

NEW ZEALAND DATASHEET

1. PRODUCT NAME

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PRADAXA 75 mg hard capsules

Each hard capsule contains 75 mg dabigatran etexilate (as mesilate)

PRADAXA 110 mg hard capsules

Each hard capsule contains 110 mg dabigatran etexilate (as mesilate)

PRADAXA 150 mg hard capsules

Each hard capsule contains 150 mg dabigatran etexilate (as mesilate)

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

PRADAXA 75 mg hard capsules

Capsules with white, opaque cap and white, opaque body of size 2 filled with yellowish pellets. The cap is imprinted in black ink with the Boehringer Ingelheim company symbol, the body with "R75".

PRADAXA 110 mg hard capsules

Capsules with light blue, opaque cap and light blue, opaque body of size 1 filled with yellowish pellets. The cap is imprinted in black ink with the Boehringer Ingelheim company symbol, the body with "R110".

PRADAXA 150 mg hard capsules

Capsules with light blue, opaque cap and white, opaque body of size 0 filled with yellowish pellets. The cap is imprinted in black ink with the Boehringer Ingelheim company symbol, the body with "R150".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with nonvalvular atrial fibrillation with one or more of the following risk factors:

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

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

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

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

4.2 Dose and method of administration

Dose (SPAF)

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation (SPAF)

The recommended daily dose of PRADAXA is 300 mg taken orally as 150 mg hard capsules twice daily, unless otherwise stated. Therapy should be continued life-long. In case of intolerability, patients should be instructed to contact their doctor.

Special populations (SPAF)

Children (SPAF)

PRADAXA has not been investigated in patients <18 years of age. Treatment of children with PRADAXA is not recommended.

Elderly (SPAF)

Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure in those patients with age-related decline of renal function. As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCl <30 ml/min). The renal function should also be assessed at least once a year in patients treated with PRADAXA or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc), see section 4.2 Renal impairment (SPAF).

Patients aged 80 years or above should be treated with a daily dose of 220 mg taken orally as 110 mg hard capsules twice daily. Patients aged 75 to 80 years may take the lower dose of 110mg capsule twice daily if their thromboembolic risk is low and bleeding risk is high.

Renal impairment (SPAF)

Renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCl <30 ml/min). There are no data to support use in patients with severe renal impairment (<30 ml/min creatinine clearance); treatment in this population with dabigatran etexilate is not recommended (see section 4.3).

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).

In patients with moderate renal impairment (CrCl 30-50 ml/min) the renal function should be assessed at least once a year.

In patients with adequate renal function (CrCl >50 ml/min) no dose adjustment is necessary. Patients should be treated with a daily dose of 300 mg taken orally as 150 mg hard capsules twice daily.

In patients with moderate renal impairment (30 to 50 ml/min creatinine clearance) a reduced dose of 220 mg given as 110 mg capsule twice daily may be considered if the bleeding risk is high and the thromboembolic risk is low.

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

Weight (SPAF)

No dose adjustment necessary.

Concomitant use of PRADAXA with strong P-glycoprotein inhibitors e.g. amiodarone, quinidine or verapamil (SPAF)

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

Concomitant use of PRADAXA with strong P-glycoprotein inducers (SPAF)

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. No dose adjustment is required when dabigatran etexilate is co-administered with atorvastatin, diclofenac, P-gp substrates and gastric pH elevating agents such as PPIs or H2-blockers (see section 5.2).

Patients at risk of bleeding (SPAF)

The presence of the following factors may increase the risk of bleeding: e.g. age ≥ 75 years, moderate renal impairment (CrCl 30-50 ml/min), concomitant treatment with strong P-gp inhibitors (see section 5.2 Special populations), antiplatelets or previous gastro-intestinal bleed (see section 4.4). For patients with one or more than one of these risk factors, a reduced daily dose of 220 mg given as 110 mg twice daily may be considered at the discretion of the physician.

Switching from PRADAXA treatment to parenteral anticoagulant (SPAF)

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

Switching from parenteral anticoagulants treatment to PRADAXA (SPAF)

Discontinue the parenteral anticoagulant and start PRADAXA 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 Vitamin K antagonists to PRADAXA (SPAF)

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

Switching from PRADAXA to Vitamin K antagonists (SPAF)

The starting time of the warfarin should be adjusted according to the patient's creatinine clearance as follows:

- For CrCl ≥ 50 ml/min, start warfarin 3 days before discontinuing PRADAXA.
- For CrCl ≥ 30 - < 50 ml/min, start warfarin 2 days before discontinuing PRADAXA.

Cardioversion (SPAF)

Patients can stay on dabigatran etexilate while being cardioverted.

Catheter ablation for atrial fibrillation (SPAF)

Catheter ablation can be conducted in non-valvular atrial fibrillation patients on 150 mg twice daily PRADAXA treatment. PRADAXA treatment does not need to be interrupted (see section 5.1 Clinical Efficacy and Safety).

Missed dose (SPAF)

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.

Dose (pVTEp orthopaedic surgery)

Primary prevention of Venous Thromboembolism in Orthopaedic Surgery (pVTEp orthopaedic surgery)

The recommended dose of PRADAXA is 220 mg once daily taken as 2 capsules of 110 mg. Patients with moderate renal impairment have an increased risk for bleeding. For those patients the recommended dose of PRADAXA is 150 mg once daily, taken as 2 capsules of 75 mg.

VTE prevention following knee replacement surgery

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

VTE prevention following hip replacement surgery

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

Special populations (pVTEp orthopaedic surgery)

Children (pVTEp orthopaedic surgery)

PRADAXA has not been investigated in patients <18 years of age. Treatment of children with PRADAXA is not recommended.

Renal impairment (pVTEp orthopaedic surgery)

Renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCl <30 ml/min). There are no data to support use in patients with severe renal impairment (CrCl <30 ml/min); treatment in this population with PRADAXA is not recommended (see section 4.3).

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.

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

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 once daily.

