asian. RE-LY had a median treatment of 20 months with dabigatran etexilate given as fixed dose without coagulation monitoring. In addition to documented non-valvular atrial fibrillation (AF) e.g., persistent AF or paroxysmal, patients had one of the following additional risk factors for stroke:

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

The concomitant diseases of patients in this trial included hypertension 79%, diabetes 23% and coronary artery disease (CAD) 28%. 50% of the patient population was VKA naïve defined as less than 2 months total life time exposure. 32% of the population had never been exposed to a VKA. For those patients randomized to warfarin, the time in therapeutic range (INR 2.0 to 3.0) for the trial was a median of 67%. Concomitant medications included ASA (25% of subjects used at least 50% of the time in study), clopidogrel (3.6%), ASA+clopidogrel (2%), NSAIDs (6.3%), beta-blockers (63.4%), diuretics (53.9%), statins (46.4%), ACE-inhibitors (44.6%), angiotensin receptor blockers (26.1%), oral hypoglycemics (17.5%), insulin (5.2%), digoxin (29.4%), amiodarone (11.3%), diltiazem (8.9%), verapamil (5.4%), and proton pump inhibitors (17.8%).

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

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

Figure 1 and tables –17 - 21 display details of key results:

Table 17: Analysis of first occurrence of stroke or SEE (primary endpoint) during the study period in the RE-LY (randomized set)

	Dabigatran etexilate 150 mg bid	Dabigatran etexilate 110 mg bid	Warfarin
Subjects randomized	6076	6015	6022
Stroke and/or SEE			
Incidences (%)	135 (1.12)	183 (1.54)	203 (1.72)
Hazard ratio over warfarin (95% CI)	0.65 (0.52, 0.81)	0.89 (0.73, 1.09)	
p value superiority	p = 0.0001	p = 0.2721	

% refers to yearly event rate

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

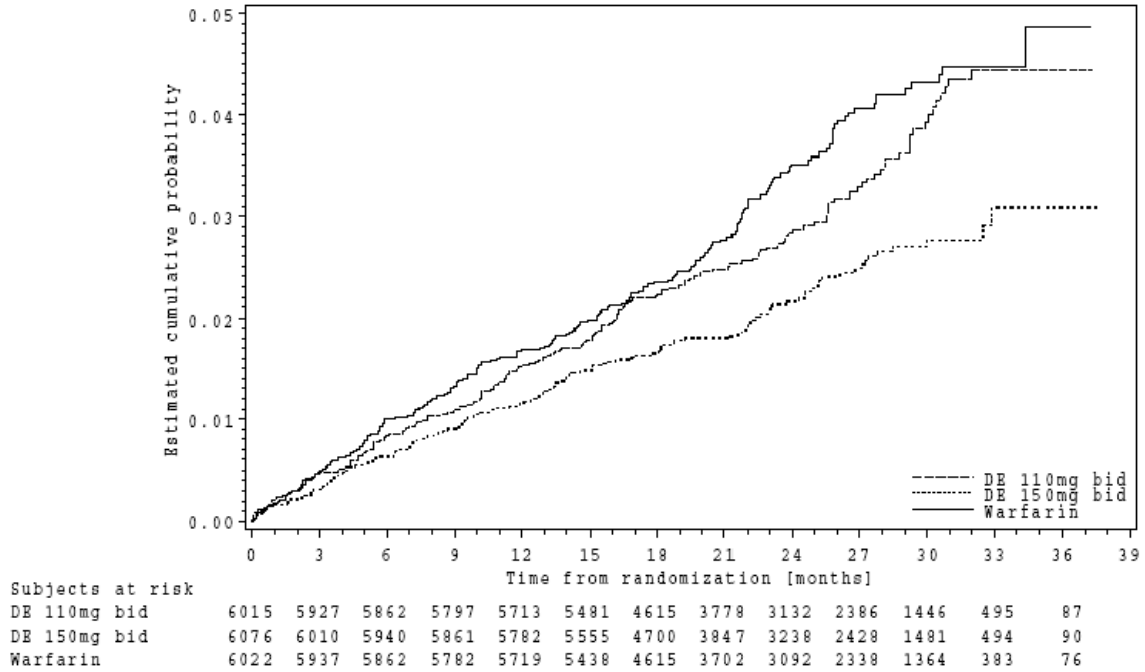

Table 18: Analysis of first occurrence of ischemic or haemorrhagic strokes during the study period in RE-LY (randomized set)

