TESIGRAN

Dabigatran Etexilate Capsules 110 mg, and 150 mg

1. NAME OF THE MEDICINAL PRODUCT

TESIGRAN 110 (Dabigatran Etexilate Capsules 110 mg)
TESIGRAN 150 (Dabigatran Etexilate Capsules 150 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:
Dabigatran Etexilate Mesylate equivalent to Dabigatran Etexilate 110 mg or 150 mg

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Hard capsule for oral use.

3.1 Product description

110 mg capsule: Size 1, powder blue opaque cap and powder blue opaque body, hard hypromellose capsule filled with light yellow to yellowish pellets, imprinted axially with VTRS over DC110 on both cap and body in black ink.

150 mg capsule: Size 0, powder blue opaque cap and white opaque body, hard hypromellose capsule filled with light yellow to yellowish pellets, imprinted axially with VTRS over DC150 on both cap and body in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

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

4.2 Posology and method of administration

Adults:

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

Primary prevention of Venous Thromboembolism (pVTEp) events in adult patients who have undergone elective hip replacement surgery:
The recommended dose of TESIGRAN is 220 mg once daily taken as 2 capsules of 110 mg. Treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for a total of 28-35 days.

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

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF):
The recommended daily dose of TESIGRAN is 300 mg taken orally as 150 mg hard capsules twice daily. Therapy should be continued life-long.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE):
The recommended daily dose of TESIGRAN is 300 mg taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days. The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4 Special warnings and precautions for use). Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.

SPAF, DVT/PE:
For the following groups the recommended daily dose of TESIGRAN is 220 mg taken as one 110 mg capsule twice daily:
- Patients aged 80 years or above
- Patients who receive concomitant verapamil

For the following groups the daily dose of TESIGRAN of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding:
- Patients between 75-80 years
- Patients with moderate renal impairment
- Patients with gastritis, esophagitis or gastroesophageal reflux
- Other patients at increased risk of bleeding

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

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

Special patient populations

Renal impairment:
Renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with TESIGRAN 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 TESIGRAN is not recommended (see section 4.3 Contraindications).

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

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

Primary prevention of venous thromboembolism events in adult patients who have undergone elective hip replacement surgery or total knee replacement surgery (pVTEp):
In patients with moderate renal impairment (creatinine clearance 30-50 mL/min), there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg (see section 4.4 Special warnings and precautions for use and Properties).

Treatment with TESIGRAN 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.

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF):
In patients with moderate renal impairment (CrCl 30-50 mL/min) the renal function should be assessed at least once a year.

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

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE):
Treatment with TESIGRAN in patients with severe renal impairment (CrCL < 30 mL/min) is contraindicated.

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

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

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

In elderly patients (> 75 years) there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg (see section 4.4

Special warnings and precautions for use and Properties).

After knee replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 10 days.
After hip replacement surgery treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 28-35 days.

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF):
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 TESIGRAN 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 TESIGRAN 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).

Patients aged 80 years and above should be treated with a dose of 220 mg of TESIGRAN daily, taken orally as one 110 mg capsule twice a day.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE):
Patients between 75-80 years should be treated with a daily dose of 300 mg taken as one 150 mg capsule twice daily. A dose of 220 mg taken as one 110 mg capsule twice daily can be individually considered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high.

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

As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the CrCL prior to initiation of treatment with TESIGRAN to exclude patients 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 TESIGRAN 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).

***Weight**:*
Given the available clinical and kinetic data no adjustment is necessary (see section 5.2 Pharmacokinetics), but close clinical surveillance is recommended in patients with a body weight < 50 kg (see section 4.4 Special warnings and precautions for use).

***Gender**:*
Given the available clinical and kinetic data, no dose adjustment is necessary.

***Concomitant use of TESIGRAN with strong P-glycoprotein inhibitors, e.g. amiodarone, quinidine or verapamil**:*
Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (pVTEp):
Dosing should be reduced to TESIGRAN 150 mg taken once daily as 2 capsules of 75 mg in patients who concomitantly receive TESIGRAN and amiodarone, quinidine or verapamil. (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Treatment initiation with verapamil should be avoided in patients who have undergone elective total hip

replacement surgery or total knee replacement surgery who are already treated with TESIGRAN. Simultaneous initiation of treatment with TESIGRAN and verapamil should also be avoided.

Treatment with TESIGRAN 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.

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF):
No dose adjustment is necessary for concomitant use of amiodarone or quinidine.
Dosing should be reduced to 220 mg taken as one 110 mg capsule twice daily in patients who receive concomitantly dabigatran etexilate and verapamil. In this situation TESIGRAN and verapamil should be taken at the same time.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE):
No dose adjustment is necessary for concomitant use of amiodarone or quinidine.
Dosing should be reduced to 220 mg taken as one 110 mg capsule twice daily in patients who receive concomitantly dabigatran etexilate and verapamil. In this situation TESIGRAN and verapamil should be taken at the same time.

Patients at risk of bleeding*:*
Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF):
The presence of the following factors may increase the risk of bleeding: e.g. age ≥ 75 years, moderate renal impairment (30-50 mL CrCL/min), concomitant treatment with strong P-gp inhibitors (see section PK in specific populations), antiplatelets or previous gastro-intestinal bleed (see section 4.4 Special warnings and precautions for use). 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.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE):
Patients with an increased bleeding risk should be closely monitored clinically (looking for signs of bleeding or anaemia). Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient. A coagulation test (see section 4.4 Special warnings and precautions for use) may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. When excessive dabigatran exposure is identified in patients at high risk of bleeding, a reduced dose of 220 mg taken as one 110 mg capsule twice daily is recommended. When clinically relevant bleeding occurs, treatment should be interrupted.

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

Hepatic impairment:
Patients with elevated liver enzymes > 2 upper limit of normal (ULN) were excluded in the main trials. No treatment experience is available for this subpopulation of patients, and therefore the use of TESIGRAN is not recommended in this population. Hepatic impairment or liver disease expected to have any impact on survival is contraindicated.

Post-surgical patients with an increased risk for bleeding:
TESIGRAN should be resumed/started after the invasive procedure or surgical intervention as soon as

possible provided the clinical situation allows and adequeate haemostasis has been established.
Patients at risk for bleeding or patients at risk of overexposure, notably patients with moderate renal impairment (creatinine clearance 30 – 50 mL/min), should be treated with caution (see sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic Properties).

Paediatric population:
pVTEp and SPAF:
TESIGRAN has not been investigated in patients <18 years of age in the indication of:

- Primary prevention of venous thromboembolic events in patients who have undergone elective total hip replacement surgery or total knee replacement surgery.
- Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Treatment of paediatric patients with TESIGRAN is therefore not recommended.

DVT/PE:
The safety and efficacy of TESIGRAN have not been established in paediatric patients <18 years of age. Therefore, TESIGRAN is not indicated in this patient population.

Switching from TESIGRAN treatment to parenteral anticoagulant:
pVTEp:
It is recommended to wait 24 hours after the last dose before switching from TESIGRAN to a parenteral anticoagulant (see section 4.5 Interaction with other medicinal products and other forms of interaction).

SPAF and DVT/PE:
It is recommended to wait 12 hours after the last dose before switching from TESIGRAN to a parenteral anticoagulant.