Elderly (pVTEp orthopaedic surgery)

Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure in those patients with age-related decline of renal function. As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCl <30 ml/min). The renal function should also be assessed 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), see section 4.2 Renal impairment (pVTEp orthopaedic surgery).

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

Weight (pVTEp orthopaedic surgery)

No dose adjustment necessary.

Concomitant use of dabigatran etexilate with strong P-glycoprotein inhibitors e.g. amiodarone, quinidine or verapamil (pVTEp orthopaedic 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 section 4.5).

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

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. No dose adjustment is required when PRADAXA is co-administered with atorvastatin, diclofenac, P-gp substrates and gastric pH elevating agents such as PPIs or H2-blockers (see section 5.2).

Switching from PRADAXA treatment to parenteral anticoagulant (pVTEp orthopaedic surgery)

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

Switching from parenteral anticoagulants treatment to PRADAXA (pVTEp orthopaedic surgery)

Discontinue the parenteral anticoagulant and start PRADAXA 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).

Missed dose (pVTEp orthopaedic surgery)

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

Dose (DVT/PE treatment)

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

The recommended daily dose of PRADAXA is 300 mg taken orally as 150 mg hard capsules twice daily following treatment with a parenteral anticoagulant for at least 5 days. Therapy should be continued for up to 6 months.

Special populations (DVT/PE treatment)

Children (DVT/PE treatment)

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.

Renal impairment (DVT/PE treatment)

Renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCl <30 ml/min). There are no data to support use in patients with severe renal impairment (CrCl <30 ml/min); treatment in this population with PRADAXA is not recommended (see section 4.3).

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.

No dose adjustment necessary in patients with renal function over CrCl 30 ml/min. Patients should be treated with a daily dose of 300 mg taken orally as 150 mg hard capsules twice daily.

Elderly (DVT/PE treatment)

Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure in those patients with age-related decline of renal function. As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCl < 30 ml/min). The renal function should also be assessed in patients treated with PRADAXA 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), see section 4.2 Renal impairment (DVT/PE treatment).

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

Weight (DVT/PE treatment)

No dose adjustment necessary.

Concomitant use of dabigatran etexilate with strong P-glycoprotein inhibitors e.g. amiodarone, quinidine or verapamil (DVT/PE treatment)

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

Patients at risk of bleeding (DVT/PE treatment)

The presence of the following factors may increase the risk of bleeding: e.g. age \geq 75 years, moderate renal impairment (30-50 ml/min CrCl) or previous gastro-intestinal bleed (see section 4.4).

No dose adjustment is necessary for patients with single risk factors.

Limited clinical data are available for patients with multiple risk factors.

In these patients, PRADAXA should only be given if the expected benefit outweighs bleeding risks.

Switching from PRADAXA treatment to parenteral anticoagulant (DVT/PE treatment)

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

Switching from parenteral anticoagulants treatment to PRADAXA (DVT/PE treatment)

Discontinue the parenteral anticoagulant and start PRADAXA 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 Vitamin K antagonists to PRADAXA (DVT/PE treatment)

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

Switching from PRADAXA to Vitamin K antagonists (DVT/PE treatment)

The starting time of the warfarin should be adjusted according to the patient's creatinine clearance as follows:

- For CrCl ≥ 50 ml/min, start warfarin 3 days before discontinuing PRADAXA.
- For CrCl ≥ 30 -<50 ml/min, start warfarin 2 days before discontinuing PRADAXA.

Missed dose (DVT/PE treatment)

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.

Dose (DVT/PE prevention)

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

The recommended daily dose of PRADAXA is 300 mg taken orally as 150 mg hard capsules twice daily. Therapy could be continued life-long depending on the individual patient risk.

Special populations (DVT/PE prevention)

Children (DVT/PE prevention)

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.

Renal impairment (DVT/PE prevention)

Renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCl <30 ml/min). There are no data to support use in patients with severe renal impairment (CrCl <30 ml/min); treatment in this population with PRADAXA is not recommended (see section 4.3).

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.

In patients with moderate renal impairment (CrCl 30-50 ml/min) the renal function should be assessed at least once a year.

No dose adjustment necessary in patients with renal function over CrCl 30 ml/min. Patients should be treated with a daily dose of 300 mg taken orally as 150 mg hard capsules twice daily.

Elderly (DVT/PE prevention)

Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure in those patients with age-related decline of renal function.

As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCl < 30 ml/min). The renal function should also be assessed at least once a year in patients treated with PRADAXA or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc), see section 4.2 Renal impairment (DVT/PE prevention).

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

Weight (DVT/PE prevention)

No dose adjustment necessary.

Concomitant use of dabigatran etexilate with strong P-glycoprotein inhibitors e.g. amiodarone, quinidine or verapamil (DVT/PE prevention)

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

Patients at risk of bleeding (DVT/PE prevention)

The presence of the following factors may increase the risk of bleeding: e.g. age \geq 75 years, moderate renal impairment (30-50 ml/min CrCl) or previous gastro-intestinal bleed (see section 4.4).

No dose adjustment is necessary for patients with single risk factors.

Limited clinical data are available for patients with multiple risk factors.

In these patients, PRADAXA should only be given if the expected benefit outweighs bleeding risks.

Switching from PRADAXA treatment to parenteral anticoagulant (DVT/PE prevention)

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

Switching from parenteral anticoagulants treatment to PRADAXA (DVT/PE prevention)

Discontinue the parenteral anticoagulant and start PRADAXA 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 Vitamin K antagonists to PRADAXA (DVT/PE prevention)

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

Switching from PRADAXA to Vitamin K antagonists (DVT/PE prevention)

The starting time of the warfarin should be adjusted according to the patient's creatinine clearance as follows:

- For CrCl \geq 50 ml/min, start warfarin 3 days before discontinuing PRADAXA.
- For CrCl \geq 30-<50 ml/min, start warfarin 2 days before discontinuing PRADAXA.

Missed dose (DVT/PE prevention)

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 (SPAF, pVTEp orthopaedic surgery, DVT/PE treatment and prevention)

PRADAXA hard capsules can be taken with or without food. PRADAXA should be taken 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.