	Dabigatran etexilate 150 mg bid	Dabigatran etexilate 110 mg bid	Warfarin
Subjects randomized	6076	6015	6022
Stroke			
Incidences (%)	123 (1.02)	171 (1.44)	187 (1.59)
Hazard ratio vs. warfarin (95% CI)	0.64 (0.51, 0.81)	0.91 (0.74, 1.12)	
p-value	0.0001	0.3535	
SEE			
Incidences (%)	13 (0.11)	15 (0.13)	21 (0.18)
Hazard ratio vs. warfarin (95% CI)	0.61 (0.30, 1.21)	0.71 (0.37, 1.38)	
p-value	0.1582	0.3099	
Ischemic stroke			
Incidences (%)	104 (0.86)	152 (1.28)	134 (1.14)
Hazard ratio vs. warfarin (95% CI)	0.76 (0.59, 0.98)	1.13 (0.89, 1.42)	
p-value	0.0351	0.3138	
Hemorrhagic stroke			
Incidences (%)	12 (0.10)	14 (0.12)	45 (0.38)
Hazard ratio vs. warfarin (95% CI)	0.26 (0.14, 0.49)	0.31 (0.17, 0.56)	
p-value	<0.0001	0.0001	

% refers to yearly event rate

Table 19: Analysis of all cause and cardiovascular survival during the study period in the RE-LY (randomized set)

	Dabigatran etexilate 150 mg bid	Dabigatran etexilate 110 mg bid	Warfarin
Subjects randomized	6076	6015	6022
All-cause mortality			

Incidences (%)	438 (3.64)	446 (3.75)	487 (4.13)
Hazard ratio vs. warfarin (95% CI)	0.88 (0.77, 1.00)	0.91 (0.80, 1.03)	
p-value	0.0517	0.1308	
Vascular mortality			
Incidences (%)	274 (2.28)	289 (2.43)	317 (2.69)
Hazard ratio vs. warfarin (95% CI)	0.85 (0.72, 0.99)	0.90 (0.77, 1.06)	
p-value	0.0430	0.2081	

% refers to yearly event rate

The net clinical benefit (NCB) as measured by the unweighted composite clinical endpoint of stroke, systemic embolism, pulmonary embolism, acute myocardial infarction, vascular deaths, and major bleeds was assessed and is presented as part of Table 20. The yearly event rates for the dabigatran etexilate groups were lower compared to the warfarin group. The risk reduction for this composite endpoint was 8% and 10% for the dabigatran etexilate 110 mg bid and 150 mg bid treatment groups.

Table 20: Other Measures Evaluated

	Dabigatran etexilate 150 mg bid	Dabigatran etexilate 110 mg bid	Warfarin
Subjects randomized	6076	6015	6022
Stroke/SEE/death			
Incidences (%)	520 (4.32)	577 (4.85)	613 (5.20)
Hazard ratio vs. warfarin (95%CI)	0.83 (0.74. 0.93)	0.93 (0.83, 1.04)	
p-value	0.0015	0.2206	
Stroke/SEE/PE/MI/death/major bleed (NCB)			
Incidences (%)	850 (7.06)	863 (7.25)	925 (7.84)
Hazard ratio vs. Warfarin (95%CI)	0.90 (0.82, 0.99)	0.92 (0.84, 1.01)	
p-value	0.0287	0.0849	
Pulmonary embolism			
Incidences (%)	18 (0.15)	14 (0.12)	12 (0.10)
Hazard ratio vs. Warfarin (95%CI)	1.41 (0.71, 3.06)	1.16 (0.54, 2.51)	
p-value	0.2980	0.7076	
Myocardial infarction (incl. silent infarction)			
Incidences (%)	97 (0.81)	98 (0.82)	75 (0.64)
Hazard ratio vs. Warfarin (95%CI)	1.27 (0.94, 1.71)	1.29 (0.96, 1.75)	
p-value	0.1240	0.0929	

There was an increased numeric imbalance in MI events in subjects treated with dabigatran compared to warfarin treated subjects. The reason for this imbalance is unknown. Patients treated with dabigatran who have risk factors for coronary artery disease should be treated according to local guidelines.

Table 21: Liver Function Tests

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

	Dabigatran etexilate 150 mg bid N (%)	Dabigatran etexilate 110 mg bid N (%)	Warfarin N (%)
Total treated	6059 (100.0)	5983 (100.0)	5998 (100.0)
ALT or AST > 3xULN	106 (1.7)	118 (2.0)	125 (2.1)
ALT or AST > 5xULN	45 (0.7)	36 (0.6)	50 (0.8)
ALT or AST > 3xULN + Bilirubin >2xULN	14 (0.2)	11 (0.2)	21 (0.4)

The RE-LY extension study (RELY-ABLE) provided additional safety information for a large cohort of patients which continued the same dose of dabigatran etexilate as assigned in the RE-LY trial. Patients were eligible for the RELY-ABLE trial if they had not permanently discontinued study medication at the time of their final RE-LY study visit. Enrolled patients continued to receive the same double-blind dabigatran etexilate dose randomly allocated in RE-LY, for up to 43 months of follow up after RE-LY (total mean follow-up RE-LY + RELY-ABLE, 4.5 years). There were 5897 patients enrolled, representing 49% of patients originally randomly assigned to receive dabigatran etexilate in RE-LY and 86% of RELY-ABLE–eligible patients.
During the additional 2.5 years of treatment in RELY-ABLE, with a maximum exposure of over 6 years (total exposure in RELY + RELY-ABLE), the long-term safety profile of dabigatran etexilate was confirmed for both test doses. No new safety findings were observed.
The rates of outcome events including, major bleed and other bleeding events were consistent with those seen in RE-LY.

