NEW ZEALAND DATASHEET

1. PRODUCT NAME

Pharmacor Dabigatran Etexilate 75 mg capsules
Pharmacor Dabigatran Etexilate 110 mg capsules
Pharmacor Dabigatran Etexilate 150 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pharmacor Dabigatran Etexilate 75 mg capsules
Each capsule contains Dabigatran Etexilate Mesilate equivalent to Dabigatran Etexilate 75 mg

Pharmacor Dabigatran Etexilate 110 mg capsules
Each capsule contains Dabigatran Etexilate Mesilate equivalent to Dabigatran Etexilate 110 mg

Pharmacor Dabigatran Etexilate 150 mg capsules
Each capsule contains Dabigatran Etexilate Mesilate equivalent to Dabigatran Etexilate 150 mg

List of excipients with known effect
For full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Capsules, Hard

Pharmacor Dabigatran Etexilate 75 mg capsules
White to pale yellow pellets filled in HPMC capsule size "1" light cream opaque cap and light cream opaque body imprinted with "75" on body and “DAB” on cap in black ink.

Pharmacor Dabigatran Etexilate 110 mg capsules
White to pale yellow pellets filled in HPMC capsule size "0" light blue opaque cap and light blue opaque body imprinted with "110" on body and "Dab" on cap in black ink.

Pharmacor Dabigatran Etexilate 150 mg capsules
White to pale yellow pellets filled in HPMC capsule size “0EL” light blue opaque cap and light cream opaque body imprinted with “150” on body and “DAB” on cap in black ink.

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 arterydisease 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 following treatment with a parenteral anticoagulant for at least 5 days.
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 Dabigatran 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)
Paediatric population (SPAF)
Dabigatran has not been investigated in patients <18 years of age in the indication of prevention of stroke, systemic embolism and reduction of vascular mortality in patients with nonvalvular atrial fibrillation. Treatment of paediatric patients with Dabigatran in this indication 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 Dabigatran 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 Dabigatran 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 Dabigatran 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 Dabigatran 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 Dabigatran with strong P-glycoprotein inducers (SPAF)
The concomitant use of Dabigatran 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 Dabigatran treatment to parenteral anticoagulant (SPAF)
Wait 12 hours after the last dose before switching from Dabigatran to a parenteral anticoagulant.

Switching from parenteral anticoagulants treatment to Dabigatran (SPAF)
Discontinue the parenteral anticoagulant and start Dabigatran 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 Dabigatran (SPAF)
The Vitamin K antagonist should be stopped. Dabigatran can be given as soon as the INR is <2.0.

Switching from Dabigatran 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 Dabigatran.
- For CrCl ≥30-<50 ml/min, start warfarin 2 days before discontinuing Dabigatran.

Cardioversion (SPAF)
Patients can stay on dabigatran etexilate while being cardioverted.

Catheter ablation for atrial fibrillation (SPAF)
Catheter ablation can be conducted in nonvalvular atrial fibrillation patients on 150 mg twice daily Dabigatran treatment. Dabigatran treatment does not need to be interrupted (see section 5.1 Clinical Efficacy and Safety).

Percutaneous coronary intervention (PCI) with stenting (SPAF)
Patients with nonvalvular atrial fibrillation who undergo a PCI with stenting can be treated with Dabigatran in combination with antiplatelets after haemostasis is achieved (see Section 5.1 Clinical Efficacy and Safety).

Missed dose (SPAF)
A forgotten Dabigatran 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 Dabigatran is 220 mg once daily taken as 2 capsules of 110 mg. Patients with moderate renal impairment have an increased risk for bleeding. For those patients the recommended dose of Dabigatran is 150 mg once daily, taken as 2 capsules of 75 mg.

VTE prevention following knee replacement surgery

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

VTE prevention following hip replacement surgery

Treatment with Dabigatran 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)

Paediatric population (pVTEp orthopaedic surgery)

Dabigatran has not been investigated in patients <18 years of age in the indication of prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery. Treatment of paediatric patients with Dabigatran in this indication 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 Dabigatran 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 Dabigatran 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 Dabigatran taken once daily as 2 capsules of 75 mg in patients with moderate renal impairment (30-50 ml/min creatinine clearance).

Treatment with Dabigatran 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 Dabigatran 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 Dabigatran 150 mg taken once daily as 2 capsules of 75 mg in patients who concomitantly receive Dabigatran 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 Dabigatran and verapamil should also be avoided.

Treatment with Dabigatran 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 Dabigatran 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 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 Dabigatran treatment to parenteral anticoagulant (pVTEp orthopaedic surgery)
Wait 24 hours after the last dose before switching from Dabigatran to a parenteral anticoagulant.

Switching from parenteral anticoagulants treatment to Dabigatran (pVTEp orthopaedic surgery)
Discontinue the parenteral anticoagulant and start Dabigatran 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.

<u>Dose (DVT/PE treatment)</u>
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 Dabigatran 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.

<u>Special populations (DVT/PE treatment)</u>
Paediatric population (DVT/PE treatment)
Treatment of paediatric patients with Dabigatran in the indication of treatment of acute DVT and/or PE and prevention of related death is not registered (see "Paediatric Use" in section 4.4).

Renal impairment (DVT/PE treatment)
Renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with Dabigatran 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 Dabigatran 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 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.

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 Dabigatran 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 Dabigatran 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).

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.

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 ≥ 75 years, moderate renal impairment (30-50 ml/min CrCl) 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.

Limited clinical data are available for patients with multiple risk factors. In these patients, Dabigatran should only be given if the expected benefit outweighs bleeding risks.

Switching from Dabigatran treatment to parenteral anticoagulant (DVT/PE treatment)
Wait 12 hours after the last dose before switching from Dabigatran to a parenteral anticoagulant.

Switching from parenteral anticoagulants treatment to Dabigatran (DVT/PE treatment)
Discontinue the parenteral anticoagulant and start Dabigatran 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 Dabigatran (DVT/PE treatment)
The Vitamin K antagonist should be stopped. Dabigatran can be given as soon as the INR is <2.0.

Switching from Dabogatran 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 Dabigatran.
- For CrCl ≥30-<50 ml/min, start warfarin 2 days before discontinuing Dabigatran.

Missed dose (DVT/PE treatment)
A forgotten Dabigatran 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 Dabigatran 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)
Paediatric population (DVT/PE prevention)
Treatment of paediatric patients with Dabigatran in the indication of prevention of recurrent DVT and/or PE and related death is not registered (see "Paediatric Use" in Section 4.4).

Renal impairment (DVT/PE prevention)
Renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with Dabigatran 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 Dabigatran 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 m/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.

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 Dabigatran to exclude patients for treatment with severe renal impairment (i.e. CrCl < 30 m/min). The renal function should also be assessed at least once a year in patients treated with Dabigatran 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).

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.

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 ≥ 75 years, moderate renal impairment (30-50 ml/min CrCl) 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 Dabigatran treatment to parenteral anticoagulant (DVT/PE prevention)
Wait 12 hours after the last dose before switching from Dabigatran to a parenteral anticoagulant.