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

Switching from Vit. K antagonists to TESIGRAN:
SPAF and DVT/PE:
The Vit. K antagonist should be stopped. TESIGRAN can be given as soon as the INR is < 2.0.

Switching from TESIGRAN to Vit. K antagonists (VKA)*:*
SPAF and DVT/PE:
The starting time of the VKA should be adjusted according to the patient´s CrCL as follows:

- CrCL ≥ 50 mL/min, start VKA 3 days before discontinuing dabigatran etexilate.
- CrCL ≥ 30-< 50 mL/min, start VKA 2 days before discontinuing dabigatran etexilate.

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

Cardioversion:
SPAF and DVT/PE:
Patients can stay on TESIGRAN while being cardioverted.

Catheter ablation for atrial fibrillation:
SPAF:
Catheter ablation can be conducted in patients on 150 mg twice daily TESIGRAN treatment.

TESIGRAN treatment does not need to be interrupted (see section 5 Pharmacological Properties).

Percutaneous coronary intervention (PCI) with stenting:
SPAF:
Patients with non-valvular atrial fibrillation who undergo a PCI with stenting can be treated with TESIGRAN in combination with antiplatelets after haemostasis is achieved (see section 5 Pharmacological Properties).

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

SPAF and DVT/PE:
A forgotten TESIGRAN 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
TESIGRAN can be taken with or without food. TESIGRAN should be swallowed as a whole with a glass of water, to facilitate delivery to the stomach.
Patients should be instructed not to open the capsule as this may increase the risk of bleeding.

Instruction For Use/Handling
When removing a hard capsule from the blister, please note the following instructions:
- Tear off one individual blister from the blister card along the perforated line
- Peel off the backing foil and remove the capsule
- The capsule should not be pushed through the blister foil

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Patients with severe renal impairment (CrCl < 30 mL/min)
- Active clinically significant bleeding
- 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. These are switching anticoagulant therapy (see section 4.2 Posology and method of administration), when UFH is given at doses necessary to maintain an open central venous or arterial catheter or when UFH is given during catheter ablation for atrial fibrillation (see section 4.5 Interaction with other medicinal products and other forms of interaction)
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with the following strong P-gp inhibitors: systemic ketoconazole, cyclosporine, itraconazole and dronedarone (see section 4.5 Interaction with other medicinal products and other forms of interaction)
- Prosthetic heart valves requiring anticoagulant treatment (see section 5 Pharmacological Properties).

4.4 Special warnings and precautions for use

Haemorrhagic risk:
As with all anticoagulants, TESIGRAN should be used with caution in conditions with an increased risk of bleeding. Bleeding can occur at any site during therapy with TESIGRAN. An unexplained fall in hemoglobin and/or hematocrit or blood pressure should lead to a search for a bleeding site.

For situation of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effects of dabigatran is required, the specific reversal agent (PRAXBIND, idarucizumab) is available (see sections Surgery and Interventions, Pre-operative Phase and section 4.9 Overdose).

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

Tests of anticoagulant activity such as thrombin time (TT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) are available to detect excessive dabigatran activity.
Dabigatran related anticoagulation can be assessed by ECT or TT. If ECT or TT is not available, the aPTT test provides an approximation of TESIGRAN's anticoagulant activity.

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

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

Patients who develop acute renal failure should discontinue TESIGRAN.

Factors, such as decreased renal function (30 – 50 mL/min CrCL), age ≥ 75 years, or strong P-gp-inhibitor comedication are associated with increased dabigatran plasma levels. The presence of one or more than one of these factors may increase the risk of bleeding (see section 4.2 Posology and method of administration).

The concomitant use of TESIGRAN 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 or during catheter ablation for atrial fibrillation) 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 P-gp inhibitors such as but not limited to itraconazole, tacrolimus, cyclosporine, ritonavir, tipranavir, nelfinavir and saquinavir.

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

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

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

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

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

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

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

For SPAF: Co-administration of antiplatelet (including ASA and clopidogrel) and NSAID therapies increase the risk of bleeding. Specifically, with concomitant intake of antiplatelets or strong P-gp inhibitors in patients aged ≥75 years, the risk of major bleeding, including gastrointestinal bleeding, increases. If bleeding is clinically suspected, appropriate measures such as testing for occult blood in stool, or testing for a drop in hemoglobin is suggested.

Interaction with P-gp inducers:
The concomitant use of TESIGRAN with the strong P-gp inducer rifampicin reduces dabigatran plasma concentrations. Other P-gp inducers such as St. John`s Wort or carbamazepine are also expected to reduce dabigatran plasma concentrations, and should be co-administered with caution (see section 4.5 Interaction with other medicinal products and other forms of interaction and PK in specific populations).

Patients with antiphospholipid syndrome:
Patients with antiphospholipid syndrome (especially if triple-positive for antiphospholipid antibodies) are at an increased risk for thromboembolic events.
While the efficacy of TESIGRAN is established for the treatment and prevention of venous thromboembolism it has not been studied specifically in the subpopulation of patients with antiphospholipid syndrome. Therefore, careful consideration of all treatment options (including standard treatment such as vitamin K antagonists) is recommended before use of TESIGRAN in patients with antiphospholipid syndrome.

Surgery and Interventions:
Patients on TESIGRAN who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore surgical interventions may require the temporary discontinuation of TESIGRAN (see section 5.2 Pharmacokinetics).

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

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

For SPAF: Patients can stay on TESIGRAN while being cardioverted. TESIGRAN treatment (150 mg twice daily) does not need to be interrupted in patients undergoing catheter ablation for atrial fibrillation (see section 4.2 Posology and method of administration).

Preoperative Phase:
Due to an increased risk of bleeding TESIGRAN may be stopped temporarily in advance of invasive or

surgical procedures.

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

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

Elective Surgery/Intervention:
If possible, TESIGRAN 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 TESIGRAN 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 1 and also section 5.2 Pharmacokinetics).

Table 1 summarizes discontinuation rules before invasive or surgical procedures.

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

*for more details see Table 13 Pharmacokinetics

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

Spinal Anaesthesia/Epidural Anaesthesia/Lumbar Puncture:
Procedures such as spinal anesthesia may require complete hemostatic function.
The risk of spinal or epidural haematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 1 hour should elapse before the administration of the first dose of TESIGRAN. These patients require frequent observation for neurological signs and symptoms of spinal or epidural hematoma.

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

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of TESIGRAN with treatments that act on haemostasis or coagulation including Vitamin K antagonists can markedly increase the risk of bleeding (see section 4.4 Special warnings and precautions for use).

Dabigatran etexilate and dabigatran are not metabolized by the cytochrome P450 system and had no effects *in vitro* on human cytochrome P450 enzymes. Therefore related drug-drug interactions are not expected with dabigatran etexilate or dabigatran (see section PK in specific populations).

P-glycoprotein interactions

P-glycoprotein inhibitors:

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

Concomitant administration of systemic ketoconazole is contraindicated.

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (pVTEp):
For the concomitant use of P-gp inhibitors and dosing of TESIGRAN in this indication, please see section 4.2 Posology and method of administration and PK in specific populations.

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF):
For the P-gp inhibitors listed above no dose adjustments are required for TESIGRAN in this indication.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE):
For the P-gp inhibitors listed above no dose adjustments are required for TESIGRAN in this indication.