The capsule should not be chewed, broken or opened as this may increase the bioavailability of dabigatran.

4.3 Contraindications

- Known hypersensitivity to dabigatran or dabigatran etexilate or to one of the excipients of the product
- Severe renal impairment (CrCl <30 ml/min)
- Haemorrhagic manifestations, patients with a bleeding diathesis, or patients with spontaneous or pharmacological impairment of haemostasis
- Organ lesions at risk of clinically significant bleeding, including haemorrhagic stroke within the last 6 months
- Concomitant treatment with systemic ketoconazole (see section 4.5)
- Prosthetic heart valve replacement

4.4 Special warnings and precautions for use

Haemorrhagic risk

As with all anticoagulants, dabigatran etexilate should be used with caution in conditions with an increased risk of bleeding. Bleeding can occur at any site during therapy with dabigatran. An unexplained fall in hemoglobin and/or hematocrit or blood pressure should lead to a search for a bleeding site. Fatal bleeding may occur as with any anticoagulant, but there were fewer fatal bleeds with dabigatran etexilate than with warfarin in the RE-LY study. In this study of prevention of stroke and SEE in adult patients with nonvalvular atrial fibrillation, dabigatran etexilate was associated with higher rates of major gastrointestinal (GI) bleeding which was statistically significant for dabigatran etexilate 150 mg twice daily. This increased risk was seen in the elderly (≥ 75 years) (see Table 4 in section 4.8).

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 haemorrhagic risk. Please also refer to contraindications in section 4.3.

Table 1: Factors which may increase the haemorrhagic risk

Factors increasing dabigatran plasma levels	<ul style="list-style-type: none"> • Moderate renal impairment (30-50 ml/min CrCl) • P-glycoprotein-inhibitor co-medication
Pharmacodynamic interactions	<ul style="list-style-type: none"> • Acetylsalicylic acid • NSAID • Clopidogrel
Diseases / procedures with special haemorrhagic risks	<ul style="list-style-type: none"> • Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Active ulcerative gastrointestinal disease • Recent gastrointestinal bleeding • Recent biopsy or major trauma • Recent intracranial haemorrhage • Brain, spinal or ophthalmic surgery • Bacterial endocarditis
Others	<ul style="list-style-type: none"> • Age ≥ 75 years

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 sections 4.4 Surgery and Interventions, Pre-operative Phase and 4.9.)

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.

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 must discontinue PRADAXA.

Factors, such as decreased renal function (30 – 50 ml/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 4.2).

The concomitant use of PRADAXA with the following treatments has not been studied and may increase the risk of bleeding: unfractionated heparins (except at doses necessary to maintain patency of central venous or arterial catheter) and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfapyrazone, rivaroxaban, prasugrel, ticagrelor, vitamin K antagonists, and the P-gp inhibitors, itraconazole, tacrolimus, ciclosporin, ritonavir, tipranavir, nelfinavir and saquinavir.

The concomitant use of dronedarone increases exposure of dabigatran and is not recommended (see section 5.2 Special 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.

- Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation
Co-administration of anti-platelet (including aspirin 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 haemoglobin is suggested.

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

Hepatic impairment

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

Interaction with P-gp inducers

The concomitant use of dabigatran etexilate with the strong P-gp inducer rifampicin reduces dabigatran plasma concentrations. Other P-gp inducers such as St. John's Wort or carbamazepine are also expected to reduce dabigatran plasma concentrations, and should be co-administered with caution (see sections 4.5 and 5.2 Special Populations).

Surgery and Interventions

Patients on dabigatran etexilate who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore surgical interventions may require the temporary discontinuation of PRADAXA (see section 5.2).

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 section 4.2).

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 section 4.4 Surgery and Interventions).

Acute Surgery/Intervention

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.

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 2 below and Table 15 in section 5.2).

Table 2 summarises discontinuation rules before invasive or surgical procedures.

Table 2: 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 15 section 5.2

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

Spinal Anaesthesia/Epidural Anesthesia/Lumbar Puncture

Procedures such as spinal anaesthesia may require complete haemostatic function.

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

Post Procedural Period

Resume treatment after complete haemostasis is achieved.

Paediatric Use

The safety and efficacy of PRADAXA in patients <18 years of age have not yet been established. Treatment of children with PRADAXA is not recommended.

4.5 Interaction with other medicines and other forms of interaction

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 sections 4.2 and 4.4).

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

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.

Anticoagulants and antiplatelet aggregation agents

The following treatments should not be administered concomitantly with dabigatran etexilate:

Anticoagulants such as unfractionated heparin (UFH), low molecular weight heparins (LMWH), and heparin derivatives (fondaparinux, desirudin), thrombolytic medicinal products, and vitamin K antagonists, rivaroxaban, apixaban or other oral anticoagulants, and platelet aggregation medicinal products such as GPIIb/IIIa receptor antagonists, ticlopidine, prasugrel, ticagrelor, dextran and sulfapyrazone. See section 4.2 for switching anticoagulant therapy.

UFH can be administered at doses necessary to maintain a patent central venous or arterial catheter.

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

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 co-administration was applied. Based on logistic regression analysis, co-administration of ASA and 150 mg dabigatran etexilate twice daily may increase the risk for any bleeding from 12% to 18% and 24% with 81 mg and 325 mg ASA, respectively.

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

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

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.

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

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 and clarithromycin) is expected to result in increased dabigatran plasma concentrations.

Concomitant administration of systemic ketoconazole is contraindicated.

For the P-gp inhibitors listed above no dose adjustments are required for PRADAXA in the indications "prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation", "treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of related death" or "prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and related death".

For the concomitant use of P-gp inhibitors and dosing of PRADAXA in the indication "Prevention of Venous Thromboembolism (VTE) in patients who have undergone major orthopaedic surgery" see section 4.2.

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.

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 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 section 4.2).

No data are available for the parenteral application of verapamil; based on the mechanism of the interaction, no meaningful interaction is expected. In patients in the RE-LY trial concentrations were increased by no more than 21% and no increased risk of bleeding was observed.