Switching from parenteral anticoagulants treatment to Dabigatran (DVT/PE prevention)
Discontinue the parenteral anticoagulant and start Dabigatran 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 Dabigatran (DVT/PE prevention)
The Vitamin K antagonist should be stopped. Dabigatran can be given as soon as the INR is <2.0.

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

Missed dose (DVT/PE prevention)
A forgotten Dabigatran 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)
Dabigatran hard capsules can be taken with or without food. Dabigatran should be taken with a glass of water, to facilitate delivery to the stomach. If gastrointestinal symptoms develop it is recommended to take Dabigatran 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
- Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.
- Indwelling spinal or epidural catheter and during the first two hours after removal (see Section 4.4 Special warnings and precautions for use).
- Hepatic impairment or liver disease expected to have any impact on survival.
- History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding.
- Gastrointestinal haemorrhage within the past year unless the cause has been permanently eliminated, e.g. by surgery.
- Conditions associated with increased risk of bleeding (see Section 4.4 Special warnings and precautions for use, Haemorrhagic risk, Table 3 Diseases / procedures with special haemorrhagic risks).
- Concomitant treatment with systemic ketoconazole, cyclosporin, itraconazole or dronedarone (see Section 4.4 Special warnings and precautions for use).
- Simultaneous initiation of treatment with dabigatran etexilate and oral verapamil.
- Treatment initiation with oral verapamil in patients following major orthopaedic surgery who are already treated with dabigatran etexilate.
- Prosthetic heart valve replacement.

4.4 Special warnings and precautions for use

Haemorrhagic risk

Dabigatran etexilate increases the risk of bleeding and can cause significant and sometimes fatal bleeding. As with all anticoagulants, dabigatran etexilate should be used with caution in conditions with an increased risk of bleeding. Bleeding can occur at any site during therapy with dabigatran. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site.

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

For situations of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effects of dabigatran is required, the specific reversal agent idarucizumab is available (see Section 4.4 Special warnings and precautions for use, Surgery and Interventions, Preoperative Phase and Section 4.9 Overdosage).

Careful clinical monitoring including renal function testing is required for all patients (see Section

4.2 Dose and Method of Administration, Special patient populations).

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

The INR test is unreliable in patients on Dabigatran etexilate mesilate and false positive INR elevations have been reported. Therefore, INR tests should not be performed. Tests of anticoagulant activity such as Thrombin Time (TT), diluted Thrombin Time (dTT), Ecarin Clotting Time (ECT) and activated Partial Thromboplastin Time (aPTT) are available to detect excessive dabigatran activity. Dabigatran related anticoagulation can be assessed by ECT or TT. If ECT, dTT or TT are not available, the aPTT test provides an approximation of Dabigatran etexilate mesilate's anticoagulant activity (see Section 4.4 Special warnings and precautions for use, Effects on laboratory tests).

Table 1: Coagulation test thresholds at trough that may be associated with an increased risk of bleeding* #

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

* dTT, ECT and aPTT tests are not standardised and results should be interpreted with caution
# Data are derived from the 90th percentile of measured dabigatran steady state trough concentrations in RENOVATE II (pVTEp, orthopaedic surgery) and RE-LY (SPAF)

In atrial fibrillation patients in RE-LY treated with 150 mg twice daily an aPTT of greater than 2.0–3.0 fold of normal range at trough was associated with an increased risk of bleeding.

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

Patients who develop acute renal failure should discontinue dabigatran etexilate.

Factors, such as decreased renal function (30–50 mL/min CrCL), age ≥75 years or P- glycoprotein (P-gp) inhibitor co-medication are associated with increased dabigatran plasma levels (see Table 3)The presence of one or more of these factors may increase the risk of bleeding, especially if combined (see Section 4.2 Dose and method of administration).

The concomitant use of Dabigatran etexilate mesilate with the following treatments has not been studied and may increase the risk of bleeding: unfractionated heparins (except at doses necessary to maintain patency of central venous or arterial catheter) and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, dextran, sulfinpyrazone, rivaroxaban, prasugrel, vitamin K antagonists, and the P-gp inhibitors itraconazole, tacrolimus, cyclosporin, ritonavir, tipranavir, nelfinavir and saquinavir (see Section 4.5 Interactions with other medicines and other forms of interactions, Anticoagulants and platelet aggregation agents).
The concomitant use of dronedarone increases exposure of dabigatran and is not recommended (see Section 4.5 Interactions with other medicines and other forms of interactions,).

The concomitant use of ticagrelor increases the exposure to dabigatran and may show pharmacodynamic interaction, which may result in an increased risk of bleeding (see Section 4.4 Special warnings and precautions for use, Effect on laboratory tests and Section 4.5 Interactions with other medicines and other forms of interactions,Co-medication with P-glycoprotein inhibitors).

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

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

Close clinical surveillance (looking for signs of bleeding or anaemia) is recommended throughout the treatment period, especially if risk factors (as summarised in Table 2) are combined. Specifically, with concomitant intake of antiplatelets or strong P-gp inhibitors in patients aged ≥75 years, the risk of major bleeding, including gastrointestinal bleeding, increases. If bleeding is clinically suspected, appropriate measures such as testing for occult blood in stool or testing for a drop in haemoglobin is suggested.

Table 2: Factors which may increase haemorrhagic risk

Pharmacodynamic and kinetic factors	• Age ≥ 75 years
Factors increasing dabigatran plasma levels	• Moderate renal impairment (30-50 mL/min CrCL) • P-glycoprotein (P-gp) inhibitor co-medication (some P-gp inhibitors are contraindicated – see Section 4.3 Contraindications)
Pharmacodynamic interactions	• Antiplatelet agents, including acetylsalicylic acid (ASA), clopidogrel, prasugrel and ticagrelor • Non-steroidal antiinflammatory drugs (NSAIDs) • Selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs) • Thrombolytic agents
Diseases / procedures with special haemorrhagic risks (note these are CONTRAINDICATIONS – see Section 4.3 Contraindications)	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Active ulcerative gastrointestinal disease • Recent gastro-intestinal bleeding • Recent biopsy or major trauma • Recent intracranial haemorrhage • Brain, spinal or ophthalmic surgery • Bacterial endocarditis

Patients ≥ 75 years of age should not be treated with Dabigatran etexilate mesilate 150 mg twice a day (see Section 4.2 Dose and method of administration, Prevention of stroke and systemic embolism in patients with non- valvular atrial fibrillation).

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

The increase in yearly event rates of major bleeds by concomitant medications in the RE-LY study are shown in Table 3.