***Amiodarone*:** Dabigatran exposure in healthy subjects was increased by 1.6 fold (+ 60 %) in the presence of amiodarone (see section PK in specific populations).

For SPAF: In patients in the RE-LY trial concentrations were increased by no more than 14% and no increased risk of bleeding was observed.

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

For SPAF: In patients in the RE-LY trial concentrations were increased by no more than 21% and no increased risk of bleeding was observed.

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

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

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

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

Tricagrelor: Dabigatran exposure in healthy subjects was increased by 1.46 fold (+ 46%) in the presence of ticagrelor at steady state or by 1.73 fold (+73%) when a loading dose of ticagrelor was administered simultaneously with a single dose of 75 mg dabigatran etexilate.

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

P- glycoprotein substrate:
Digoxin: In a study performed with 24 healthy subjects, when TESIGRAN was coadministered with digoxin, no changes on digoxin and no clinical relevant changes on dabigatran exposure have been observed (see section PK in specific populations).

P-glycoprotein inducers:
After 7 days of treatment with 600 mg rifampicin qd total dabigatran $AUC_{0-\infty}$ and C_{max} were reduced by 67% and 66% compared to the reference treatment, respectively.
The concomitant use with P-gp inducers (e.g., rifampicin) reduces exposure to dabigatran and should be avoided (see sections 4.4 Special warnings and precautions for use and PK in specific populations).

4.6 Fertility, pregnancy and lactation

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF):
In the RE-LY trial investigating the prevention of stroke and systemic embolism in patients with atrial fibrillation a total of 12,042 patients were treated with dabigatran etexilate. Of these 6,059 were treated with 150 mg twice daily of dabigatran etexilate, while 5,983 received doses of 110 mg twice daily. 22% of patient with atrial fibrillation treated for the prevention of stroke and systemic embolism (long-term treatment for up to 3 years) experienced adverse reactions.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE):
In the acute DVT/PE treatment trials (RE-COVER, RE-COVER II) a total of 2,553 patients were

included in the safety analysis for dabigatran etexilate. All patients were treated with dabigatran etexilate 150 mg bid. 14% of patients treated for acute DVT/PE treatment (long-term treatment up to 6 months) experienced adverse reactions.

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

Bleeding
Bleeding is the most relevant adverse reaction of TESIGRAN; dependent 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, in long-term treatment in yearly 16.6 % of patient with atrial fibrillation treated for the prevention of stroke and systemic embolism and in 14.4% of patients with acute DVT and/or PE. In the recurrent DVT/PE trial RE-MEDY 19.4% and in the RE-SONATE trial 10.5% of patients experienced any bleeding.

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

Known bleeding complications such as compartment syndrome and acute renal failure due to hypoperfusion and anticoagulant-related nephropathy in patients with predisposing risk factors have been reported for dabigatran etexilate.

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (pVTEp):
Overall bleeding rates were similar between treatment groups and not significantly different.

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF):
Major bleeding fulfilled one or more of the following criteria:
- Bleeding associated with a reduction in hemoglobin of at least 20 grams per liter 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 liter; transfusion of at least 4 units of blood or packed cells; a bleed associated with hypotension requiring the use of intravenous inotropic agents; a bleed that necessitated surgical intervention.

Subjects randomized to dabigatran etexilate 110 mg twice daily and 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 randomized to dabigatran etexilate 110 mg twice daily had a signficantly lower risk for major bleeds compared with warfarin (hazard ratio 0.81, $p=0.0027$).

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

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

In a pooled analysis of the two pivotal trials (RE-COVER, RE-COVER II) in acute DVT/PE treatment, subjects randomized to dabigatran etexilate had lower rates of the following bleeding events, which were statistically significant:
- Major bleeding events (hazard ratio 0.60 (0.36, 0.99))
- Major or clinically relevant bleeding events (CRBEs) (hazard ratio 0.56 (0.45, 0.71))
- Any bleeding events (hazard ratio 0.67 (0.59, 0.77))

All of which were superior vs. warfarin.

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

<u>Prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE):</u>
The definition of MBEs followed the recommendations of the International Society on Thrombosis and Haemostasis. A bleeding in RE-MEDY event was categorised as an MBE if it fulfilled at least one of the following criteria:
- Fatal bleeding
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial, or intramuscular with compartment syndrome. In order for bleeding in a critical area or organ to be classified as an MBE it had to be associated with a symptomatic clinical presentation.
- Bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or red cells.

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

A bleeding event in RE-SONATE was categorised as an MBE if it fulfilled at least one of the following criteria:
- Fatal bleeding
- Associated with a fall in haemoglobin of 2 g/dL or more
- Led to the transfusion of ≥ 2 units packed cells or whole blood
- Occurred in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal

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

Tabulated summary 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.
Table 2 lists identified adverse reactions applicable to all indications.
Table 3 lists indication specific adverse reactions identified.

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.

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

Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF):
The observed incidences of adverse reactions of dabigatran etexilate in patients treated for stroke prevention in patients with atrial fibrillation were in the range of warfarin except gastrointestinal disorders which appeared at a higher rate in the dabigatran etexilate arms.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE):
The overall frequency of adverse reactions in patients receiving TESIGRAN for acute DVT/PE treatment was lower for TESIGRAN compared to warfarin (14.2% vs. 18.9%).

Prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE):
The overall frequency of adverse reactions in patients treated for recurrent DVT/PE prevention was lower for TESIGRAN compared to warfarin (14.6% vs. 19.6%); compared to placebo the frequency was higher (14.6% vs. 6.5%).

Table 2: Adverse reactions identified from studies and post-marketing data in:
- *Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (pVTEp)*
- *Reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF)*
- *Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults*

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

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

Nervous system disorders
Intracranial haemorrhage

Vascular disorders
Haematoma, haemorrhage

Respiratory, thoracic and mediastinal disorders
Epistaxis, haemoptysis

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

Hepatobiliary disorders
Hepatic function abnormal

Skin and subcutaneous tissue disorders
Skin haemorrhage, alopecia*

Musculoskeletal, connective tissue and bone disorders
Haemarthrosis

Renal and urinary disorders
Urogenital haemorrhage

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

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

* including post-marketing data

Table 3: Additional specific adverse reactions identified per indication

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

Vascular disorders
Wound haemorrhage

General disorders and administration site conditions
Bloody discharge

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

Surgical and medical procedures
Wound drainage, post-procedural drainage

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

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

4.9 Overdose

Symptoms

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

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

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

For situations when rapid reversal is required the specific reversal agent (PRAXBIND, idarucizumab) antagonising the pharmacodynamics effect of TESIGRAN is available (see sections 4.4 Special warnings and precautions for use; Surgery and Interventions, Pre-operative Phase).

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

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

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

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

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

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

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

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

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

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

In RE-MODEL and RE-NOVATE the randomisation to the respective study medication was done pre-surgery, and in the RE-MOBILIZE and the Japanese placebo controlled trial the randomisation to the respective study medication was done post-surgery. This is of note especially in the safety evaluation of these trials. For this reason the trials are grouped in pre- and post surgery randomised trials in Table 4.

Data for the major VTE and VTE-related mortality end-point and adjudicated major bleeding endpoints are shown in the Table 4 below. VTE was defined as the composite incidence of deep vein thrombosis and Pulmonary Embolism.