Patients undergoing catheter ablation for atrial fibrillation
A prospective, randomized, open-label, multicenter, exploratory study with blinded, centrally adjudicated endpoint evaluation (RE-CIRCUIT) was conducted in 704 patients who were under stable anticoagulant treatment. The study compared 150 mg twice daily uninterrupted dabigatran etexilate with uninterrupted INR-adjusted warfarin in catheter ablation of paroxysmal or persistent atrial fibrillation. Of the 704 enrolled patients, 317 underwent atrial fibrillation ablation on uninterrupted dabigatran and 318 underwent atrial fibrillation ablation on uninterrupted warfarin. All patients underwent a Trans-oesophageal Echocardiography (TEE) prior to catheter ablation. The primary outcome (adjudicated major bleeding according to 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 and until 8 weeks post-ablation. The composite incidence of MBEs and thromboembolic events (stroke/systemic embolism/TIA) was lower in the dabigatran etexilate arm (5 [1.6%] vs. 23 [7.2%] patients). This exploratory study demonstrated that dabigatran etexilate was associated with a significant reduction in 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 (P2Y12 antagonist) vs. triple-therapy with warfarin (adjusted to a INR 2.0 – 3.0) plus clopidogrel or ticagrelor and aspirin was conducted in 2725 patients with non valvular atrial fibrillation who underwent a PCI with stenting (RE-DUAL PCI). Patients were randomized to dabigatran etexilate 110 mg bid dual-therapy, dabigatran etexilate 150 mg bid dual-therapy or warfarin triple-therapy. Elderly patients outside of the United States (≥80 years of age for all countries, ≥70 years of age for Japan) were randomly assigned to the dabigatran etexilate 110 mg dual-therapy group or the warfarin triple-therapy group. The primary endpoint was a combined endpoint of major bleeds based on ISTH definition or clinically relevant non-major bleeding event.

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 and P=0.002 for superiority). As part of the descriptive analysis, TIMI (Thrombolysis In Myocardial Infarction) major bleeding events was lower in both dabigatran etexilate dual-therapy groups than in the warfarin triple-therapy group: 14 events (1.4%) in the dabigatran etexilate 110 mg dual-therapy group as compared with 37 events (3.8%) in the warfarin triple-therapy group (HR 0.37; 95% CI 0.20, 0.68; P=0.002) and 16 events (2.1%) in the dabigatran etexilate 150 mg dual-therapy group as compared with 30 events (3.9%) in the corresponding warfarin triple-therapy group (HR 0.51; 95% CI 0.28, 0.93; P=0.03). Both dabigatran etexilate dual-therapy groups had lower rates of intracranial hemorrhage than the corresponding warfarin triple- therapy group: 3 events (0.3%) in the 110 mg dabigatran etexilate dual-therapy group as compared with 10 events (1.0%) in the warfarin triple-therapy group (HR 0.30; 95% CI 0.08, 1.07; P=0.06) and 1 event (0.1%) in the 150 mg dabigatran etexilate dual-therapy group as compared with 8 events (1.0%) 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).There were no statistical differences in the individual components of the efficacy endpoints between either dabigatran etexilate dual-therapy groups and warfarin triple-therapy.

This study demonstrated that dual-therapy, with dabigatran etexilate and a P2Y12 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.

Clinical trials for the prevention of thromboembolism in patients with prosthetic heart valves:
A phase II study examined dabigatran etexilate and warfarin in a total of 252 patients with recent mechanical heart valve replacement surgery (i.e. within the current hospital stay) and in patients who received a mechanical heart valve replacement more than three months ago. More thromboembolic events (mainly strokes and asymptomatic prosthetic valve thrombosis) and more bleeding events were observed with dabigatran etexilate than with warfarin. In the early post-operative patients, major bleeding manifested predominantly as haemorrhagic pericardial effusions, specifically in patients who started dabigatran etexilate early (i.e. on Day 3) after heart valve replacement surgery.

Clinical trials in treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE):

Clinical evidence has demonstrated dabigatran etexilate to be an effective and safe treatment for DVT and/or PE in two multi-center, randomised, double blind, parallel-group, replicate studies RE-COVER and RE-COVER II. These studies 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. The index events at baseline: DVT - 68.5%, PE -22.2%, PE and DVT - 9.1%. The most frequent risk factors were history of DVT and/or PE - 21.5%, surgery/trauma -18.1%, venous insufficiency - 17.6%, and prolonged immobilisation -14.6%. Patients' baseline characteristics: mean age was 54.8 years, males 59.5%, Caucasian 86.1%, Asian 11.8%, blacks 2.1%. The co-morbidities included: hypertension 35.5%, diabetes mellitus 9.0%, CAD 6.8% and gastric or duodenal ulcer 4.1%.
The duration of treatment with fixed dose of dabigatran was 174.0 days without coagulation monitoring. For patients 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%).
Two trials in patients presenting with acute DVT and/or PE treated initially for at least 5 days of parenteral therapy, RE-COVER and RE-COVER II, demonstrated that treatment with dabigatran etexilate 150 mg twice daily was non-inferior to the treatment with warfarin (p values for non-inferiority: RE-COVER $p<0.0001$, RE-COVER II $p=0.0002$). Bleeding events (MBEs, MBE/CRBEs and any bleeding) were significantly lower in patients receiving dabigatran etixilate 150 mg twice daily as compared with those receiving warfarin.