Table 3: Analysis of increase in major bleeding events by concomitant medications in RE-LY

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

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

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

Gastrointestinal bleeds

Gastrointestinal (GI) haemorrhage occurred at a higher frequency with dabigatran etexilate compared to warfarin (see Section 4.8 Adverse effects (undesirable effects)/ Table 11 Number (%) of subjects with dyspepsia and gastritis-like symptoms (safety set) in RE-LY). The underlying mechanism of the increased rate of GI bleeding has not been established. Patients with an increased risk of bleeding (e.g. recent gastrointestinal bleeding), should be closely monitored clinically (looking for signs of bleeding or anaemia). In such patients, a dose of 220 mg, given as 110 mg twice daily may be considered. A coagulation test, such as aPTT (see Section 4.4 Special warnings and precautions for use, Effects on laboratory tests) may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure.

Anticoagulant-related nephropathy

There have been post-marketing reports of anticoagulant-related nephropathy (ARN) following anticoagulant use, presenting as acute kidney injury.

In patients with altered glomerular integrity or with a history of kidney disease, acute kidney injury may occur, possibly in relation to episodes of excessive anticoagulation and haematuria. A few cases have been reported in patients with no pre-existing kidney disease.Close monitoring including renal function evaluation is advised in patients with excessive anticoagulation, compromised renal function and haematuria (including microscopic).

Achlorhydria

See Section 4.5 Interactions with other medicines and other forms of interactions, Co-medication with gastric pH-elevating agents, Pantoprazole for effect of elevated gastric pH on dabigatran bioavailability.

Myocardial Infarction

<u>Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation</u>

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

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

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

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

Active Cancer Patients

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

Interaction with P-glycoprotien inducers

The concomitant use of dabigatran etexilate with the strong P-gp inducer rifampicin reduces dabigatran plasma concentrations. Other P-gp inducers such as St. John's Wort or carbamazepine are also expected to reduce dabigatran plasma concentrations, and should generally be avoided (see Section 4.4 Special warnings and precautions for use and Section 4.5 Interactions with other medicines and other forms of interactions).

Interaction with P-glycoprotein inhibitors

Coadministration of dabigatran etexilate with strong P-gp inhibitors (amiodarone, clarithromycin, nelfinavir, ritonavir, saquinavir, and verapamil) should be used with caution and close clinical surveillance (looking for signs of active bleeding or anaemia) is required, due to a potential risk of higher plasma levels of dabigatran and consequent potentially exaggerated pharmacodynamic effect of dabigatran etexilate (notably bleeding risk) (see Section 4.4 Special warnings and precautions for use, Section 4.5 Interactions with other medicines and other forms of interactions). The concomitant use of dabigatran etexilate with tacrolimus is not recommended. Concomitant use of dabigatran etexilate with cyclosporin, itraconazole, ketoconazole or dronedarone or the fixed-dose combination glecaprevir/pibrentasvir is contraindicated.

Patients with antiphospholipid syndrome

The safety and efficacy of dabigatran have not been established in patients with antiphospholipid syndrome. In a clinical study, treatment with another direct acting oral anticoagulant (DOAC) was associated with an increased rate of recurrent thrombotic events compared with a vitamin K antagonist (VKA) in patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome and are persistently triple positive. DOACs including dabigatran etexilate are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti–beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Pulmonary

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

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

Surgery and Interventions

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

Patients can stay on Dabigatran etexilate mesilate while being cardioverted. Dabigatran etexilate mesylate treatment (150 mg twice daily) does not need to be interrupted in patients undergoing catheter ablation for atrial fibrillation. There are no clinical data on continuation of Dabigatran etexilate mesilate treatment during catheter ablation in those non-valvular atrial fibrillation patients receiving 110 mg twice daily (see Section 4.2 Dose and method of administration).

Caution should be exercised when treatment is temporarily discontinued for interventions and anticoagulant monitoring is warranted.Clearance of dabigatran in patients with renal insufficiency may take longer (see Section 5.2 Pharmacokinetic properties, Tables 31 and 32). This should be considered in advance of any procedures. In such cases a coagulation test (see Sections 4.4 Special warnings and precautions for use (Haemorrhagic risk and effect on laboratory tests) and Section 5.1 Pharmacodynamic properties, Mechanism of action) may help to determine whether haemostasis is still impaired.

In case of emergency surgery or urgent procedures when rapid reversal of the anticoagulation effect is required the specific reversal agent idarucizumab for Dabigatran etexilate mesilate is available.

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

Preoperative Phase

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

Emergency Surgery or Urgent Procedure

Dabigatran etexilate should be temporarily discontinued. The specific reversal agent (idarucizumab) of Dabigatran etexilate is available for the rapid reversal of the anticoagulation effect (see Section 4.4 Special warnings and precautions for use, Surgery and Interventions).

Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Dabigatran etexilate mesilate treatment can be re-initiated 24 hours after administration of idarucizumab, If the patient is clinically stable and adequate haemostasis has been achieved.

Elective Surgery/Intervention

If possible, dabigatran etexilate should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete

hemostasis may be required consider stopping dabigatran etexilate 2-4 days before surgery. Clearance of dabigatran in patients with renal insufficiency may take longer. This should be considered in advance of any procedures (see Table 4 below).

Table 4: 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 5.2 Pharmacokinetic Properties, Absorption

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

Acute Surgery/Intervention

Dabigatran etexilate should be temporarily discontinued. An acute surgery/intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed there may be an increase in the risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

Spinal Anesthaesia/Epidural Anesthesia/Lumbar Puncture

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

The risk of spinal or epidural 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 2 hour should elapse before the administration of the first dose ofdabigatran etexilate. These patients require frequent observation for neurological signs and symptoms.

Post Procedural Period

Dabigatran treatment can be resumed / started after complete haemostasis is achieved.

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

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

Body Weight
Limited data in patients <50 kg are available (see Section 5.2 Pharmacokinetic properties, Special populations, Body weight).

Use in hepatic impairment
Patients with liver disease expected to have any impact on survival or with elevated liver enzymes >2 Upper Limit Normal (ULN) were excluded in clinical trials. Therefore, the use of dabigatran etexilate is contraindicated in this population. A liver function test is recommended prior to initiating treatment.

Use in renal impairment
Pharmacokinetic studies demonstrated up to a 3fold increase in drug exposure in patients with reduced renal function including age-related decline of renal function (see Section 5.2 Pharmacokinetic properties).

In patients with mild renal impairment increases in dabigatran concentration were observed (see Section 5.2 Pharmacokinetic properties, Special populations, Renal impairment).

In patients with moderate renal impairment in RE-LY, the observed major bleeding rate was comparable between dabigatran 110 mg and 150 mg (dabigatran 110 mg 5.65%/year versus dabigatran 150 mg 5.27%/year versus warfarin 5.68%/year). Based on theoretical considerations of drug exposure a reduced dose may be considered in these patients (see Section 4.2 Dose and method of administration).

The presence of one or more factors known to increase haemorrhagic risk (see Table 3) may increase the risk of bleeding. Caution should be exercised. Close clinical surveillance is recommended.

Dabigatran etexilate is contraindicated in cases of severe renal impairment (CrCL <30 mL/min). Patients who develop acute renal failure should discontinue dabigatran etexilate.