Table 4: Analysis of major VTE and VTE-related mortality during the treatment period in the RE-MODEL and the RE-NOVATE orthopaedic surgery studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
RE-NOVATE (hip) [1]			
N	909	888	917
Incidences (%)	28 (3.1)	38 (4.3)	36 (3.9)
Risk differences vs. enoxaparin (%)	- 0.8	0.4	
95 % CI	- 2.5, 0.8	- 1.5, 2.2	
Risk ratio over enoxaparin	0.78	1.09	
95% CI	0.48, 1.27	0.70, 1.70	
RE-MODEL (knee) [1]			

N	506	527	511
Incidences (%)	13 (2.6)	20 (3.8)	18 (3.5)
Risk differences vs. enoxaparin (%)	- 1.0	0.3	
95 % CI	- 3.1, 1.2	-2.0, 2.6	
Risk ratio over enoxaparin	0.73	1.08	
95% CI	0.36, 1.47	0.58, 2.01	
RE-MOBILIZE (knee) [2]			Enoxaparin 60 mg
N	618	656	668
Incidences (%)	21 (3.4)	20 (3.0)	15 (2.2)
Risk differences vs. enoxaparin (%)	1.2	0.8	
95 % CI	(-0.7, 3.0)	(-0.9, 2.5)	
Risk ratio over enoxaparin	1.51	1.36	
95% CI	(0.79, 2.91)	(0.70, 2.63)	
Japanese knee study [2]			
			Placebo
N	102	113	104
Incidences (%)	0	2 (1.8)	6 (5.8)
Risk differences vs. placebo (%)	−5.8	−4.0	
95 % CI	(−10.3, −1.3)	(−9.1, 1.1)	
[1]pre-operative randomisation studies [2]post-operative randomisation studies			

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

The clinical evidence for the efficacy of dabigatran etexilate is derived from the RE-LY study (Randomized Evaluation of Long-term anticoagulant therapy) a multi-center, multi-national, randomized parallel group study of two blinded doses of dabigatran etexilate (110 mg bid and 150 mg bid) compared to open-label warfarin in patients with atrial fibrillation at moderate to high risk of stroke or systemic embolism. The primary objective in this study was to determine if dabigatran was non-inferior to warfarin in reducing the occurrence of the composite endpoint, stroke and systemic embolic events (SEE).

In the RE-LY study, a total of 18,113 patients were randomized, with a mean age of 71.5 years and a mean $CHADS_2$ score of 2.1. The population had approximately equal proportions of patients with $CHADS_2$ score 1, 2 and ≥3. The patient population was 64% male, 70% Caucasian and 16% Asian. RE-LY had a median treatment of 20 months with dabigatran etexilate given as fixed dose without coagulation monitoring. In addition to documented non-valvular atrial fibrillation (AF) e.g., persistent AF or paroxysmal, patients had one of the following additional risk factors for stroke:

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

The concomitant diseases of patients in this trial included hypertension 79%, diabetes 23% and coronary artery disease (CAD) 28%. 50% of the patient population was VKA naïve defined as less than 2 months total life time exposure. 32% of the population had never been exposed to a VKA. For those patients randomized to warfarin, the time in therapeutic range (INR 2.0 to 3.0) for the trial was a median of 67%. Concomitant medications included ASA (25% of subjects used at least 50% of the time in study), clopidogrel (3.6%), ASA+clopidogrel (2%), NSAIDs (6.3%), beta-blockers (63.4%), diuretics (53.9%),

statins (46.4%), ACE-inhibitors (44.6%), angiotensin receptor blockers (26.1%), oral hypoglycemics (17.5%), insulin (5.2%), digoxin (29.4%), amiodarone (11.3%), diltiazem (8.9%), verapamil (5.4%), and proton pump inhibitors (17.8%).

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

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

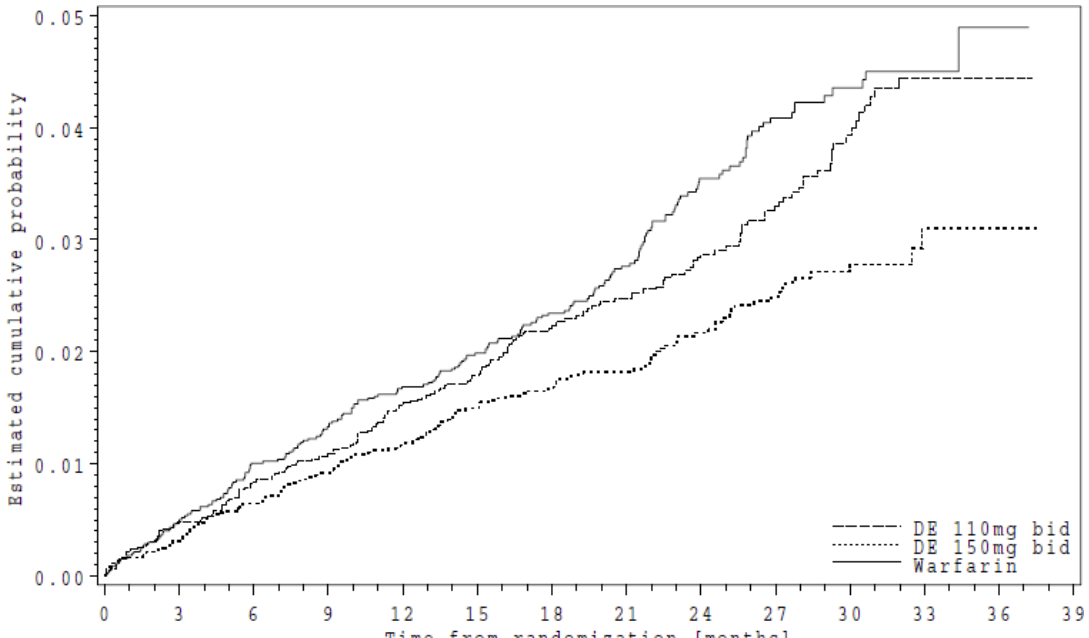
Figure 1 and tables 5-9 display details of key results:

Table 5: Analysis of first occurrence of stroke or SEE (primary endpoint) during the study period in the RE-LY (randomized set)

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

% refers to yearly event rate

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



Subjects at risk

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

Table 6: Analysis of first occurrence of ischemic or haemorrhagic strokes during the study period in RE-LY (randomized set)

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

% refers to yearly event rate

Table 7: Analysis of all cause and cardiovascular survival during the study period in the RE-LY (randomized set)

	Dabigatran etexilate 150 mg bid	Dabigatran etexilate 110 mg bid	Warfarin
Subjects randomized	6076	6015	6022
All-cause mortality			
Incidences (%)	438 (3.64)	446 (3.75)	487 (4.13)
Hazard ratio vs. warfarin (95% CI)	0.88 (0.77, 1.00)	0.91 (0.80, 1.03)	
p-value	0.0517	0.1308	
Vascular mortality			
Incidences (%)	274 (2.28)	289 (2.43)	317 (2.69)
Hazard ratio vs. warfarin (95% CI)	0.85 (0.72, 0.99)	0.90 (0.77, 1.06)	
p-value	0.0430	0.2081	

% refers to yearly event rate

The net clinical benefit (NCB) as measured by the unweighted composite clinical endpoint of stroke, systemic embolism, pulmonary embolism, acute myocardial infarction, vascular deaths, and major bleeds was assessed and is presented as part of Table 8. The yearly event rates for the dabigatran etexilate groups were lower compared to the warfarin group. The risk reduction for this composite endpoint was 8% and 10% for the dabigatran etexilate 110 mg bid and 150 mg bid treatment groups. Other components evaluated included all hospitalizations which had statistically significant fewer hospitalizations at dabigatran etexilate 110 mg bid compared to warfarin (7% risk reduction, 95% CI 0.87, 0.99, p=0.021).