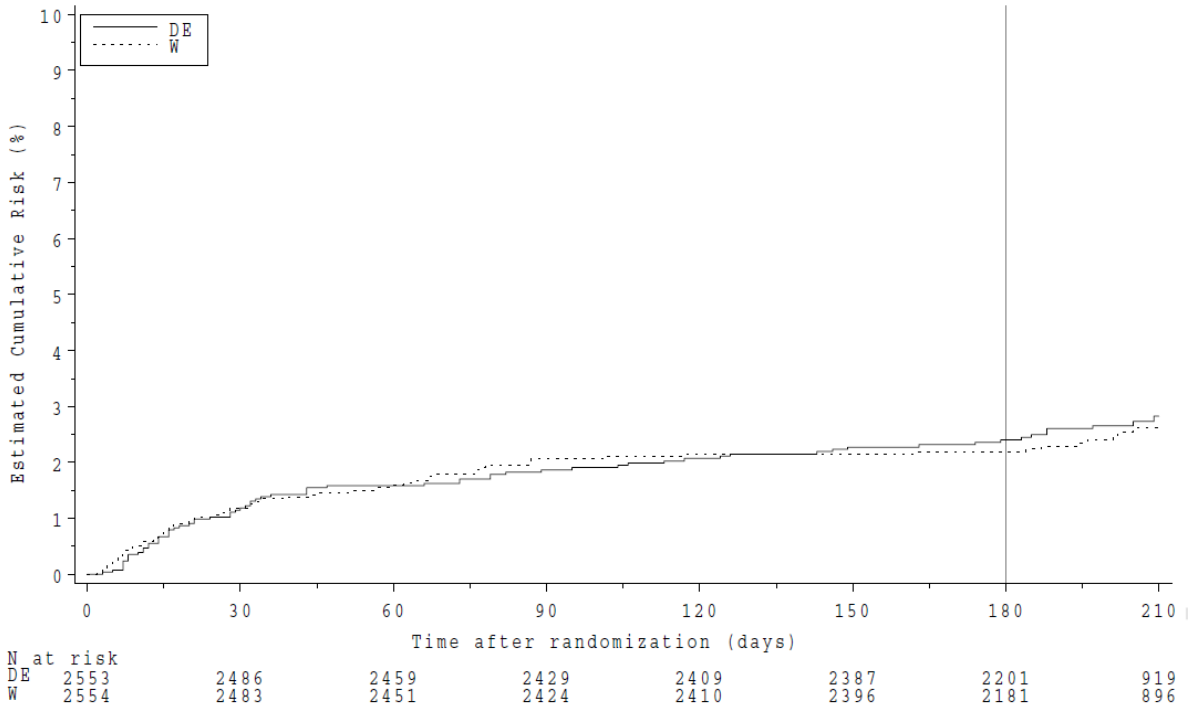

Figure 2: Time to first adjudicated VTE and VTE-related death until the end of post-treatment period for the RE-COVER and RE-COVER II pooled

Table 22: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the pooled studies RE-COVER and RE-COVER II

	Dabigatran etexilate 150 mg	Warfarin
RE-COVER/RE-COVER II pooled		
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	1.09	
95% CI	(0.77, 1.54)	
Secondary efficacy endpoints		
Recurrent symptomatic VTE and all-cause deaths	109 (4.3)	104 (4.1)
95% CI	3.52, 5.13	3.34, 4.91
Symptomatic DVT	45 (1.8)	39 (1.5)
95% CI	1.29, 2.35	1.09, 2.08
Symptomatic PE	27 (1.1)	26 (1.0)
95% CI	0.70, 1.54	0.67, 1.49
VTE-related deaths	4 (0.2)	3 (0.1)
95% CI	0.04, 0.40	0.02, 0.34
All-cause deaths	51 (2.0)	52 (2.0)
95% CI	1.49, 2.62	1.52, 2.66

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

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 were performed in patients previously treated with anticagulation therapy. RE-MEDY, warfarin controlled study, enrolled patients already treated for 3 to 12 months with the need for further anticoagulant treatment and RE-SONATE, the placebo controlled study, enrolled patients already treated for 6 to 18 months with Vitamin K inhibitors.