Use in the elderly
The clinical studies have been conducted in a patient population with a mean age >65 years. Patients should be treated with the dose of dabigatran etexilate as recommended in the Section 4.2 Dose and method of administration. Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure in those patients with age-related decline of renal function (see Section 4.4 Special warnings and precautions for use, Use in renal impairment). The risk of stroke is higher in the elderly, however the risk of bleeding increases with increasing age. Careful clinical observation is advised and a dosage adjustment is recommended in elderly patients (≥75 years) due in part to age-related impairment of renal function. These patients should be treated with caution (see Section 4.2 Dose and method of administration), particularly if they are also taking a drug which is a P-glycoprotein inhibitor (see Section 4.4 Special warnings and precautions for use, Interaction with P-glycoprotein inhibitors).

Paediatric Use
See Section 4.2 Dose and Method of Administration, Special patient populations, Paediatric population.

Effects on laboratory tests
The aPTT test may be useful in determining an excess of anticoagulant activity. Dabigatran concentration exceeding 450 – 500 ng/mL would result in an aPTT of greater than 2.5 times control. An aPTT greater than 2.5 times control is suggestive of excess anticoagulation (see Section 4.4 Special warnings and precautions for use, Haemorrhagic risk, and Section 5.1 Pharmacodynamic properties).

4.5 Interactions with other medicines and other forms of interactions

Interaction studies have only been performed in adults.

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, clopidogrel, ticlopidine, prasugrel, ticagrelor, dextran and sulfinpyrazone.

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

Unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter (see Section 4.2 Dose and method of administration and Section 4.4 Special warnings and precautions for use, Haemorrhagic risk).

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

Interactions linked to dabigatran etexilate and dabigatran metabolic profile

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

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

Diclofenac: When dabigatran etexilate was coadministered with diclofenac, the plasma exposure of both medicinal products remained unchanged indicating a lack of a pharmacokinetic interaction between dabigatran etexilate and diclofenac. However, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives >12 hours, close observation for signs of bleeding is recommended (see Section 4.4 Special warnings and precautions for use, Haemorrhagic risk).

P-glycoprotein inhibitors/inducers

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

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

Amiodarone: When dabigatran etexilate was coadministered with a single 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 the population pharmacokinetics study from RE-LY, no

important changes in dabigatran trough levels were observed in patients who received amiodarone.

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

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

Dronedarone: When dabigatran etexilate and dronedarone were given at the same time total dabigatran AUC0-∞ and Cmax 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 AUC0-∞ were 1.3-fold and 1.6-fold, respectively.

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

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

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

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

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

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

Quinidine: Quinidine was given as 200 mg dose every 2nd hour up to a total dose of 1000 mg. Dabigatran etexilate was given twice daily over 3 consecutive days, on the 3rd day 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. Concomitant

administration of systemic ketoconazole is contraindicated.

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

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

Co-medication with P-glycoprotein inducers

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

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

Co-medication with P-glycoprotein substrates

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

Co-medication with platelet inhibitors

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

From the data gathered in the phase III study RE-LY it was observed that ASA or clopidogrel co-medication with dabigatran etexilate at dosages of 110 mg or 150 mg twice daily may increase the risk of major bleeding. The higher rate of bleeding events by ASA or clopidogrel comedication was, however, also observed for warfarin (see Section 4.4 Special warnings and precautions for use, Haemorrhagic risk).

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

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

Clopidogrel: In a phase I study in young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times (CBT) compared to clopidogrel monotherapy. In addition, dabigatran $AUC_{T,ss}$ 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 monotreatments. With a loading dose of 300 or 600 mg clopidogrel, dabigatran AUCt,ss and Cmax,ss were increased by about 1.3- to 1.4-fold (+30% to 40%) (see ASA section above).

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

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

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

Co-medication with gastric pH-elevating agents:

Pantoprazole: When dabigatran etexilate was 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.

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 systemic embolism, especially in comparison with warfarin, and hence, the reduced bioavailability by pantoprazole co-administration seemed to be of no clinical relevance.
An increased risk of bleeding with PPIs and H2 antagonists was observed for both the dabigatran and warfarin treatment groups (see Section 4.4 Special warnings and precautions for use, Haemorrhagic risk). Patients taking PPIs or H2-blockers may be at increased risk of gastrointestinal bleeding due to the associated gastrointestinal conditions for which these drugs are prescribed.

4.6 Fertility, pregnancy and lactation

Effects on fertility

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

Use in pregnancy (Category C)

Anticoagulants and thrombolytic agents can produce placental haemorrhage and subsequent

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

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

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

Use in lactation

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

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

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

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 Dabigatran, 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.

Adverse reactions 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 adverse reactions of dabigatran etexilate were in the range of enoxaparin.

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

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

Table 5 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, the studies in DVT/PE treatment and in DVT/PE prevention and post-marketing surveillance. They are ranked under headings of SOC and frequency using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000); not known (cannot be estimated from available data).

Table 5: Adverse reactions

System Organ Class / Preferred Term.	Stroke and SEE prevention in patients with atrial fibrillation	Primary VTE and 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
Neutropenia*	Not known	Not known	Not known	Not known
Agranulocytosis*	Not known	Not known	Not known	Not known
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, thoriac 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
Vomitting	Uncommon	Uncommon	Uncommon	Uncommon
Hepatobiliary disorders				
Hepatic function abnormal	Uncommon	Common	Uncommon	Uncommon
Skjn and subcutaneous tissue disorders				
Skin haemorrhage	Common	Uncommon	Common	Common
Alopecia*	Not known	Not known	Not known	Not known
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	-	-

* derived from post-marketing experience

c. Description of selected adverse reactions

Bleeding

Bleeding is the most relevant adverse reaction 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 patients with atrial fibrillation treated for the prevention of stroke and systemic embolism and in 14.4% of adult patients with acute DVT and/or PE. In the recurrent DVT/PE trial RE-MEDY (adult patients) 19.4% and in the RE-SONATE trial (adult patients) 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 signficantly lower risk for major bleeds compared with warfarin (hazard ratio 0.81, $p=0.0027$).

Table 6: 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
Subject 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 7, 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 randomised 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 randomised 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 to https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

For advise 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. Coagulation tests can help to determine a potential bleeding risk in this setting.

Doses of dabigatran etexilate beyond those recommended expose the patient to increased risk of bleeding. Excessive anticoagulation may require discontinuation of dabigatran etexilate. In the event of haemorrhagic complications, treatment must be discontinued, and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. Depending on the clinical situation, appropriate standard treatment including patient monitoring, resuscitation and haemostasis is essential. Management should be guided by local protocols.

For situations of life-threatening or uncontrolled bleeding, or in cases of emergency surgery or urgent procedures when rapid reversal of the anticoagulation effects of dabigatran is required, the specific reversal agent idarucizumab is available (see Section 4.4 Special warnings and precautions for use, Surgery and Interventions, Preoperative Phase).

As protein binding is low dabigatran is dialysable, however there is limited clinical experience in using dialysis in this setting (see Section 5.2 Pharmacokinetic properties, Special Populations, Renal Impairment).

