Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dabigatran Etexilate Krka 110 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule (capsule)

Capsule cap is blue, capsule body is blue with longitudinally imprinted black mark 110. Capsule content are yellowish white to light yellow pellets. Capsule size: 1, approximately 19 mm in length.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.

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

Treatment of VTE and prevention of recurrent VTE in paediatric patients from the time the child is able to swallow soft food to less than 18 years of age.

For age appropriate dose forms, see section 4.2.

4.2 Posology and method of administration

Posology
Dabigatran Etexilate Krka capsules can be used in adults and paediatric patients aged 8 years or older who are able to swallow the capsules whole. There are other age appropriate dose forms for the treatment of children below 8 years.

When changing between the formulations, the prescribed dose may need to be altered. The dose stated in the relevant dosing table of a formulation should be prescribed based on the weight and age of the child.

Primary prevention of VTE in orthopaedic surgery
The recommended doses of dabigatran etexilate and the duration of therapy for primary prevention of VTE in orthopaedic surgery are shown in table 1.

Table 1: Dose recommendations and duration of therapy for primary prevention of VTE in orthopaedicsurgery

	Treatment initiation on the day of surgery	Maintenance dose starting on the first day after	Duration of maintenance dose

	1-4 hours after completed surgery	**surgery**	
Patients following elective knee replacement surgery	single capsule of 110 mg dabigatran etexilate	220 mg dabigatran etexilate once daily taken as 2 capsules of 110 mg	10 days
Patients following elective hip replacement surgery			28-35 days
Dose reduction recommended			
Patients with moderate renal impairment (creatinine clearance (CrCL 30-50 mL/min)	single capsule of 75 mg dabigatran etexilate	150 mg dabigatran etexilate once daily taken as 2 capsules of 75 mg	10 days (knee replacement surgery) or 28-35 days (hip replacement surgery)
Patients who receive concomitant verapamil*, amiodarone, quinidine			
Patients aged 75 or above			

*For patients with moderate renal impairment concomitantly treated with verapamil see Special populations

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.

Assessment of renal function prior to and during dabigatran etexilate treatment

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

- Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with dabigatran etexilate to exclude patients with severe renal impairment (i.e. CrCL < 30 mL/min) (see sections 4.3, 4.4 and 5.2).
- Renal function should also be assessed when a decline in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products).

The method to be used to estimate renal function (CrCL in mL/min) is the Cockcroft-Gault method.

Missed dose
It is recommended to continue with the remaining daily doses of dabigatran etexilate at the same time of the next day.

No double dose should be taken to make up for missed individual doses.

Discontinuation of dabigatran etexilate
Dabigatran etexilate treatment should not be discontinued without medical advice. Patients should be instructed to contact the treating physician if they develop gastrointestinal symptoms such as dyspepsia (see section 4.8).

Switching
Dabigatran etexilate treatment to parenteral anticoagulant:
It is recommended to wait 24 hours after the last dose before switching from dabigatran etexilate to a parenteral anticoagulant (see section 4.5).

Parenteral anticoagulants to dabigatran etexilate:

The parenteral anticoagulant should be discontinued and dabigatran etexilate should be started 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous Unfractionated Heparin (UFH)) (see section 4.5).

Special populations

Renal impairment
Treatment with dabigatran etexilate in patients with severe renal impairment (CrCL < 30 mL/min) is contraindicated (see section 4.3).

In patients with moderate renal impairment (CrCL 30-50 mL/min), a dose reduction is recommended (see table 1 above and sections 4.4 and 5.1).

Concomitant use of dabigatran etexilate with mild to moderate P-glycoprotein (P-gp) inhibitors, i.e. amiodarone, quinidine or verapamil

Dosing should be reduced as indicated in table 1 (see also sections 4.4 and 4.5). In this situation dabigatran etexilate and these medicinal products should be taken at the same time.

In patients with moderate renal impairment and concomitantly treated with verapamil, a dose reduction of dabigatran etexilate to 75 mg daily should be considered (see sections 4.4 and 4.5).

Elderly
For elderly patients > 75 years, a dose reduction is recommended (see table 1 above and sections 4.4 and 5.1).

Weight
There is very limited clinical experience in patients with a body weight < 50 kg or > 110 kg at the recommended posology. Given the available clinical and kinetic data no adjustment is necessary (see section 5.2), but close clinical surveillance is recommended (see section 4.4).

Gender
No dose adjustment is necessary (see section 5.2).

Paediatric population
There is no relevant use of dabigatran etexilate in the paediatric population for the indication of primary prevention of VTE in patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors (SPAF).
Treatment of DVT and PE and prevention ofrecurrent DVT and PE in adults (DVT/PE)

The recommended doses of dabigatran etexilate in the indications SPAF, DVT and PE are shown in table 2.

Table 2 : Dose recommendations for SPAF, DVT and PE

	Dose recommendation
Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors (SPAF)	300 mg dabigatran etexilate taken as one 150 mg capsule twice daily
Treatment of DVT and PE and prevention of recurrent DVT and PE in adults (DVT/PE)	300 mg dabigatran etexilate taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days
Dose reduction recommended	
Patients aged ≥ 80 years	daily dose of 220 mg dabigatran etexilate taken as one 110 mg capsule twice daily
Patients who receive concomitant verapamil	
Dose reduction for consideration	
Patients between 75-80 years	daily dose of dabigatran etexilate of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding
Patients with moderate renal impairment (CrCL 30-50 mL/min)	
Patients with gastritis, esophagitis or gastroesophageal reflux	
Other patients at increased risk of bleeding	

For DVT/PE the recommendation for the use of 220 mg dabigatran etexilate taken as one 110 mg capsule twice daily is based on pharmacokinetic and pharmacodynamic analyses and has not been studied in this clinical setting. See further down and sections 4.4, 4.5, 5.1 and 5.2.