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. The index events at baseline: DVT - 65.1%, PE - 23.1%, PE and DVT -11.7%. Patients' baseline characteristics: mean age 54.6 years, males 61.0%, Caucasian 90.1%, Asian 7.9%, blacks 2.0%. Co-morbidities included hypertension 38.6 %, diabetes mellitus 9.0%, CAD 7.2 % and gastric or duodenal ulcer 3.8 %. Concomitant medications: agents acting on the renin-angiotensin system 27.9 %, vasodilators 26.7%, lipid lowering agents 20.6%, NSAIDs 18.3%, beta-blockers 16.3%, calcium channel blockers 11.1%, aspirin 7.7%, P-gp inhibitors 2.7% (verapamil 1.2% and amiodarone 0.7%), antiplatelets 0.9%. Duration of dabigatran exilate treatment ranged from 6 to 36 months (median - 534.0 days). For patients randomized to warfarin, the median time in therapeutic range (INR 2.0-3.0) was 64.9%.

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

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

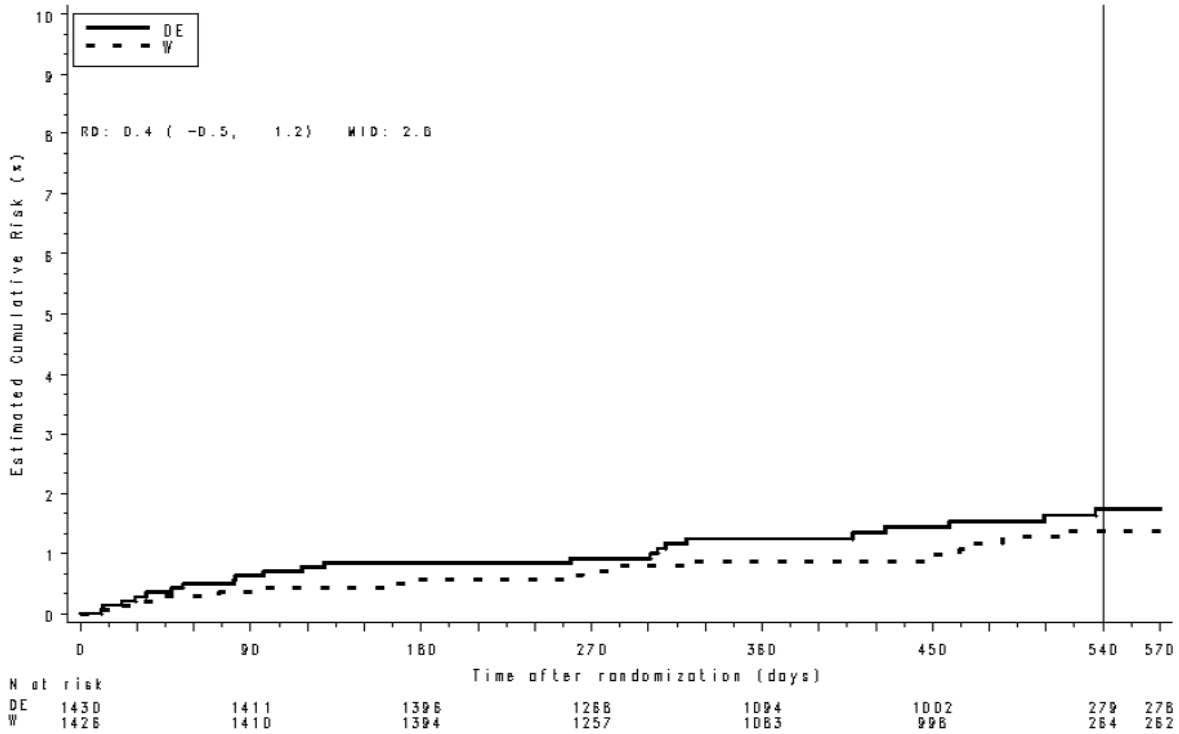

Figure 3: Time to first adjudicated VTE and VTE-related death until the end of the planned treatment period for the RE-MEDY study

Table 23 displays details of key results of the RE-MEDY study.

Table 23: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the RE-MEDY study

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

The objective of the RE-SONATE study was to evaluate superiority of dabigatran etexilate versus placebo for the prevention of recurrent symptomatic DVT and/or PE in patients who had already completed 6 to 18 months of treatment with VKA. The intended therapy was 6 months dabigatran etexilate 150 mg twice daily without need for monitoring.
The index events at baseline: DVT 64.5%, PE 27.8%, PE and DVT 7.7%. A total of 1,353 patients were randomized and 1,343 patients treated. Patients' baseline characteristics: mean age 55.8 years, males 55.5%, Caucasian 89.0%, Asian 9.3%, blacks 1.7%. Co-morbidities included hypertension 38.8%, diabetes mellitus 8.0%, CAD 6.0 % and gastric or duodenal ulcer 4.5%. Concomitant medications: agents acting on the renin-angiotensin system 28.7%, vasodilators 19.4%, lipid lowering agents 17.9%, beta-blockers 18.5%, calcium channel blockers 8.9%, NSAIDs 12.1%, aspirin 8.3%, antiplatelets 0.7% and P-gp inhibitors 1.7% (verapamil 1.0% and amiodarone 0.3%).

RE-SONATE demonstrated dabigatran etexilate was superior to placebo for the prevention of recurrent symptomatic DVT/PE events including unexplained deaths, with a risk reduction of 92% 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).