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

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

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

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

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

Concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg dabigatran etexilate (in steady state) increased the dabigatran $AUC_{T,SS}$ 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 $AUC_{T,SS}$ 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_{T,ss} and and C_{max,ss} 1.26-fold 1.29-fold, respectively, compared with dabigatran etexilate given alone.

P-glycoprotein substrate

Digoxin: In a study performed with 24 healthy subjects, when PRADAXA was coadministered with digoxin, no changes on digoxin and no clinically relevant changes on dabigatran exposure have been observed.

P-glycoprotein inducers

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

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:

Pantoprazole: When dabigatran etexilate was co-administered 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.

In the phase III study, RE-LY, PPI co-medication did not result in lower trough levels and on average only slightly reduced post-dose concentrations (- 11%). Accordingly, PPI comedication seemed to be not associated with a higher incidence of stroke or SEE, especially in comparison with warfarin, and 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.

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

There are limited amount of data from the use of dabigatran etexilate in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

PRADAXA should not be used during pregnancy unless clearly necessary.

Breast-feeding

There are no clinical data of the effect of dabigatran on infants during breast-feeding. Breast-feeding should be discontinued during treatment with PRADAXA.

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

a. Summary of the safety profile

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

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

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

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

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.

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

b. Tabulated list of adverse reactions

Adverse reactions classified by SOC and MedDRA preferred terms reported from any treatment group per population of all controlled studies are shown in the listings below.

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

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

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

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

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

Table 3 shows the adverse reactions identified from the primary VTE prevention studies after hip or knee replacement surgery, the study in the prevention of thromboembolic stroke and SEE in patients with atrial fibrillation and the studies in DVT/PE treatment and in DVT/PE prevention. They are ranked under headings of SOC and frequency using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1000$); very rare ($< 1/10,000$); not known (cannot be estimated from available data).

Table 3: Adverse reactions

SOC / Preferred term	Stroke and SEE prevention in patients with atrial fibrillation	Primary VTE prevention after hip or knee replacement surgery	DVT/PE treatment	DVT/PE prevention
Blood and lymphatic system disorders				
Anaemia	Common	Uncommon	Uncommon	Rare
Thrombocytopenia	Uncommon	Rare	Rare	Rare
Immune system disorder				
Drug hypersensitivity	Uncommon	Uncommon	Uncommon	Uncommon
Pruritus	Uncommon	Rare	Rare	Uncommon
Rash	Uncommon	Rare	Uncommon	Uncommon
Urticaria	Rare	Rare	Rare	Rare
Bronchospasm	Not known	Not known	Not known	Not known
Anaphylactic reaction	Not known	Not known	Not known	Not known
Angioedema	Rare	Rare	Rare	Rare
Nervous system disorders				
Intracranial haemorrhage	Uncommon	Rare	Rare	Rare
Vascular disorders				
Haematoma	Uncommon	Uncommon	Uncommon	Uncommon
Haemorrhage	Uncommon	Rare	Uncommon	Uncommon
Wound haemorrhage	-	Uncommon	-	-
Respiratory, thoracic and mediastinal disorders				
Epistaxis	Common	Uncommon	Common	Common
Haemoptysis	Uncommon	Rare	Uncommon	Uncommon
Gastrointestinal disorders				
Gastrointestinal haemorrhage	Common	Uncommon	Common	Common
Abdominal pain	Common	Rare	Uncommon	Uncommon
Diarrhoea	Common	Uncommon	Uncommon	Uncommon
Dyspepsia	Common	Rare	Common	Common
Dysphagia	Uncommon	Rare	Rare	Rare
Gastrointestinal ulcer	Uncommon	Rare	Uncommon	Rare
Gastroesophagitis	Uncommon	Rare	Uncommon	Uncommon
Gastroesophageal reflux disease	Uncommon	Rare	Uncommon	Uncommon
Nausea	Common	Uncommon	Uncommon	Uncommon
Vomiting	Uncommon	Uncommon	Uncommon	Uncommon
Hepatobiliary disorders				
Hepatic function abnormal	Uncommon	Common	Uncommon	Uncommon
Skin and subcutaneous tissue disorders				
Skin haemorrhage	Common	Uncommon	Common	Common

SOC / Preferred term	Stroke and SEE prevention in patients with atrial fibrillation	Primary VTE prevention after hip or knee replacement surgery	DVT/PE treatment	DVT/PE prevention
Musculoskeletal and connective tissue disorders				
Haemarthrosis	Rare	Uncommon	Uncommon	Rare
Renal and urinary disorders				
Urogenital haemorrhage	Common	Uncommon	Common	Common
Haematuria	Common	Uncommon	Common	Common
General disorders and administration site conditions				
Injection site haemorrhage	Rare	Rare	Rare	Rare
Catheter site haemorrhage	Rare	Rare	Rare	Rare
Bloody discharge	-	Rare	-	-
Injury, poisoning and procedural complications				
Traumatic haemorrhage	Rare	Uncommon	Uncommon	Rare
Incision site haemorrhage	Rare	Rare	Rare	Rare
Post procedural haematoma	-	Uncommon	-	-
Post procedural haemorrhage	-	Uncommon	-	-
Anaemia postoperative	-	Rare	-	-
Post procedural discharge	-	Uncommon	-	-
Wound secretion	-	Uncommon	-	-
Surgical and medical procedures				
Wound drainage	-	Rare	-	-
Post procedural drainage	-	Rare	-	-

c. Description of selected adverse reactions

Bleeding

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

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

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

Major bleeding fulfilled one or more of the following criteria:

- Bleeding associated with a reduction in hemoglobin of at least 20 grams per 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 randomised to dabigatran etexilate 110 mg twice daily and 150 mg 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 randomised to dabigatran etexilate 110 mg twice daily had a significantly lower risk for major bleeds compared with warfarin (hazard ratio 0.81, $p=0.0027$).

Table 4: Bleeding events broken down to major and any bleeding in the pivotal study testing the prevention of thromboembolic SSE in patients with atrial fibrillation.