Table 8: Other Measures Evaluated

	Dabigatran etexilate 150 mg bid	Dabigatran etexilate 110 mg bid	Warfarin
Subjects randomized	6076	6015	6022
Stroke/SEE/death			

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

Table 9: Liver Function Tests

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

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

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

During the additional 2.5 years of treatment in RELY-ABLE, with a maximum exposure of over 6 years (total exposure in RELY + RELY-ABLE), the long-term safety profile of dabigatran etexilate was confirmed for both test doses. No new safety findings were observed.
The rates of outcome events including, major bleed and other bleeding events were consistent with those seen in RE-LY.

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

Both initial management strategies (taking TESIGRAN after a meal and adding pantoprazole 40 mg

daily) provided complete relief of the primary GIS in over 55% of patients who reported GIS (TESIGRAN after a meal: 55.9%; pantoprazole: 67.2%).

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

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

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

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

Patients undergoing catheter ablation for atrial fibrillation

A prospective, randomized, open-label, multicenter, exploratory study with blinded, centrally adjudicated endpoint evaluation (RE-CIRCUIT) was conducted in 704 patients who were under stable anticoagulant treatment. The study compared 150 mg twice daily uninterrupted dabigatran etexilate with uninterrupted INR-adjusted warfarin in catheter ablation of paroxysmal or persistent atrial fibrillation. Of the 704 enrolled patients, 317 underwent atrial fibrillation ablation on uninterrupted dabigatran and 318 underwent atrial fibrillation ablation on uninterrupted warfarin. All patients underwent a Trans-oesophageal Echocardiography (TEE) prior to catheter ablation. The primary outcome (adjudicated major bleeding according to ISTH criteria) occurred in 5 (1.6 %) patients in the dabigatran etexilate group and 22 (6.9 %) patients in the warfarin group (risk difference −5.3%; 95% CI −8.4, −2.2; P=0.0009). There was no stroke/systemic embolism/TIA (composite) event in the dabigatran etexilate arm, and one event (TIA) in the warfarin arm from the time of ablation and until 8 weeks post-ablation. The composite incidence of MBEs and thromboembolic events (stroke/systemic embolism/TIA) was lower in the dabigatran etexilate arm (5 [1.6%] vs. 23 [7.2%] patients). This exploratory study demonstrated that dabigatran etexilate was associated with a 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.

Patients who underwent Percutaneous Coronary Intervention (PCI) with stenting

A prospective, randomized, open-label, blinded endpoint (PROBE) study (Phase IIIb) to evaluate dual-therapy with dabigatran etexilate (110 mg or 150 mg bid) plus clopidogrel or ticagrelor (P2Y12 antagonist) vs. triple-therapy with warfarin (adjusted to a INR 2.0 – 3.0) plus clopidogrel or ticagrelor and aspirin was conducted in 2725 patients with non valvular atrial fibrillation who underwent a PCI with stenting (RE-DUAL PCI). Patients were randomized to dabigatran etexilate 110 mg bid dual-therapy, dabigatran etexilate 150 mg bid dual-therapy or warfarin triple-therapy. Elderly patients outside of the United States (≥80 years of age for all countries, ≥70 years of age for Japan) were randomLy assigned to the dabigatran etexilate 110 mg dual-therapy group or the warfarin triple-therapy group. The primary endpoint was a combined endpoint of major bleeds based on ISTH definition or clinically relevant non-major bleeding event.

The incidence of the primary endpoint was 15.4 % (151 patients) in the dabigatran etexilate 110 mg dual-therapy group as compared with 26.9 % (264 patients) in the warfarin triple-therapy group (HR 0.52; 95% CI 0.42, 0.63; P<0.0001 for non-inferiority and P<0.0001 for superiority) and in 20.2% (154 patients) in the dabigatran etexilate 150 mg dual-therapy group as compared with 25.7 % (196 patients)

in the corresponding warfarin triple-therapy group (HR 0.72; 95% CI 0.58, 0.88; P<0.0001 for non-inferiority and P=0.002 for superiority). As part of the descriptive analysis, TIMI (Thrombolysis In Myocardial Infarction) major bleeding events was lower in both dabigatran etexilate dual-therapy groups than in the warfarin triple-therapy group: 14 events (1.4%) in the dabigatran etexilate 110 mg dual-therapy group as compared with 37 events (3.8%) in the warfarin triple-therapy group (HR 0.37; 95% CI 0.20, 0.68; P=0.002) and 16 events (2.1%) in the dabigatran etexilate 150 mg dual-therapy group as compared with 30 events (3.9%) in the corresponding warfarin triple-therapy group (HR 0.51; 95% CI 0.28, 0.93; P=0.03). Both dabigatran etexilate dual-therapy groups had lower rates of intracranial hemorrhage than the corresponding warfarin triple-therapy group: 3 events (0.3%) in the 110 mg dabigatran etexilate dual-therapy group as compared with 10 events (1.0%) in the warfarin triple-therapy group (HR 0.30; 95% CI 0.08, 1.07; P=0.06) and 1 event (0.1%) in the 150 mg dabigatran etexilate dual-therapy group as compared with 8 events (1.0%) in the corresponding warfarin triple-therapy group (HR 0.12; 95% CI 0.02, 0.98; P=0.047). The incidence of the composite efficacy endpoint of death, thromboembolic events (myocardial infarction, stroke, or systemic embolism) or unplanned revascularization in the two dabigatran etexilate dual-therapy groups combined was non-inferior to the warfarin triple-therapy group (13.7% vs. 13.4% respectively; HR 1.04; 95% CI: 0.84, 1.29; P=0.0047 for non-inferiority).There were no statistical differences in the individual components of the efficacy endpoints between either dabigatran etexilate dual-therapy groups and warfarin triple-therapy.

This study demonstrated that dual-therapy, with dabigatran etexilate and a P2Y12 antagonist, significantly reduced the risk of bleeding vs. warfarin triple-therapy, with non-inferiority for composite of thromboembolic events, in patients with atrial fibrillation who underwent a PCI with stenting.

Clinical trials for the prevention of thromboembolism in patients with prosthetic heart valves:

A phase II study examined dabigatran etexilate and warfarin in a total of 252 patients with recent mechanical heart valve replacement surgery (i.e. within the current hospital stay) and in patients who received a mechanical heart valve replacement more than three months ago. An imbalance in thromboembolic and total (mainly minor) bleeding events in disfavour of dabigatran etexilate was observed in this trial. In the early post-operative patients, major bleeding manifested predominantly as haemorrhagic pericardial effusions, specifically in patients who started dabigatran etexilate early (i.e. on Day 3) after heart valve replacement surgery.