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

present or long acting antiplatelet drugs have been used. All symptomatic treatment has to be given according to the physician's judgement.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 competitive (Ki = 4.5 nM) and reversible direct thrombin inhibitor and is the main metabolite of dabigatran etexilate in plasma.Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

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

There is a close correlation between plasma dabigatran concentration and degree of anticoagulant effect. Prothrombin time (PT, expressed as International Normalised Ratio (INR)) is too insensitive to reliably detect anticoagulant activity of dabigatran and is therefore not recommended as a suitable tool for monitoring anticoagulant activity. Ecarin Clotting Time (ECT), Thrombin Time (TT) and diluted Thrombin Time (dTT) are sensitive assays that increase in direct proportion to dabigatran plasma concentration without any deviation from linearity at high plasma concentrations. However, ECT is not readily available in clinical practice. Activated Partial Thromboplastin Time (aPTT) increases in a non-linear manner to dabigatran concentration and is less proportional at higher dabigatran concentrations (see Section 4.4 Special warnings and precautions for use, Effects on laboratory tests). ECT, TT and aPTT are not standardised or validated with dabigatran for commercial use. In cases of emergency, TT and aPTT are the most accessible qualitative methods for determining the presence or absence of the anticoagulant effect of dabigatran.

Interpretation of coagulation assay results should consider time of dabigatran etexilate administration relative to time of blood sampling (see Section 5.2 Pharmacokinetic properties, Absorption).

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

Whilst Dabigatran does not require routine laboratory anticoagulant monitoring, careful clinical monitoring including renal function testing is required for all patients (see Section 4.2 Dose and method of administration, Special patient populations, and Section 4.4 Special warnings and precautions for use, Haemorrhagic risk).

Clinical trials

<u>Prevention of venous thromboembolic events (VTE) in adult patients who have undergone major orthopaedic surgery (pVTEp orthopaedic surgery)</u>
In 2 large randomised, parallel group, double-blind, dose–confirmatory trials, patients undergoing elective major orthopaedic surgery (one for knee replacement surgery and one for hip replacement surgery) received dabigatran etexilate 75 mg or 110 mg within 1–4 hours of surgery followed by 150 or 220 mg once daily thereafter, haemostasis having been secured, or enoxaparin

40 mg on the day prior to surgery and once daily thereafter.

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

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

Enrolled patients were scheduled to have total knee or hip replacement surgery; 18 years of age or older and weighing at least 40 kg. Patients were excluded if there was a history of bleeding diathesis; coagulation disorders; major surgery or trauma (e.g. hip fracture) within the last 3 months; recent unstable cardiovascular disease or history of myocardial infarction within the last 3 months; greater than 3 attempts or traumatic placement for spinal or epidural anaesthesia; history of haemorrhagic stroke or intracranial pathology such as bleeding, neoplasm, AV malformation or aneurysm; history of VTE or pre-existing condition requiring anticoagulant therapy; clinically relevant bleeding within the last 6 months; gastric or duodenal ulcer within the last 6 months; liver disease which was expected to have a potential impact on survival; elevated AST or ALT >2 X ULN; severe renal insufficiency (CrCl <30 mL/min); elevated creatinine which contraindicated venography; treatment within 7 days with anticoagulants – clopidogrel, ticlopidine, abciximab, aspirin >160 mg/day or NSAID with t1/2 >12 hours or requiring these medicines during the study treatment period; intermittent pneumatic compression and electric stimulation of lower limb; pregnant or nursing women and pre- menopausal women without acceptable birth control; allergy to radio-opaque contrast media or iodine; thrombocytopenia or platelet count <100,000 cells/μL; allergy to heparins or dabigatran and dabigatran etexilate; active malignant disease or currently receiving cytostatic treatment; participated in a clinical trial in the last 30 days; leg amputee; alcohol or drug abuse and contraindications to enoxaparin.

For the knee study (RE-MODEL), the median age was 68 years for all treatment groups. The majority of patients were female in all treatment groups (64.2–68.9%). The mean BMI was also similar in all 3 treatment groups with 29.9 (dabigatran etexilate 220 mg), 30.1 (dabigatran etexilate 150 mg), and 29.8 kg/m2 (enoxaparin), respectively.

For the hip study (RE-NOVATE), the median age was 65 years for all treatment groups. The majority of patients were female in all treatment groups (55.5–57.4%) and almost all patients were of white ethnic origin. The median BMI was 27.3 kg/m2 in both dabigatran etexilate groups and 27.1 kg/m2 in the enoxaparin group.

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

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

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

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

Data for the major VTE and VTE-related mortality end-point and adjudicated major bleeding endpoints are shown in Table 21 below. VTE was defined as the composite incidence of deep vein thrombosis and pulmonary embolism.

A third trial involving patients undergoing total knee replacement surgery received dabigatran etexilate 75 mg or 110 mg within 6–12 hours of surgery followed by 150 mg and 220 mg once daily thereafter for 12–15 days (RE-MOBILIZE). The comparator dosage of enoxaparin was 30 mg twice daily according to the US label. In the RE-MOBILIZE trial, non-inferiority was not established. There were no statistical differences in bleeding between the comparators.

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

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

In RE-MODEL and RE-NOVATE and RE-NOVATE II the randomisation to the respective study medication was done pre-surgery, and in the RE-MOBILIZE and Japanese placebo-controlled trial the randomisation to the respective study medication was done post-surgery. This is of note especially in the safety evaluation of these trials. In Table 8, three of the trials have been grouped in to pre- and post-surgery randomised trials.

Table 8: Analysis of major VTE and VTE-related mortality during the treatment period in the orthopaedic surgery studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
Pre-operative randomisation studies			
RE-NOVATE (hip)			
N	909	888	917
Incidences (%)	28 (3.1)	38 (4.3)	36 (3.9)
Risk differences vs. enoxaparin (%)	- 0.8	0.4	
95% CI	- 2.5, 0.8	- 1.5, 2.2	
Risk ratio over enoxaparin	0.78	1.09	
95% CI	0.48, 1.27	0.70, 1.70	
RE-NOVATE II (hip)			
N	805		794
Incidences (%)	18 (2.2)		33 (4.2)
Risk differences vs. enoxaparin (%)	- 1.92		
95% CI	- 3.64, - 0.2		
Risk ratio over enoxaparin	0.49		
95% CI	0.28, 0.86		
RE-MODEL (knee)			
N	506	527	511
Incidences (%)	13 (2.6)	20 (3.8)	18 (3.5)
Risk differences vs. enoxaparin (%)	- 1.0	0.3	
95% CI	- 3.1, 1.2	-2.0, 2.6	
Risk ratio over enoxaparin	0.73	1.08	
95% CI	0.36, 1.47	0.58, 2.01	

Post-operative randomisation studies			
Japanese knee study			
			Placebo
N	102	113	104
Incidences (%)	0	2 (1.8)	6 (5.8)
Risk differences vs. placebo (%)	−5.8	−4.0	
95% CI	(−10.3, −1.3)	(−9.1, 1.1)	

Table 9 presents the combined incidences of major VTE and VTE related mortality for RE-MODEL and RE-NOVATE trials. The most frequent component of the composite endpoint was proximal DVT in all three treatment groups. Non-fatal pulmonary embolism (PE) during the treatment period in the two trials were observed in 1 patient in the dabigatran etexilate 150 mg group, 3 patients receiving enoxaparin and 5 patients receiving dabigatran etexilate 220 mg. VTE related mortality was observed for 1 patient in each of the dabigatran etexilate 220 mg and enoxaparin groups and for 4 patients in the dabigatran etexilate 150 mg group.