	Dabigatran etexilate 110 mg twice daily	Dabigatran etexilate 150 mg twice daily	Warfarin
Subjects randomised	6,015	6,076	6,022
Major Bleeding	342 (2.87 %)	399 (3.32 %)	421 (3.57 %)
Intracranial bleeding	27 (0.23 %)	38 (0.32 %)	90 (0.76 %)
Gastrointestinal bleeding	134 (1.14 %)	186 (1.57 %)	125 (1.07 %)
Fatal bleeding	23 (0.19 %)	28 (0.23 %)	39 (0.33 %)
Minor bleeding	1,566 (13.16 %)	1,787 (14.85%)	1,931 (16.37%)
Any bleeding	1,754 (14.74 %)	1,993 (16.56 %)	2,166 (18.37 %)

% refers to yearly event rate

VTE prevention following major orthopaedic surgery

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

Table 5, below, shows the number (%) of patients experiencing bleeding events during the treatment period in the VTE prevention in the two pivotal clinical trials, according to dose.

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

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

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) and related death:

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%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

Overdose following administration of dabigatran etexilate may lead to haemorrhagic complications due to its pharmacodynamic properties. Doses of dabigatran etexilate beyond those recommended expose the patient to increased risk of bleeding. Excessive anticoagulation may require discontinuation of dabigatran etexilate. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained.

Depending on the clinical situation, appropriate standard treatment, 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 4.4; 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 section 5.2 Special Populations).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism 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.

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.

Pharmacodynamic effects

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

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

Clinical efficacy and safety

Clinical trials in prevention of stroke and systemic embolism in patients with atrial fibrillation (SPAF)

The clinical evidence for the efficacy of dabigatran etexilate is derived from the RE-LY study (Randomised Evaluation of Long-term anticoagulant therapy) a multi-center, multi-national, randomised parallel group study of two blinded doses of dabigatran (110 mg bd and 150 mg bd) 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 randomised, with a mean age of 71.5 years and a mean CHADS₂ score of 2.1. The population had approximately equal proportions of patients with CHADS₂ score 1, 2 and ≥3. The patient population was 64% male, 70% Caucasian and 16%

Asian. RE-LY had a median treatment of 20 months with dabigatran etexilate given as fixed dose without coagulation monitoring. In addition to documented non-valvular atrial fibrillation (AF) e.g., persistent AF or paroxysmal, patients had one of the following additional risk factors for stroke:

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

The concomitant diseases of patients in this trial included hypertension 79%, diabetes 23% and CAD 28%. 50% of the patient population was VKA naïve defined as less than 2 months total life time exposure. 32% of the population had never been exposed to a VKA. For those patients randomised to warfarin, the time in therapeutic range (INR 2 to 3) for the trial was a median of 67%. Concomitant medications included aspirin (25% of subjects used at least 50% of the time in study), clopidogrel (3.6%), ASA+clopidogrel (2%), NSAIDs (6.3%), beta-blockers (63.4%), diuretics (53.9%), statins (46.4%), ACE-inhibitors (44.6%), angiotensin receptor blockers (26.1%), oral hypoglycemics (17.5%), insulin (5.2%), digoxin (29.4%), amiodarone (11.3%), diltiazem (8.9%), verapamil (5.4%), and proton pump inhibitors (17.8%).

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

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

Figure 1 and Tables 6 - 10 display details of key results.

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

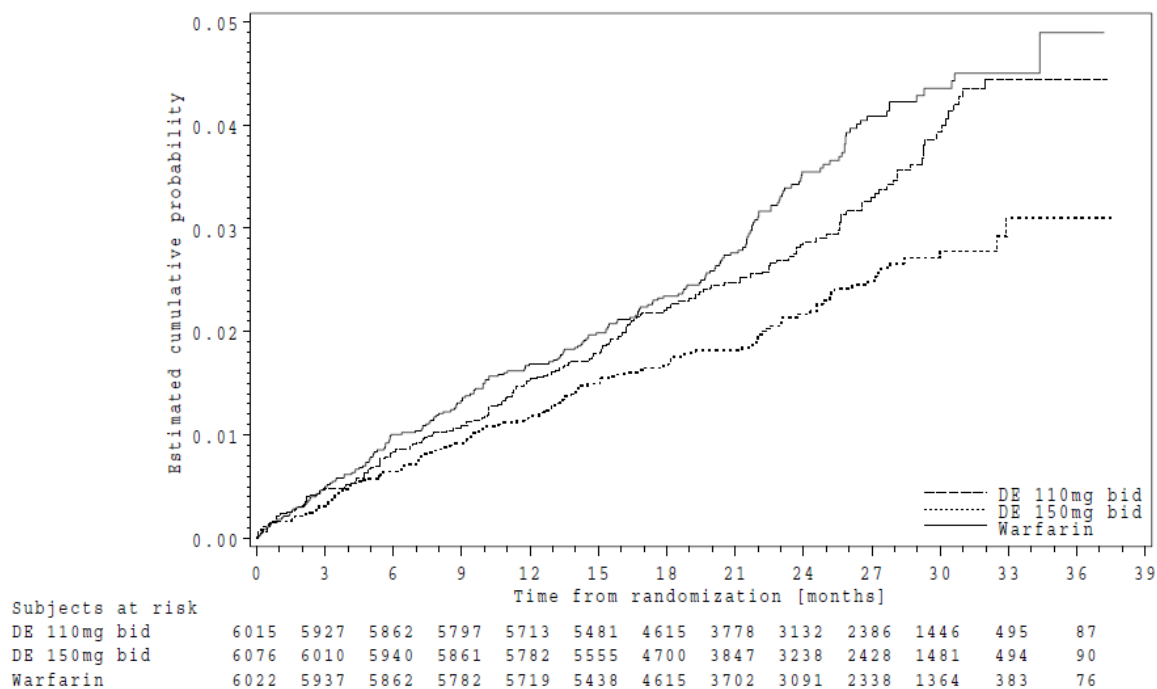


Table 7: Analysis of first occurrence of ischemic or haemorrhagic strokes during the study period in the RE-LY (randomised set)

	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	0.3553	
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 8: Analysis of all cause and cardiovascular survival during the study period in the RE-LY (randomised 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 9. 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 bd and 150 mg bd treatment groups. Other components evaluated included all hospitalisations which had statistically significant fewer hospitalizations at dabigatran etexilate 110 mg bd compared to warfarin (7% risk reduction, 95% CI 0.87, 0.99, p=0.021).