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

Clinical evidence has demonstrated dabigatran etexilate to be an effective and safe treatment for DVT and/or PE in two multi-center, randomised, double blind, parallel-group, replicate studies RE-COVER and RE-COVER II. These studies compared dabigatran etexilate (150 mg bid) with warfarin (target INR 2.0-3.0) in patients with acute DVT and/or PE. The primary objective of these studies was to determine if dabigatran was non-inferior to warfarin in reducing the occurrence of the primary endpoint which was the composite of recurrent symptomatic DVT and/or PE and related deaths within the 6 month acute treatment period.

In the pooled RE-COVER and RE-COVER II studies, a total of 5153 patients were randomized and 5107 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 immobilization -14.6%. Patients' baseline characteristics: mean age was 54.8 years, males 59.5%, Caucasian 86.1%, Asian 11.8%, blacks 2.1%. The co-morbidities included: hypertension 35.5%, diabetes mellitus 9.0%, CAD 6.8% and gastric or duodenal ulcer 4.1%.

The duration of treatment with fixed dose of dabigatran was 174.0 days without coagulation monitoring. For patients randomized to warfarin, the median time in therapeutic range (INR 2.0 to 3.0) was 60.6%. Concomitant medications included vasodilators 28.5%, agents acting on the renin-angiotensin system 24.7%, lipids lowering agents 19.1%, beta-blockers 14.8%, calcium channel blockers 9.7%, NSAIDs

21.7%, aspirin 9.2%, antiplatelet agents 0.7%, P-gp inhibitors 2.0% (verapamil -1.2% and amiodarone -0.4%).

Two trials in patients presenting with acute DVT and/or PE treated initially for at least 5 days of parenteral therapy, RE-COVER and RE-COVER II, demonstrated that treatment with dabigatran etexilate 150 mg twice daily was non-inferior to the treatment with warfarin (p values for non-inferiority: RE-COVER p<0.0001, RE-COVER II p=0.0002). Bleeding events (MBEs, MBE/CRBEs and any bleeding) were significantly lower in patients receiving dabigatran etixilate 150 mg twice daily as compared with those receiving warfarin.

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

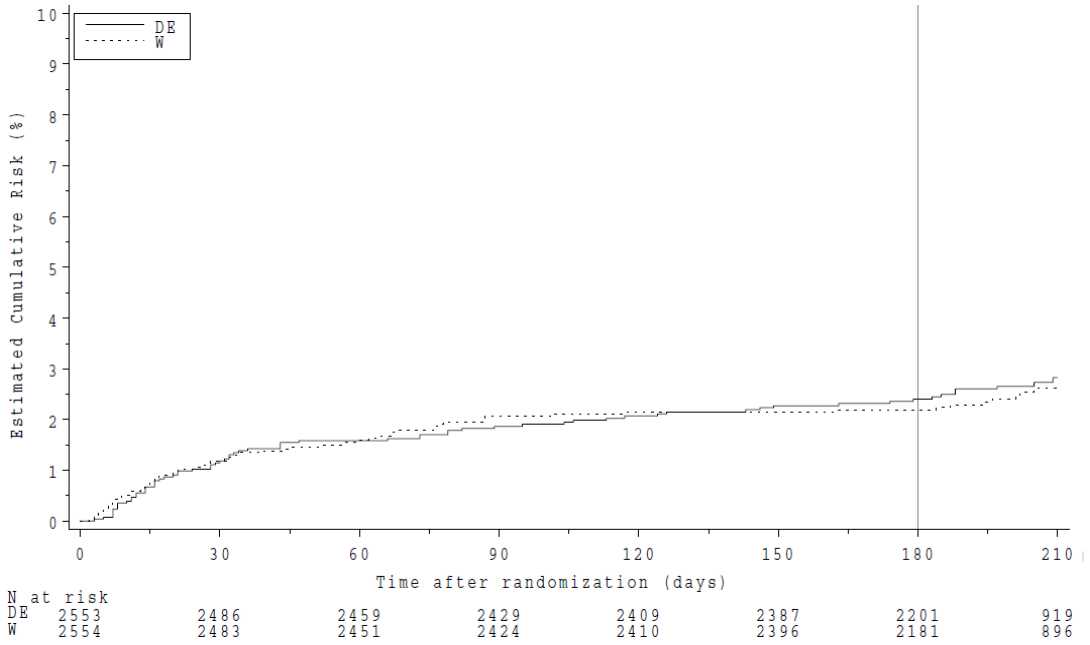


Table 10: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the pooled studies RE-COVER and RE-COVER II

	Dabigatran etexilate 150 mg	Warfarin
RE-COVER/RE-COVER II pooled		
Patients, n (%)	2553 (100.0)	2554 (100.0)
Recurrent symptomatic VTE and VTE-related death	68 (2.7)	62 (2.4)
Hazard ratio vs. warfarin	1.09	
95% CI	(0.77, 1.54)	
Secondary efficacy endpoints		
Recurrent symptomatic VTE and all-cause deaths	109 (4.3)	104 (4.1)
95% CI	3.52, 5.13	3.34, 4.91
Symptomatic DVT	45 (1.8)	39 (1.5)
95% CI	1.29, 2.35	1.09, 2.08
Symptomatic PE	27 (1.1)	26 (1.0)
95% CI	0.70, 1.54	0.67, 1.49
VTE-related deaths	4 (0.2)	3 (0.1)
95% CI	0.04, 0.40	0.02, 0.34
All-cause deaths	51 (2.0)	52 (2.0)

95% CI	1.49, 2.62	1.52, 2.66

Other Measures Evaluated:

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

Myocardial infarction occurred at a low frequency in all four of the VTE studies for all treatment groups. Cardiac death occurred in one patient in the warfarin treatment group.
In the three active controlled studies a higher rate of myocardial infarction was reported in patients who received dabigatran etexilate (20; 0.5%) than in those who received warfarin (5; 0.1%).
In the RE-SONATE study, which compared dabigatran etexilate to placebo, there was 1 MI event in each of the treatment groups, resulting in MI rates with dabigatran equal to MI rates with placebo.

Liver Function Tests:
Treatment of acute deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE):

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

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

Clinical evidence has demonstrated dabigatran etexilate to be an effective and safe treatment for recurrent DVT and/or PE. Two randomized, parallel group, double-blind studies were performed in patients previously treated with anticagulation therapy. RE-MEDY, warfarin controlled study, enrolled patients already treated for 3 to 12 months with the need for further anticoagulant treatment and RE-SONATE, the placebo controlled study, enrolled patients already treated for 6 to 18 months with Vitamin K inhibitors.

The objective of the RE-MEDY study was to compare the safety and efficacy of oral dabigatran etexilate (150 mg bid) to warfarin (target INR 2.0-3.0) for the long-term treatment and prevention of recurrent, symptomatic DVT and/or PE. A total of 2866 patients were randomized and 2856 patients were treated. The index events at baseline: DVT - 65.1%, PE - 23.1%, PE and DVT -11.7%. Patients' baseline characteristics: mean age 54.6 years, males 61.0%, Caucasian 90.1%, Asian 7.9%, blacks 2.0%. Co-morbidities included hypertension 38.6 %, diabetes mellitus 9.0%, CAD 7.2 % and gastric or duodenal ulcer 3.8 %. Concomitant medications: agents acting on the renin-angiotensin system 27.9 %, vasodilators 26.7%, lipid lowering agents 20.6%, NSAIDs 18.3 %, beta-blockers 16.3 %, calcium channel blockers 11.1 %, aspirin 7.7 %, P-gp inhibitors 2.7% (verapamil 1.2% and amiodarone 0.7%), antiplatelets 0.9 %. Duration of dabigatran exilate treatment ranged from 6 to 36 months (median - 534.0 days). For patients randomized to warfarin, the median time in therapeutic range (INR 2.0-3.0) was 64.9%.