Table 9: Summary of primary endpoint components (N [%]) in the RE-NOVATE and RE-MODEL trials

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

*Full analysis set – major

Table 10: Major bleeding events by treatment in the individual RE-MODEL and the RE-NOVATE studies

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

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

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

The clinical evidence for the efficacy of dabigatran etexilate is derived from the RE-LY study (Randomised Evaluation of Long–term anticoagulant therapy) a multi-centre, multinational, randomised parallel group study of two blinded doses of dabigatran (110 mg twice daily and 150 mg twice daily) compared to open-label warfarin in patients with non-valvular atrial fibrillation (AF) at moderate to high risk of stroke or systemic embolism. This trial used the Prospective Randomised Open label trial with Blinded Evaluation of outcomes (PROBE) design. The primary objective in this study was to determine if dabigatran was non-inferior to warfarin in reducing the

occurrence of the composite endpoint, stroke and systemic embolic events (SEE).

In the RE-LY study, a total of 18,113 patients were randomised, with a mean age of 71.5 years and a mean 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 AF e.g. persistent, paroxysmal or permanent AF, patients had one of the following additional risk factors for stroke:

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

Patients were excluded if they had prosthetic heart valves requiring anticoagulation or with haemodynamically relevant valve disease that was expected to require surgical intervention during the course of the study; severe disabling stroke within the previous 6 months or any stroke within the previous 14 days; conditions associated with an increased risk of bleeding – major surgery in the previous month, planned surgery or intervention in the next 3 months, history of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding unless the causative factor has been permanently eliminated or repaired (e.g. by surgery); gastrointestinal haemorrhage within the past year unless the cause has been permanently eliminated (e.g. surgery); symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days; haemorrhagic disorder or bleeding diathesis; need for anticoagulant treatment for disorders other than atrial fibrillation; fibrinolytic agents within 48 hours of study entry; uncontrolled hypertension (SBP >180 mmHg and/or DBP >100 mmHg); recent malignancy or radiation therapy (≤6 months) and not expected to survive 3 years; contraindication to warfarin treatment; reversible causes of atrial fibrillation (e.g. cardiac surgery, pulmonary embolism, untreated hyperthyroidism); plan to perform a pulmonary vein ablation or surgery for cure of the AF; severe renal impairment (estimated creatinine clearance ≤30 mL/min); active infective endocarditis; active liver disease, including but not limited to persistent ALT, AST, alkaline phosphatase ≥2 X ULN, known active hepatitis C, active hepatitis B, active hepatitis A; women who were pregnant, lactating or of childbearing potential who refused to use a medically acceptable form of contraception throughout the study; anaemia (haemoglobin <100 g/L) or thrombocytopenia (platelet count <100 X 109/L); patients who had developed transaminase elevations upon exposure to ximelagatran; patients who had received an investigational drug in the past 30 days or were participating in another drug study; patients considered unreliable by the investigator concerning the requirements for follow-up during the study and/or compliance with study drug administration.

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

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

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

warfarin (see Table 24).

Dabigatran etexilate 150 mg twice daily reduces other clinically relevant endpoints: ischaemic stroke, haemorrhagic stroke, intracranial haemorrhage and total bleeding compared to warfarin, with similar rates of major bleeding (see Tables 25 and 27). Dabigatran etexilate 110 mg twice daily reduces the risk of intracranial haemorrhage, major bleeding and total bleeding (see Table 27). The yearly event rate for vascular death for dabigatran etexilate 150 mg twice daily was 2.28%, 110 mg twice daily was 2.43% and warfarin was 2.69%.

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

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

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

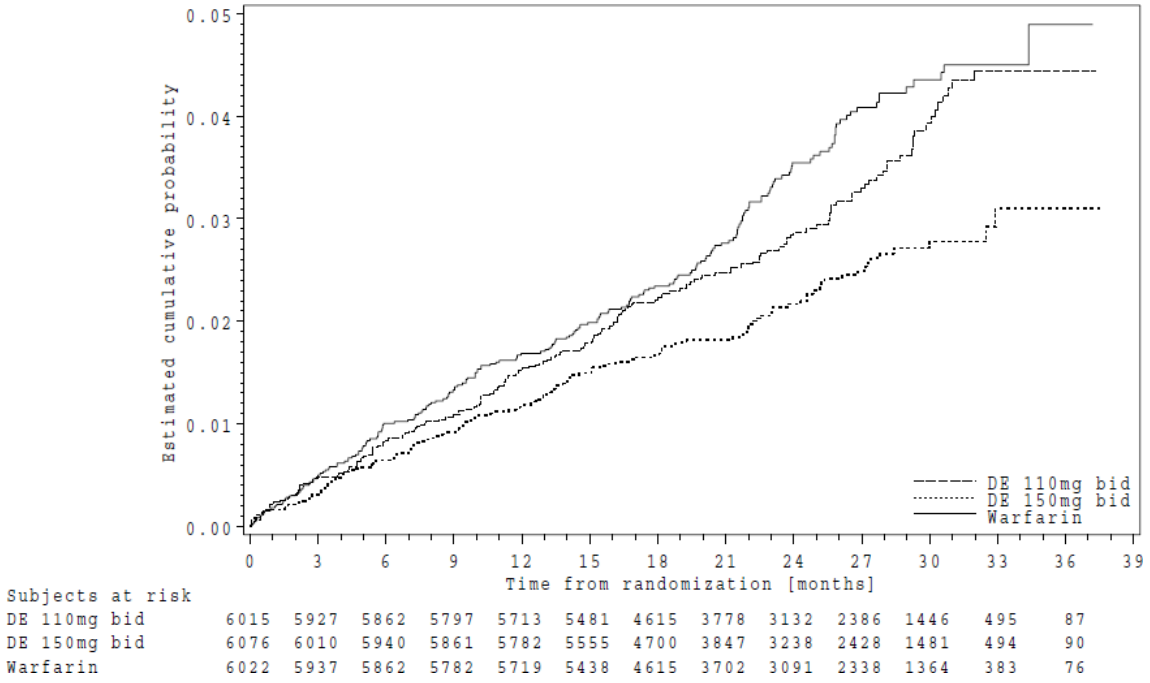

Table 11: Analysis of first occurrence of stroke or systemic embolism (primary endpoint) during the study period in RE-LY (randomised set)