Table 9: 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, 1.045)	
p-value	0.0015	0.2206	
Stroke/SEE/PE/MI/death/major bleed (net clinical benefit)			
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			
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	

In the RE-LY study, in comparison to warfarin the annual myocardial infarction rate for dabigatran etexilate was increased from 0.64% (warfarin) to 0.82% (dabigatran etexilate 110 mg twice daily) / 0.81% (dabigatran etexilate 150 mg twice daily). In the RE-LY AF patients, the modest imbalance

in MI to the disfavor of dabigatran etexilate compared to warfarin is counterbalanced by dabigatran etexilate's larger beneficial effects on stroke reduction and lower observed rates of CV mortality and total mortality, compared to warfarin. The totality of the evaluated data with dabigatran etexilate allows the conclusion that MI is not an adverse consequence of the administration of dabigatran etexilate.

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

Table 10: Summary of abnormal liver function tests, Number (%) of subjects (safety set) in RE-LY

	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.

In an exploratory study the efficacy of two gastrointestinal symptoms (GIS)-management strategies was tested: taking PRADAXA within 30 minutes after a meal and adding pantoprazole 40 mg daily. In total n = 1067 patients on PRADAXA entered the study; 117 patients developed GIS and were randomised to one of two treatments.

Both initial management strategies (taking PRADAXA after a meal and adding pantoprazole 40 mg daily) provided complete relief of the primary GIS in over 55% of patients who reported GIS (PRADAXA after a meal: 55.9%; when adding pantoprazole: 67.2%).

As a single GIS management strategy, adding pantoprazole 40 mg daily provided complete resolution of their symptoms in 67.2% of patients after 4 weeks of treatment while taking PRADAXA after a meal resulted in 55.9% of patients having complete resolution of symptoms. After 1 week of treatment, complete resolution of symptoms was achieved in 51.7% when adding pantoprazole vs. 39.0% when PRADAXA is taken after a meal.

Patients who did not have a complete response to the initial strategy after 4 weeks were to receive the alternate strategy in addition (= combined strategies) for another 4 weeks.

Complete or partial effectiveness after 4 weeks of the combined management strategies (8 weeks, total treatment) was reported by 12 of 14 (85.7%) patients taking PRADAXA after a meal in the first part of the trial and 12 of 15 (80.0%) patients taking pantoprazole in the first part of the trial.

Ultimately, 92 (78.6%) patients (79 with complete effectiveness and 13 with partial effectiveness) experienced positive outcomes using the two GIS management strategies, 45 in the Pradaxa after a meal group (39 complete effectiveness + 6 partial effectiveness) and 47 in the pantoprazole group (40 complete effectiveness + 7 partial effectiveness).

Patients undergoing catheter ablation for atrial fibrillation (SPAF)

A prospective, randomised, open-label, multicentre, 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 statistically significant and clinically relevant reduction in MBE rate compared with INR-adjusted warfarin, and there were no differences in incidence of stroke or systemic embolism in the setting of ablation.

Clinical trials in primary VTE prevention following major joint replacement surgery (pVTEp orthopaedic surgery)

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

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

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

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

Furthermore in a third randomised, 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 randomised, parallel group, double-blind, placebo-controlled phase II study in Japanese patients where dabigatran etexilate 110 mg, 150 mg, and 220 mg was administered at the next day after elective total knee replacement surgery was evaluated. The Japanese study

showed a clear dose response relationship for the efficacy of dabigatran etexilate and a placebo like bleeding profile.

In RE-MODEL and RENOVATE the randomisation to the respective study medication was done pre-surgery, and in the RE-MOBILIZE and the Japanese placebo controlled trial the randomisation to the respective study medication was done post-surgery. This is of note especially in the safety evaluation of these trials. For this reason the trials are grouped in pre and post surgery randomised trials in Table 11.

Data for the major VTE and VTE-related mortality end-point and adjudicated major bleeding endpoints are shown in Table 11 below. VTE was defined as the composite incidence of deep vein thrombosis and Pulmonary Embolism.

Table 11: 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 treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of related death

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 etexilate 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