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

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

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

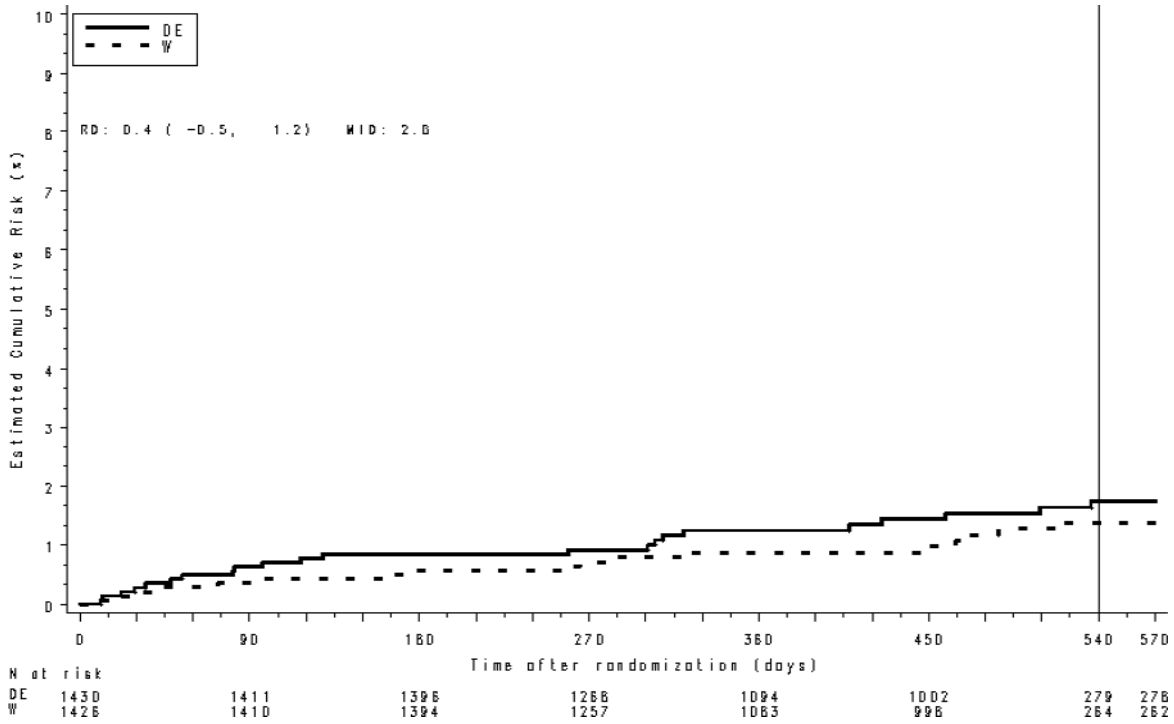


Table 11 displays details of key results of the RE-MEDY study.

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

	Dabigatran etexilate 150 mg	Warfarin
RE-MEDY,		
Patients, n (%)	1430 (100.0)	1426 (100.0)
Recurrent symptomatic VTE and VTE-related death	26 (1.8)	18 (1.3)
Hazard ratio vs. warfarin	1.44	
95% CI	0.78, 2.64	
p-value (non-inferiority)	0.0135	
Patients with event at 18 months	22	17
Cumulative risk at 18 months (%)	1.7	1.4
Risk difference vs. warfarin (%)	0.4	
95% CI	-0.5, 1.2	
p-value (non-inferiority)	<0.0001	
Secondary efficacy endpoints		
Recurrent symptomatic VTE and all-cause deaths	42 (2.9)	36 (2.5)
95% CI	2.12, 3.95	1.77, 3.48
Symptomatic DVT	17 (1.2)	13 (0.9)
95% CI	0.69, 1.90	0.49, 1.55
Symptomatic PE	10 (0.7)	5 (0.4)
95% CI	0.34, 1.28	0.11, 0.82
VTE-related deaths	1 (0.1)	1 (0.1)
95% CI	0.00, 0.39	0.00, 0.39

All-cause deaths	17(1.2)	19(1.3)
95% CI	0.69, 1.90	0.80, 2.07

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

The index events at baseline: DVT 64.5%, PE 27.8%, PE and DVT 7.7%. A total of 1353 patients were randomized and 1343 patients treated. Patients' baseline characteristics: mean age 55.8 years, males 55.5%, Caucasian 89.0%, Asian 9.3%, blacks 1.7%. Co-morbidities included hypertension 38.8%, diabetes mellitus 8.0%, CAD 6.0 % and gastric or duodenal ulcer 4.5%. Concomitant medications: agents acting on the renin-angiotensin system 28.7%, vasodilators 19.4%, lipid lowering agents 17.9%, beta-blockers 18.5%, calcium channel blockers 8.9%, NSAIDs 12.1%, aspirin 8.3%, antiplatelets 0.7% and P-gp inhibitors 1.7% (verapamil 1.0% and amiodarone 0.3%).

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

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

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

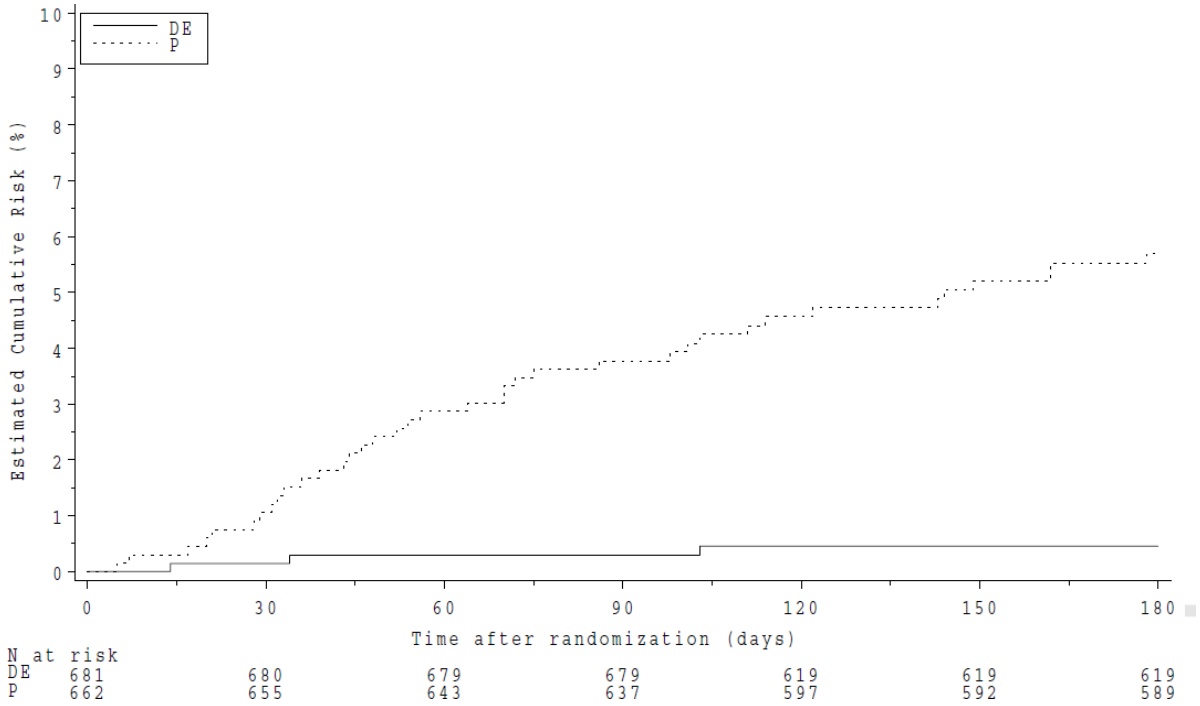


Table 12 displays details of key results of the RE-SONATE study.