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

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

Table 12: Analysis of first occurrence of stroke, systemic embolism, ischaemic or haemorrhagic strokes during the study period in RE-LY (randomized set)

	Dabigatran etexilate 150 mg twice daily	Dabigatran etexilate 110 mg twice daily	Warfarin
Subjects randomised	6076	6015	6022
Subject-years	12033	11899	11794
Stroke			
Yearly event rate (%)	123 (1.02)	171 (1.44)	187 (1.59)
Hazard ratio vs. warfarin (95% CI)	0.64 (0.51, 0.81)	0.91 (0.74, 1.12)	
SEE			
Yearly event rate (%)	13 (0.11)	15 (0.13)	21 (0.18)
Hazard ratio vs. warfarin (95% CI)	0.61 (0.30, 1.21)	0.71 (0.37, 1.38)	
Ischaemic stroke			
Yearly event rate (%)	104 (0.86)	152 (1.28)	134 (1.14)
Hazard ratio vs. warfarin (95% CI)	0.76 (0.59, 0.98)	1.13 (0.89, 1.42)	
Haemorrhagic stroke			
Yearly event rate (%)	12 (0.10)	14 (0.12)	45 (0.38)
Hazard ratio vs. warfarin (95% CI)	0.26 (0.14, 0.49)	0.31 (0.17, 0.56)	

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

Table 13: Analysis of pulmonary embolism and myocardial infarction during the study period in RE-LY (randomized set)

	Dabigatran etexilate 150 mg twice daily	Dabigatran etexilate 110 mg twice daily	Warfarin
Subjects randomised	6075	6015	6022
Subject-years	12033	11899	11794
Pulmonary embolism			
Yearly event rate (%)	18 (0.15)	14 (0.12)	12 (0.10)
Hazard ratio vs. warfarin (95% CI)	1.41 (0.71, 3.06)	1.16 (0.54, 2.51)	
Myocardial infarction			
Yearly event rate (%)	97 (0.81)	98 (0.82)	75 (0.64)
Hazard ratio vs. warfarin (95% CI)	1.27 (0.94, 1.71)	1.29 (0.96, 1.75)	

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

Table 14: Major bleeding events by age group during the study period in RE-LY

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

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

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

etexilate in RE-LY and 86% of RELY-ABLE–eligible patients.

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

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

Patients undergoing catheter ablation for atrial fibrillation

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.

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

The efficacy and safety was investigated in two multi-centre, randomised, double blind, parallel-group, replicate studies RE-COVER and RE-COVER II. These studies compared dabigatran etexilate (150 mg twice daily) with warfarin (target INR 2.0-3.0) in patients with acute DVT and/or PE. Patients were to be included in the studies if they had objectively confirmed symptomatic uni- or bi-lateral DVT of the leg and/or confirmed symptomatic PE. Patients were not eligible to participate in any study if they had of any of the following at screening: excessive risk of bleeding, CrCL below 30 mL/min, known liver disease expected to have any potential impact on survival or pregnancy, breast feeding, or not using adequate contraceptive methods. The primary objective of these studies was to determine if dabigatran was non-inferior to warfarin in reducing the occurrence of the primary endpoint which was the composite of recurrent symptomatic DVT and/or PE and related deaths within the 6-month acute treatment period. The lower bound of the non-inferiority margin was 2.75 in hazard ratio.

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

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

Two trials in patients presenting with acute DVT and/or PE treated initially for at least 5 days of parenteral therapy, RE-COVER and RE-COVER II, demonstrated that treatment with dabigatran etexilate 150 mg twice daily was non-inferior to the treatment with warfarin (p values for non-inferiority: RE-COVER p<0.0001, RE-COVER II p=0.0002). Refer to Section 4.8 Adverse Effects (undesirable effectes) for information on bleeding events in RE-COVER and RE-COVER II.

Table 15: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the pooled studies RE-COVER and RE-COVER II

	Dabigatran etexilate 150 mg twice daily	Warfarin
Treated patients, n	2553	2554
Recurrent symptomatic VTE and VTE-related death (%)	68 (2.7)	62 (2.4)
Hazard ratio vs. warfarin (95% CI)	1.09 (0.77, 1.54)	
Secondary efficacy endpoints		
Recurrent symptomatic VTE and all-cause deaths (%)	109 (4.3)	104 (4.1)
95% CI	3.52, 5.13	3.34, 4.91
Symptomatic DVT (%)	45 (1.8)	39 (1.5)
95% CI	1.29, 2.35	1.09, 2.08
Symptomatic PE (%)	27 (1.1)	26 (1.0)
95% CI	0.70, 1.54	0.67, 1.49
VTE-related deaths (%)	4 (0.2)	3 (0.1)
95% CI	0.04, 0.40	0.02, 0.34
All-cause deaths (%)	51 (2.0)	52 (2.0)
95% CI	1.49, 2.62	1.52, 2.66

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

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

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

RE-MEDY demonstrated that treatment with dabigatran etexilate 150 mg twice daily was non-inferior to warfarin (p=0.0135 for non-inferiority). Refer to Section 4.8 Adverse Effects (undesirable effects) for information on bleeding events in RE-MEDY.

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

Table 16 displays details of key results of the RE-MEDY study.

Table 16: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the RE-MEDY study

	Dabigatran etexilate 150 mg twice daily	Warfarin
Treated patients, n	1430	1426
Recurrent symptomatic VTE and VTE-related death (%)	26 (1.8)	18 (1.3)
Hazard ratio vs. warfarin (95% CI)	1.44 (0.78, 2.64)	
p-value (non-inferiority)	0.0135	
Patients with event at 18 months	22	17
Cumulative risk at 18 months (%)	1.7	1.4
Risk difference vs. warfarin (%)	0.4	
95% CI	-0.5, 1.2	
p-value (non-inferiority)	<0.0001	
Secondary efficacy endpoints		
Recurrent symptomatic VTE and all-cause deaths (%)	42 (2.9)	36 (2.5)
95% CI	2.12, 3.95	1.77, 3.48
Symptomatic DVT (%)	17 (1.2)	13 (0.9)
95% CI	0.69, 1.90	0.49, 1.55
Symptomatic PE (%)	10 (0.7)	5 (0.4)
95% CI	0.34, 1.28	0.11, 0.82
VTE-related deaths (%)	1 (0.1)	1 (0.1)
95% CI	0.00, 0.39	0.00, 0.39
All-cause deaths (%)	17 (1.2)	19 (1.3)
95% CI	0.69, 1.90	0.80, 2.07

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

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

RE-SONATE demonstrated dabigatran etexilate was superior to placebo for the prevention of recurrent symptomatic DVT/PE events including unexplained deaths, with a risk reduction of 92% (absolute risk reduction 5.2%) during the treatment period (p<0.0001). All secondary and sensitivity analyses of the primary endpoint and all secondary endpoints showed superiority of

dabigatran etexilate over placebo. The rates of MBEs and the combination of MBEs/CRBEs were significantly higher in patients receiving dabigatran etexilate as compared with those receiving placebo.