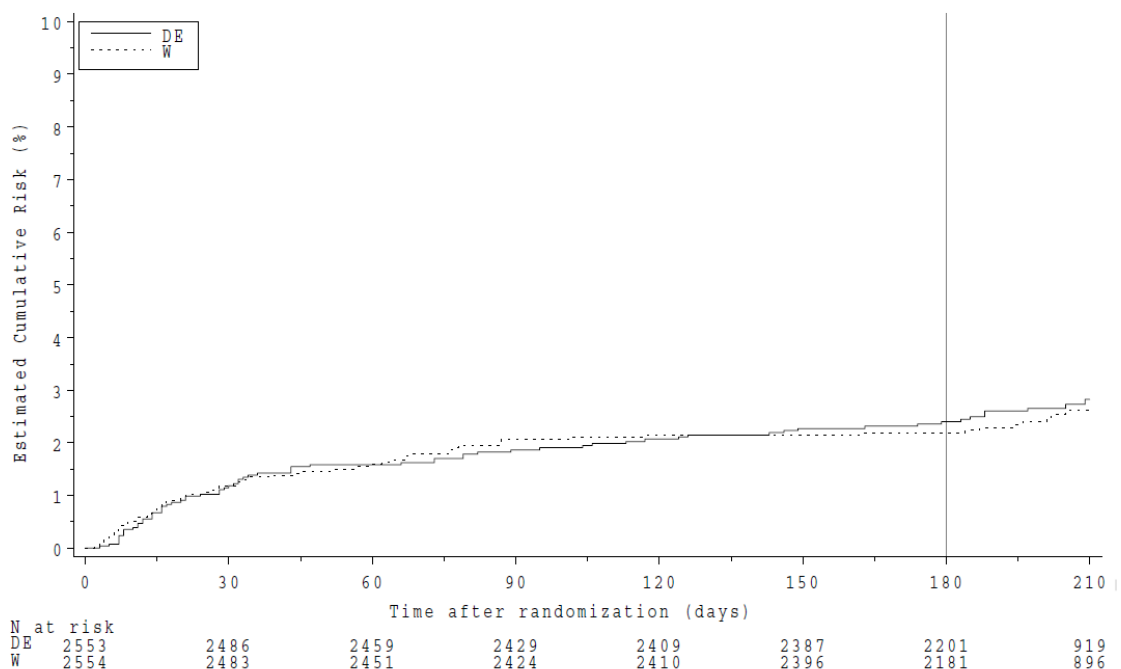


Table 12: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the pooled studies RE-COVER and RE-COVER II

	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

Other Measures Evaluated (DVT/PE treatment)

Myocardial infarction occurred at a low frequency in all four of the VTE studies for all treatment groups. Cardiac death occurred in one patient in the warfarin treatment group.

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

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

Liver Function Tests (DVT/PE treatment)

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.

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

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.

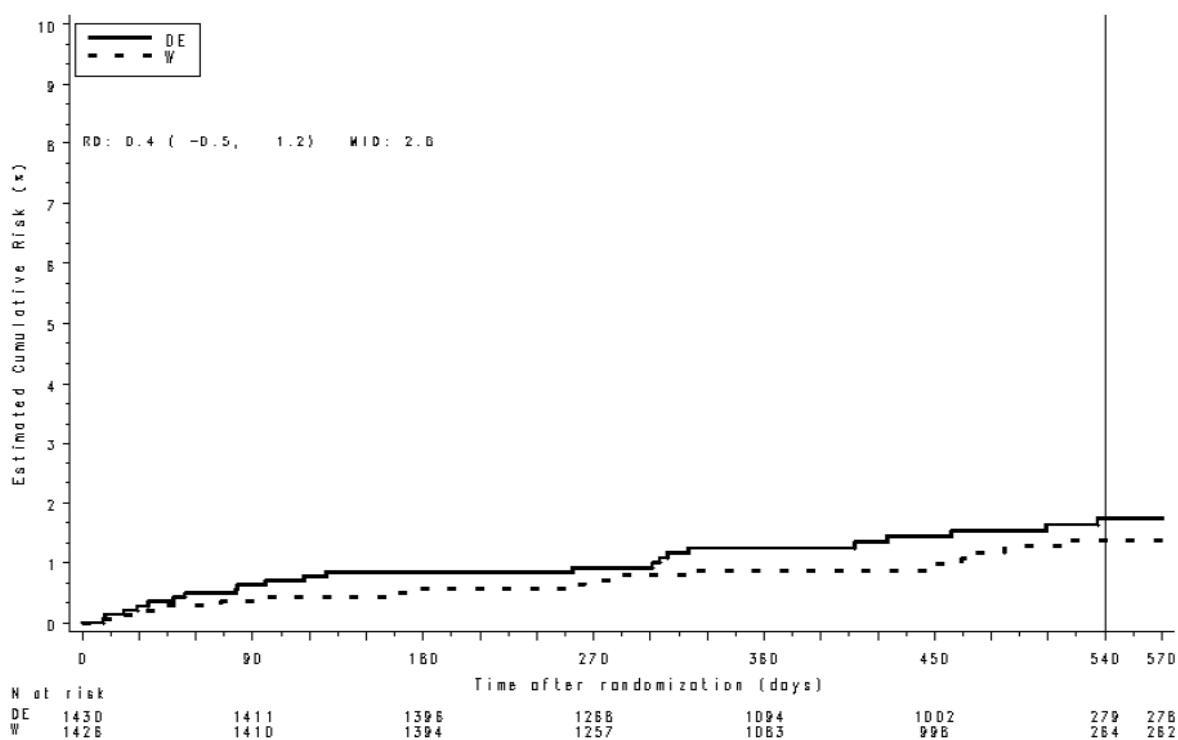


Table 13 displays details of key results of the RE-MEDY study.