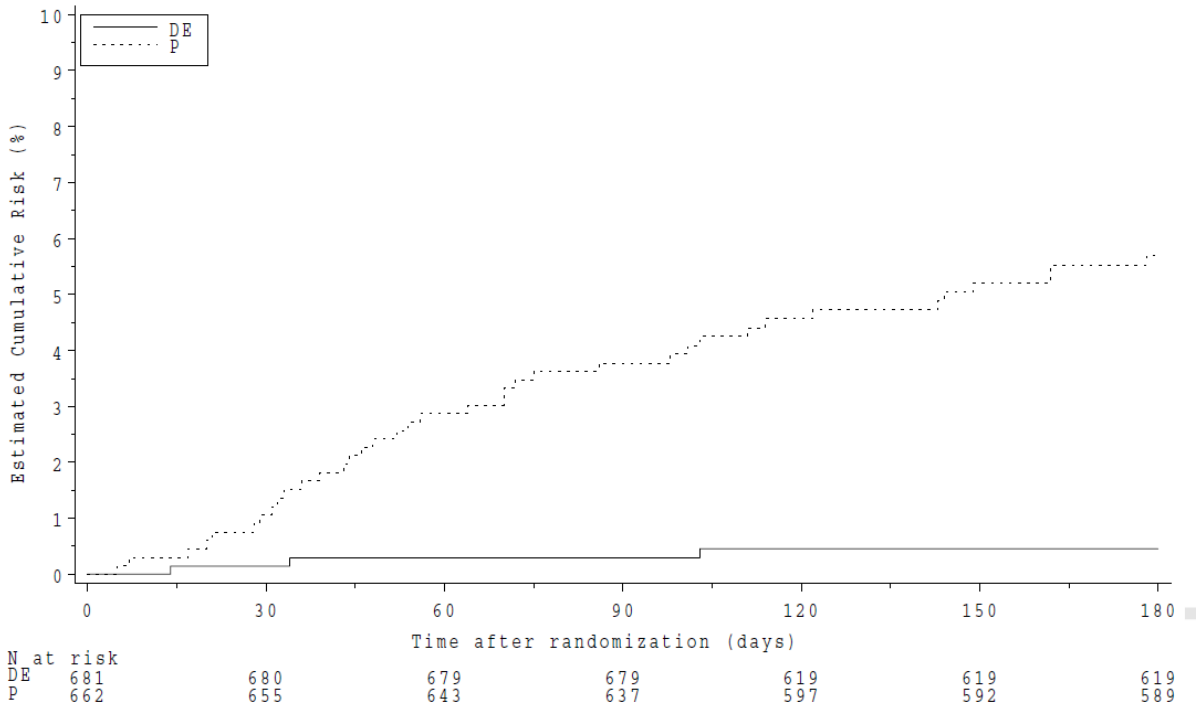

Figure 4: Time to first adjudicated VTE and VTE-related death until the end of the planned treatment period for the RE-SONATE study

Table 24 displays details of key results of the RE-SONATE study.

Table 24: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the RE-SONATE study

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

Other Measures Evaluated

Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE):

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

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

Liver Function Tests

Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE):

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

5.2 Pharmacokinetics

Absorption
After oral administration of dabigatran etexilate in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterized by a rapid increase in plasma concentrations with peak concentration (C_{max}) attained within 0.5 and 2.0 hours post administration. C_{max} and the area under the plasma concentration-time curve (AUC) were dose proportional.
The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate as HPMC capsule was approximately 6.5 %.

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

The oral bioavailability may be increased by about 1.4-fold (+37%) compared to the reference capsule formulation when the pellets are taken without the HPMC capsule shell. Hence, the integrity of the HPMC capsules should always be preserved in clinical use to avoid unintentionally increased bioavailability of dabigatran etexilate. Therefore, patients should be advised not to open the capsules and taking the pellets alone (e.g. sprinkled over food or into beverages) (see section on “Dosage and Administration”).

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

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

Biotransformation
After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran, which is the active form in plasma. The cleavage of the prodrug dabigatran etexilate by esterase-catalysed hydrolysis to the active principle dabigatran is the predominant metabolic reaction. Dabigatran is subject to conjugation

forming pharmacologically active acylglucuronides. Four positional isomers, 1-O, 2-O, 3-O, 4-O-acylglucuronide exist, each accounts for less than 10% of total dabigatran in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods. Dabigatran is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 ml/min corresponding to the glomerular filtration rate.

Elimination
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. After multiple doses a terminal half-life of about 12-14 hours was observed. The half-life was independent of dose. However, half-life is prolonged if renal function is impaired as shown below, in Table 25.

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

Table 25: Half-life of total dabigatran in healthy subjects and subjects with impaired renal function

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

PK in specific populations

Renal impairment:
The exposure (AUC) of dabigatran after the oral administration of dabigatran etexilate in a phase 1 study was approximately 3-fold higher in volunteers with moderate renal insufficiency (CrCL between 30-50ml/min) than in those without renal insufficiency.
In a small number of volunteers with severe renal insufficiency (CrCL 10 - 30 ml/min), the exposure (AUC) to dabigatran was approximately 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal insufficiency (see sections “Dosage and Administration” and “Contraindications”).