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

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

Other Measures Evaluated:
Prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE):

Myocardial infarction occurred at a low frequency in all four of the VTE studies for all treatment groups. Cardiac death occurred in one patient in the warfarin treatment group.
In the three active controlled studies a higher rate of myocardial infarction was reported in patients who received dabigatran etexilate (20; 0.5%) than in those who received warfarin (5; 0.1%).

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

Liver Function Tests:

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

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

5.2 Pharmacokinetic properties

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

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

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

The oral bioavailability may be increased by about 1.4 fold (+37%) compared to the reference capsule formulation when the pellets are taken without the HPMC capsule shell. Hence, the integrity of the HPMC capsules should always be preserved in clinical use to avoid unintentionally increased bioavailability of dabigatran etexilate. Therefore, patients should be advised not to open the capsules and taking the pellets alone (e.g. sprinkled over food or into beverages) (see section 4.2 Posology 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 (BISTRO Ib). It is noted however that contributing factors such as anesthesia, gastrointestinal paresis, and surgical effects will mean that a proportion of patients will experience absorption delay independent of the oral drug formulation. Although this study did not predict whether impaired absorption persists with subsequent doses, it was demonstrated in a further study that slow and delayed absorption is usually only present on the day of surgery. On subsequent days absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after drug administration.

Distribution

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

Biotransformation

After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran, which is the active form in plasma. The cleavage of the prodrug dabigatran etexilate by esterase-catalysed hydrolysis to the active principle dabigatran is the predominant metabolic reaction. Dabigatran is subject to conjugation forming pharmacologically active acylglucuronides. Four positional isomers, 1-O, 2-O, 3-O, 4-O-acylglucuronide exist, each accounts for less than 10% of total dabigatran in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods. Dabigatran is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 mL/min corresponding to the glomerular filtration rate.

Elimination

After C_{max}, plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half- life of approximately 11 hours in healthy elderly subjects. After multiple doses a terminal half-life of about 12-14 hours was observed. The half-life was independent of dose. However, half-life is prolonged if renal function is impaired as shown below, in Table 13.

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

Table 13: Half-life of total dabigatran in healthy subjects and subjects with impaired renal function

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

PK in specific populations

Renal impairment:
The exposure (AUC) of dabigatran after the oral administration of dabigatran etexilate in a phase I study was approximately 3-fold higher in volunteers with moderate renal insufficiency (CrCL between 30 - 50 mL/min) than in those without renal insufficiency.

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

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

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

Treatment of acute deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE):
The median CrCl in the RE-COVER study was 100.3 mL/min. 21.7% of patients had mild renal impairment (CrCl > 50-< 80 mL/min) and 4.5% of patients had a moderate renal impairment (CrCl between 30-50 mL/min). Patients with mild and moderate renal impairment had on average 1.7-fold and 3.4-fold higher steady state dabigatran trough concentrations compared with patients with CrCl > 80 mL/min. Similar values for CrCl were found in RE-COVER II.

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

Elderly:
Specific pharmacokinetic studies with elderly subjects in phase 1 studies showed an increase of 1.4- to 1.6-fold (+40 to 60%) in the AUC and of more than 1.25-fold (+25 %) in C_{max} compared to young subjects.

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

The observed increase of dabigatran exposure correlated with the age-related reduction in creatinine clearance.
The effect by age on exposure to dabigatran was confirmed in the RE-LY study with an about 1.3 fold (+31 %) higher trough concentration for subjects ≥ 75 years and by about 22 % lower trough level for subjects < 65 years compared to subjects of age between 65 and 75 years.

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

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

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

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

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

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

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

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

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

Drug-drug interactions (studies):

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

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

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

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

Co-medication with P-gp inhibitors:

***Amiodarone*:** When dabigatran etexilate was co-administered 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.

For SPAF: In the population pharmacokinetics study from RE-LY, no important changes in dabigatran trough levels were observed in patients who received amiodarone (see section 4.5 Interaction with other medicinal products and other forms of interaction).

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

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

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

There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increase of C_{max} by about 10% and AUC by about 20%). This is explained by completed dabigatran absorption after 2 hours (see section 4.2 Posology and method of administration).

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

For SPAF: In the population pharmacokinetics study from RE-LY, no important changes in dabigatran trough levels were observed in patients who received verapamil (see section 4.5 Interaction with other medicinal products and other forms of interaction).

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

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

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

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

Co-medication with P-gp substrates:

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

Co-medication with P-gp inducers:

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

Co-medications with platelet-inhibitors:

Acetylsalicylic acid (ASA): The effect of concomitant administration of dabigatran etexilate and acetylsalicylic acid (ASA) on the risk of bleeds was studied in patients with atrial fibrillation in a phase II study in which a randomized ASA coadministration was applied. Based on logistic regression analysis, co-administration of ASA and 150 mg dabigatran etexilate twice daily may increase the risk

for any bleeding from 12 % to 18 % and 24% with 81 mg and 325 mg ASA, respectively.

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

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

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

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

Antiplatelets or other anticoagulants**:** The concomitant use of dabigatran etexilate and antiplatelets or other anticoagulants may increase the risk of bleeding (see section 4.4 Special warnings and precautions for use).

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

Co-medication with gastric pH-elevating agents:

The changes in dabigatran exposure determined by population pharmacokinetic analysis caused by PPIs and antacids were not considered clinically relevant because the magnitude of the effect were minor (fractional decrease in bioavailability not significant for antacids and 14.6% for PPIs.

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content: Tartaric acid, Hypromellose, Talc, Isopropyl Alcohol, Hydroxypropyl cellulose, Methylelene Chloride

Capsule shell: FD&C Blue 1/ Brilliant Blue FCF, Titanium dioxide, Hypromellose

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C. Store in original package in order to protect from moisture.
Do not put the capsules in pill boxes or pill organizers, unless capsules can be maintained in the original package.
Please refer to the packaging for information on shelf-life.

6.5 Nature and contents of container

Cold form blister pack (Desiccant embedded): Comprises of form pack laminated with desiccant layer on one side and hard tempered aluminium foil (dull side lacquered and bright side PE extrusion coated) on the other side.

Pack size: 10's, 30's & 60's
Not all presentations are available locally.

7. Name and address of manufacturer

Mylan Laboratories Limited
Plot No. H-12 & H-13,
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431136, India.

8. Product Registration Holder:

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