Table 13: 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

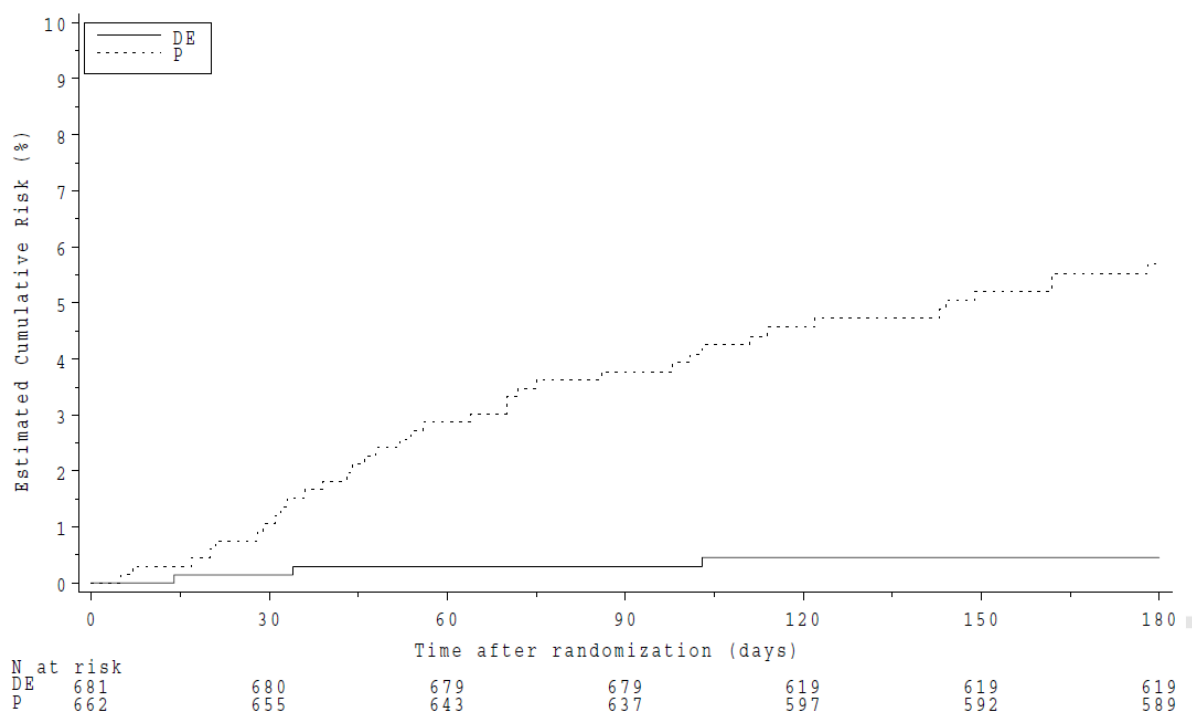


Table 14 displays details of key results of the RE-SONATE study.

Table 14: 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 (DVT/PE prevention)

Myocardial infarction occurred at a low frequency in all four of the VTE studies for all treatment groups. Cardiac death occurred in one patient in the warfarin treatment group.

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

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

Liver Function Tests (DVT/PE prevention)

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.

Clinical trials for the prevention of thromboembolism in patients with prosthetic heart valves (SPAF, pVTEp orthopaedic surgery, DVT/PE treatment and prevention)

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. An imbalance in thromboembolic and total (mainly minor) bleeding events in disfavour of dabigatran etexilate was observed in this trial. 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.

5.2 Pharmacokinetic properties

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.

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

After oral administration of dabigatran etexilate in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterised by a rapid increase in plasma concentrations with peak concentration (C_{max}) attained within 0.5 and 2.0 hours post administration.

Absorption

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

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 Dosage and Administration).

Distribution

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

C_{max} and the area under the plasma concentration-time curve were dose proportional. After C_{max} , plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of 11 hours in healthy elderly subjects. After multiple dose a terminal half-life of about 12-14 hours was observed. The half-life was independent of dose. However, half-life is prolonged if renal function is impaired as shown below, in Table 15.

Biotransformation

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

Dabigatran is 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.

Special Populations

Renal impairment:

The exposure (AUC) of dabigatran after the oral administration of dabigatran etexilate in a phase I study was approximately 2.7 fold higher in volunteers with moderate renal insufficiency (CrCl between 30 – 50 ml/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 4.2 and 4.3).

Table 15: Half-life of total dabigatran in healthy subjects and subjects with impaired renal function

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

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. The anticoagulant activity of

dabigatran decreased with decreasing plasma concentrations and the PK/PD relationship was not affected by the procedure.

- Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with 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) and prevention of related death:
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) and related death:
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 in the RE-MEDY and RE-SONATE studies.

Elderly patients:

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 years) were approximately 1.9 fold and 1.6-fold higher for elderly females compared to young females and 2.2 and 2.0 fold higher for elderly males than in male subjects of 18 - 40 years of age. The observed increase of dabigatran exposure correlated with the age-related reduction in creatinine clearance.

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

Hepatic insufficiency:

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

- Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation.
Patients with active liver disease including but not limited to the persistent elevation of liver enzymes ≥2 Upper Limit Normal (ULN), or hepatitis A, B or C were excluded in clinical trials.
- VTE prevention following major orthopaedic surgery.
Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes ≥2 Upper Limit Normal (ULN) were excluded in clinical trials.

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

Drug exposure in the primary VTE prevention studies was about 1.4 to 1.5-fold (+40% to 50%) higher in female patients. In atrial fibrillation 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.

Pharmacokinetic interactions:

The pro-drug dabigatran etexilate but not dabigatran is a substrate of the efflux transporter P-gp. Therefore concomitant use of P-gp transporter inhibitors (amiodarone, verapamil, clarithromycin, quinidine, dronedarone, ticagrelor and ketoconazole) and inducers (rifampicin) had been investigated (see sections 4.2, 4.4 and 4.5).

In vitro interaction studies did not show any inhibition or induction of the principal isoenzymes of cytochrome P450. This has been confirmed by *in vivo* studies with healthy volunteers, who did not show any interaction between dabigatran treatment and the following drugs: atorvastatin (CYP3A4), digoxin (P-gp transporter interaction) and diclofenac (CYP2C9).

5.3 Preclinical safety data

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

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill

- tartaric acid
- acacia
- hypromellose
- dimeticone
- purified talc
- hypromellose

Capsule shell

- carrageenan
- potassium chloride
- titanium dioxide
- indigo carmine (E132) (110 mg and 150 mg capsules only)
- hypromellose
- purified water

Printing ink

- shellac
- butan-1-ol
- ethanol anhydrous
- ammonia solution
- isopropyl alcohol
- potassium hydroxide
- iron oxide black (E172)
- purified water
- propylene glycol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

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 organisers, unless capsules can be maintained in the original package.

6.5 Nature and contents of container

Capsules 75 mg: Blister packs: 10, 30, 60 capsules.
Capsules 110 mg : Blister packs: 10, 30, 60 capsules.
Capsules 150 mg : Blister packs: 10, 30, 60 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

When taking PRADAXA capsules out of the blister pack, the following instructions should be followed:

- 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.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Boehringer Ingelheim (N.Z.) Limited
P.O. Box 76-216
Manukau City
Auckland
NEW ZEALAND

Telephone (09) 274-8664
Facsimile: (09) 271-0629

9. DATE OF FIRST APPROVAL

75 mg and 110 mg: 19 June 2008
150 mg: 23 December 2010

10. DATE OF REVISION OF THE TEXT

11 August 2017

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Revised Dosage instructions for: Switching from parenteral anticoagulants treatment to PRADAXA
4.5	Revised Interactions: Anticoagulants and antiplatelet aggregation agents
10	Date of revision of the text updated