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 free- or total dabigatran concentrations, respectively. The amount of drug cleared by dialysis is proportional to the blood flow rate up to a blood flow rate of 300ml/min. The anticoagulant activity of dabigatran decreased with decreasing plasma concentrations and the PK/PD relationship was not affected by the procedure.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:
The median CrCL in RE-LY was 68.4 ml/min. Almost half (45.8 %) of the RE-LY patients had a CrCL > 50-< 80 ml/min. Patients with moderate renal impairment (CrCL between 30-50 ml/min) had on average 2.29-fold and 1.81-fold higher pre- and post-dose dabigatran plasma concentrations, respectively, when compared with patients without renal impairment (CrCL ≥80 ml/min).

Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE):
The median CrCl in the RE-COVER study was 100.3 mL/min. 21.7% of patients had mild renal impairment (CrCl > 50-< 80 mL/min) and 4.5% of patients had a moderate renal impairment (CrCl between 30-50 mL/min). Patients with mild and moderate 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. Similar values for CrCl were found in RE-COVER II.

Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE):
The median CrCl in the RE-MEDY and RE-SONATE studies were 99.0 mL/min and 99.7 mL/min respectively. 22.9 % and 22.5% of the patients had a CrCl > 50-< 80 mL/min, and 4.1% and 4.8% had a CrCl between 30-50 mL/min in the RE-MEDY and RE-SONATE studies.

Elderly:
Specific pharmacokinetic studies with elderly subjects in phase 1 studies showed an increase of 1.4- to 1.6-fold (+40 to 60%) in the AUC and of more than 1.25-fold (+25 %) in C_{max} compared to young subjects.
The $AUC_{\tau,ss}$ and $C_{max,ss}$ in male and female elderly subjects (> 65 y) were approximately 1.9 fold and 1.6-fold higher for elderly females compared to young females and 2.2 and 2.0 fold higher for elderly males than in male subjects of 18 - 40 years of age.
The observed increase of dabigatran exposure correlated with the age-related reduction in creatinine clearance .
The effect by age on exposure to dabigatran was confirmed in the RE-LY study with an about 1.3-fold (+31 %) higher trough concentration for subjects ≥ 75 years and by about 22 % lower trough level for subjects < 65 years compared to subjects of age between 65 and 75 years.

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

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery:
Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes ≥ 2 Upper Limit Normal (ULN) were excluded in clinical trials.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:
Patients with active liver disease including but not limited to the persistent elevation of liver enzymes ≥ 2 Upper Limit Normal (ULN), or hepatitis A, B or C were excluded in clinical trials.

Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE):
Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes ≥ 2 Upper Limit Normal (ULN) were excluded in clinical trials.

Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE):
Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes ≥ 2 Upper Limit Normal (ULN) were excluded in clinical trials.

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

Gender:
Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery:
Drug exposure in the primary VTE prevention studies was about 1.4- to 1.5-fold (+40 % to 50 %) higher in female patients.This finding had no clinical relevance.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:
In atrial fibrillation patients females had on average 1.3-fold (+30 %) higher trough and post-dose concentrations. This finding had no clinical relevance.

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

Drug-drug interactions (studies):
In vitro interaction studies did not show any inhibition or induction of cytochrome P450. This has been confirmed by in vivo studies in healthy volunteers, who did not show any interaction between dabigatran etexilate treatment and the following drugs: atorvastatin (CYP3A4) and diclofenac (CYP2C9).

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

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

P-gp inhibitor / inducer interactions
The pro-drug dabigatran etexilate but not dabigatran is a substrate of the efflux transporter P-glycoprotein (P-gp). Therefore co-medications with P-gp transporter inhibitors and inducers have been investigated.

Co-medication with P-gp inhibitors
***Amiodarone*:** When dabigatran etexilate was coadministered with a single oral dose of 600 mg amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The dabigatran AUC and C_{max} were increased by about 1.6-fold and 1.5-fold (+60 % and 50 %), respectively.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fribrillation:
In the population pharmacokinetics study from RE-LY, no important changes in dabigatran trough levels were observed in patients who received amiodarone (see “Drug Interactions”).

***Dronedarone*:** When dabigatran etexilate and dronedarone were given at the same time total dabigatran $AUC_{0-\infty}$ and C_{max} values increased by about 2.4-fold and 2.3-fold (+136 % and 125%), respectively, after multiple dosing of 400 mg dronedarone bid, and about 2.1-fold and 1.9-fold (+114% and 87%), respectively, after a single dose of 400 mg. The terminal half-life and renal clearance of dabigatran were not affected by dronedarone. When single and multiple doses of dronedarone were given 2 h after dabigatran etexilate, the increases in dabigatran $AUC_{0-\infty}$ were 1.3-fold and 1.6 fold, respectively.