The study included observational follow-up for 12 months after the conclusion of treatment. After discontinuation of study medication the effect was maintained until the end of the follow-up, indicating that the initial treatment effect of dabigatran etexilate was sustained. No rebound effect was observed. At the end of the follow-up VTE events in patients treated with dabigatran etexilate was 6.9% vs. 10.7% among the placebo group (hazard ratio 0.61 (0.42, 0.88), p=0.0082).

Table 17 displays details of key results of the RE-SONATE study.

Table 17: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the RE-SONATE study

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

Other Measures Evaluated

Liver Function Tests

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

Prevention of thromboembolism in patients with prosthetic heart valves

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

5.2 Pharmacokinetic properties

Absorption

After oral administration of dabigatran etexilate in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterised by a rapid increase in plasma concentrations with Cmax attained within 0.5 and 2.0 hours post administration. Cmax and the area under the plasma concentration-time curve were dose proportional. After Cmax, plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of 12–14 hours in elderly healthy volunteers and 14–17 hours in patients undergoing major orthopaedic surgery. The half-life was independent of dose. However, half-life is prolonged if renal function is impaired as shown below, in Table 18.

Table 18: Half-life of total dabigatran in healthy subjects and subjects with impaired renal function

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

gMean – Geometric mean
gCV% - Geometric coefficient of variation

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

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

The oral bioavailability may be increased by 75% after a single dose and 37% at steady state compared to the reference capsule formulation when the pellets are taken without the HPMC capsule shell. Hence, the integrity of the HPMC capsules should always be preserved in clinical use to avoid unintentionally increased bioavailability of dabigatran etexilate. Therefore, patients should be advised not to open the capsules and take the pellets alone (e.g., sprinkled over food or into beverages) (see Section 4.2 Dose and method of administration).

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

Distribution

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

Metabolism and Excretion

Metabolism and excretion of dabigatran were studied following a single intravenous dose of

radiolabelled dabigatran in healthy male subjects. After an intravenous dose, the dabigatran-derived radioactivity was eliminated primarily in the urine (85%). Faecal excretion accounted for 6% of the administered dose. Recovery of the total radioactivity ranged from 88 - 94% of the administered dose by 168 hours post dose. Dabigatran is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 mL/min corresponding to the glomerular filtration rate.

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

Special Populations

Renal impairment:

An open, parallel-group single-centre study compared dabigatran pharmacokinetics in healthy subjects and patients with mild to moderate renal impairment receiving a single dose of dabigatran etexilate 150 mg. Based on pharmacokinetic modeling, estimated exposure to dabigatran increases with the severity of renal function impairment (Table 19).

Table 19: Estimated Pharmacokinetic Parameters of Dabigatran by Renal Function

Renal Function	CrCL (mL/min)	Increase in AUC	Increase in Cmax	t1/2 (h)
Normal	80	1x	1x	13
Mild	50	1.5x	1.1x	15
Moderate	30	3.2x	1.7x	18

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

In a small number of volunteers with severe renal insufficiency (CrCL 10–30 mL/min), the exposure (AUC) to dabigatran was approximately 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal insufficiency (see Section 4.2 Dose and method of administration and Section 4.3 Contraindications).

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

The median CrCL in the RE-COVER study was 100.4 mL/min. 21.7% of patients had mild renal impairment (CrCL > 50-< 80 mL/min) and 4.5% of patients had moderate renal impairment (CrCL between 30-50 mL/min). Patients with mild and moderate renal impairment had on average 1.8-fold and 3.6-fold higher steady state dabigatran trough concentrations compared with patients with CrCL > 80 mL/min. Similar values for CrCL were found in RE-COVER II.

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

Elderly patients:

The $AUC_{T,ss}$ and $C_{max,ss}$ in male and female elderly subjects (>65 years) were approximately 1.9-fold and 1.6-fold higher for elderly females compared to young females and 2.2 and 2.0-fold higher for elderly males than in male subjects of 18-40 years of age.

The observed increase of dabigatran exposure correlated with the age-related reduction in creatinine clearance. The effect by age on exposure to dabigatran was confirmed in the RE-LY and RE-COVER studies: in RE-LY, compared with subjects aged < 65 years, dabigatran trough concentrations were 28% higher in subjects aged between 65 and 75 years and 68% higher in subjects aged ≥75 years. In RE-COVER, compared with patients aged between 50 and < 65 years, dabigatran trough concentrations were 20% and 106% higher in patients aged between 65 and 75 years and ≥ 75 years, respectively (see Section 4.4 Special warnings and precautions for use, Use in the elderly and Section 4.2 Dose and method of administration).

Hepatic insufficiency:

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

- *Prevention of 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.
- *Prevention of venous thromboembolic events (VTE) in adult patients who have undergone major orthopaedic surgery*: Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes ≥2 Upper Limit Normal (ULN) were excluded in clinical trials.
- *Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) in adults:* Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes ≥ 2 Upper Limit Normal (ULN) were excluded in clinical trials.

Body weight:

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

Gender:

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

5.3 Preclinical safety data

Genotoxicity

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

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill:
Butylated hydroxytoluene
Microcrystalline cellulose
Citric acid monohydrate
Hyprolose (Hydroxy Propyl Cellulose)
Hypromellose phthalate
Povidone
Purified Talc
Tartaric Acid
Macrogol 600 (Polyethylene Glycol 600)
Opadry White YS-1-7040
Opadry 200 White (200F280000)

HPMC capsule shell
Hypromellose
Titanium dioxide
Sunset yellow FCF (for 75 mg, 110 mg and 150 mg strengths)
Brilliant blue FCF (110 mg and 150 mg strength)
Allura red AC (110 mg and 150 mg strength)

Printing ink
TekPrint™ SW-9008 Black Ink / TekPrint™ SW-9009 Black Ink

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

24 Months. The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25ºC.

6.5 Nature and contents of container

The capsules are packed in Alu-Alu dessicant blister pack and HDPE bottle pack with dessicant.

Pharmacor Dabigatran Etexilate 75 mg Capsules
Blister packs: 10, 30, 60 capsules.
HDPE bottle pack: 60 capsules

Pharmacor Dabigatran Etexilate 110 mg Capsules
Blister packs: 10, 30, 60 capsules.
HDPE bottle pack: 60 capsules

Pharmacor Dabigatran Etexilate 150 mg Capsules
Blister packs: 10, 30, 60 capsules.
HDPE bottle pack: 60 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MEDICINE SCHEDULE

(S4) Prescription Only Medicine.

8. SPONSOR

Pharmacor Limited
c/- Wynn Williams
Level 25, Vero Centre
48 Shortland Street
Auckland Central
AUCKLAND 1010
New Zealand
Ph: +64 800 172 553 or 0800 172 553

9. DATE OF FIRST APPROVAL

24/04/2025

10. DATE OF REVISION OF THE TEXT

DD/MM/YY

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information