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

The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to dabigatran etexilate intake (increase of C_{max} by about 2.8-fold (+180%) and AUC by about 2.5-fold (+150%)). The effect was progressively decreased with administration of an extended release formulation (increase of C_{max} by about 1.9-fold (+90%) and AUC by about 1.7-fold (+70%)) or administration of multiple doses of verapamil (increase of C_{max} by about 1.6-fold (+60%) and AUC by about 1.5-fold (+50%)). This can be explained by the induction of P-gp in the gut by chronic verapamil treatment.

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

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

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: In the population pharmacokinetics study from RE-LY, no important changes in dabigatran trough levels were observed in patients who received verapamil (see “ Drug Interactions”).

***Ketoconazole*:** Systemic ketoconazole increased total dabigatran $AUC_{0-\infty}$ and C_{max} values by about 2.4-fold (+138 % and 135%), respectively, after a single dose of 400 mg, and about 2.5-fold (+153% and 149%), respectively, after multiple dosing of 400 mg ketoconazole qd. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole.

Clarithromycin: When clarithromycin 500 mg twice daily was administered together with dabigatran etexilate a modest PK-interaction was observed (increased of C_{max} by about 15 % and AUC by about 19%).

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

Ticagrelor: When a single dose of 75mg dabigatran etexilate was coadministered simultaneously with a loading dose of 180 mg ticagrelor, the dabigatran AUC and Cmax were increased by 1.73-fold and 1.95-fold (+73% and 95%), respectively. After multiple doses of ticagrelor 90 mg b.i.d. the increase of dabigatran exposure is reduced to 1.56-fold and 1.46-fold (+56% and 46%) for Cmax and AUC, respectively. Concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg dabigatran etexilate (in steady state) increased the dabigatran $AUC_{\tau,ss}$ and by $C_{max,ss}$ by 1.49-fold and 1.65-fold (+49% and 65%), respectively, compared with dabigatran etexilate given alone. When a loading dose of 180 mg ticagrelor was given 2 hours after 110 mg dabigatran etexilate (in steady state), the increase of dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ was reduced to 1.27-fold and 1.23-fold (+27% and 23%), respectively, compared with dabigatran etexilate given alone. Concomitant administration of 90 mg ticagrelor BID (maintenance dose) with 110 mg dabigatran etexilate increased the adjusted dabigatran $AUC_{\tau,ss}$ and and $C_{max,ss}$ 1.26-fold 1.29-fold, respectively, compared with dabigatran etexilate given alone.

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

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

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

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

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:
NSAIDs increased the risk of bleeding in RE-LY in all treatment groups.

***Clopidogrel*:** In a phase I study in young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times (CBT) compared to clopidogrel monotherapy. In addition, dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ and the coagulation measures for dabigatran effect, aPTT, ECT or TT (anti FIIa), or the inhibition of platelet aggregation (IPA) as measure of clopidogrel effect remained essentially unchanged comparing combined treatment and the respective mono-treatments. With a loading dose of 300 or 600 mg clopidogrel, dabigatran $AUC_{t,ss}$ and $C_{max,ss}$ were increased by about 1.3- to 1.4-fold (+30 to 40%) (see above subsection on ASA).

***Antiplatelets or other anticoagulants*:** The concomitant use of dabigatran etexilate and antiplatelets or other anticoagulants may increase the risk of bleeding (see “Special warnings and precautions”).

Co-medication with selective serotonin re-uptake inhibitors:
SSRIs increased the risk of bleeding in RE-LY in all treatment groups.

Co-medication with gastric pH-elevating agents:
The changes in dabigatran exposure determined by population pharmacokinetic analysis caused by PPIs and antacids were not considered clinically relevant because the magnitude of the effect were minor (fractional decrease in bioavailability not significant for antacids and 14.6% for PPIs).

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

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:
In the phase III study, RE-LY, PPI co-medication did not result in lower trough levels and on average only slightly reduced post-dose concentrations (- 11%). Accordingly, PPI co-medication seemed to be not associated with a higher incidence of stroke or SEE, especially in comparison with warfarin, and hence, the reduced bioavailability by pantoprazole co-administration seemed to be of no clinical relevance.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content: Tartaric acid, acacia, hypromellose, dimethicone 350, talc, hydroxypropyl cellulose.

HPMC capsule shell: Carragenan, potassium chloride, titanium dioxide, Indigo Carmin (E132), hypromellose and purified water.

Printing ink: Shellac, butyl alcohol, isopropyl alcohol, Iron oxide black (E172), purified water, propylene glycol, ethanol, anhydrous, potassium hydroxide, concentrated ammonia solution.

6.2 Nature and contents of container
10 x 1 hard capsules per aluminium blister strips.
Cartons containing 1, 3, or 6 blister strips (10 x 1, 10 x 3 or 10 x 6 capsules).
Not all presentations available locally.

6.3 Storage conditions
Store below 30˚C.
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.
Please refer to the packaging for information on shelf-life.

7. Product Owner
Boehringer Ingelheim International GmbH
Ingelheim am Rhein
Germany

Date of Revision: 3 January 2020

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