In case of intolerability to dabigatran etexilate, 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 systemic embolism associated with atrial fibrillation or for DVT/PE.

Assessment of renal function prior to and during dabigatran etexilate treatment

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

- Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with dabigatran etexilate to exclude patients with severe renal impairment (i.e. CrCL < 30 mL/min) (see sections 4.3, 4.4 and 5.2).
- Renal function should also be assessed when a decline in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products).

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

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

The method to be used to estimate renal function (CrCL in mL/min) is the Cockcroft-Gault method.

Duration of use
The duration of use of dabigatran etexilate in the indications SPAF, DVT and PE are shown in table 3.

Table 3: Duration of use for SPAF and DVT/PE

Indication	Duration of use
SPAF	Therapy should be continued long term.
DVT/PE	The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4). 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.

Missed dose
A forgotten dabigatran etexilate 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.

No double dose should be taken to make up for missed individual doses.

Discontinuation of dabigatran etexilate
Dabigatran etexilate treatment should not be discontinued without medical advice. Patients should be instructed to contact the treating physician if they develop gastrointestinal symptoms such as dyspepsia (see section 4.8).

Switching
Dabigatran etexilate treatment to parenteral anticoagulant:

It is recommended to wait 12 hours after the last dose before switching from dabigatran etexilate to a parenteral anticoagulant (see section 4.5).

Parenteral anticoagulants to dabigatran etexilate:
The parenteral anticoagulant should be discontinued and dabigatran etexilate should be started 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous Unfractionated Heparin (UFH)) (see section 4.5).

Dabigatran etexilate treatment to Vitamin K antagonists (VKA):

The starting time of the VKA should be adjusted based on CrCL as follows:

- CrCL ≥ 50 mL/min, VKA should be started 3 days before discontinuing dabigatran etexilate
- CrCL ≥ 30-< 50 mL/min, VKA should be started 2 days before discontinuing dabigatran etexilate

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

VKA to dabigatran etexilate:
The VKA should be stopped. Dabigatran etexilate can be given as soon as the INR is < 2.0.

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

Catheter ablation for atrial fibrillation (SPAF)
There are no data available for 110 mg twice daily dabigatran etexilate treatment.

Percutaneous coronary intervention (PCI) with stenting (SPAF)
Patients with non valvular atrial fibrillation who undergo a PCI with stenting can be treated with dabigatran etexilate in combination with antiplatelets after haemostasis is achieved (see section 5.1).

Special populations

Elderly
For dose modifications in this population see table 2 above.

Patients at risk of bleeding
Patients with an increased bleeding risk (see sections 4.4, 4.5, 5.1 and 5.2) 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 (see table 2 above). A coagulation test (see section 4.4) 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, a dose reduction may be considered due to the elevated risk of major gastro-intestinal bleeding (see table 2 above and section 4.4).

Renal impairment
Treatment with dabigatran etexilate in patients with severe renal impairment (CrCL < 30 mL/min) is contraindicated (see section 4.3).

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 dabigatran etexilate is also 300 mg taken as one 150 mg capsule twice daily. However, for patients with high risk of bleeding, a dose reduction of dabigatran etexilate to 220 mg taken as one 110 mg capsule twice daily should be considered (see sections 4.4 and 5.2). Close clinical surveillance is recommended in patients with renal impairment.

Concomitant use of dabigatran etexilate with mild to moderate P-glycoprotein (P-gp) inhibitors, i.e. amiodarone, quinidine or verapamil

No dose adjustment is necessary for concomitant use of amiodarone or quinidine (see sections 4.4, 4.5 and 5.2).

Dose reductions are recommended for patients who receive concomitantly verapamil (see table 2 above and sections 4.4 and 4.5). In this situation dabigatran etexilate and verapamil should be taken at the same time.

Weight

No dose adjustment is necessary (see section 5.2), but close clinical surveillance is recommended in patients with a body weight < 50 kg (see section 4.4).

Gender
No dose adjustment is necessary (see section 5.2).

Paediatric population
There is no relevant use of dabigatran etexilate in the paediatric population for the indication of prevention of stroke and systemic embolism in patients with NVAF.

Treatment of VTE and prevention of recurrent VTE in paediatric patients
For the treatment of VTE in paediatric patients, treatment should be initiated following treatment with a parenteral anticoagulant for at least 5 days. For prevention of recurrent VTE, treatment should be initiated following previous treatment.

Dabigatran etexilate capsules should be taken twice daily, one dose in the morning and one dose in the evening, at approximately the same time every day. The dosing interval should be as close to 12 hours as possible.

The recommended dose of dabigatran etexilate capsules is based on the patient's weight and age as shown in table 4. The dose should be adjusted according to weight and age as treatment progresses.

For weight and age combinations not listed in the dosing table no dosing recommendation can be provided.

Table 4 : Single and total daily dabigatran etexilate doses in milligrams (mg) by weight in kilograms (kg) and age in years of the patient

Weight/age combinations		**Single dose in mg**	**Total daily dose in mg**
Weight in kg	**Age in years**		
11 to <13	8 to <9	75	150
13 to <16	8 to <11	110	220
16 to <21	8 to <14	110	220
21 to <26	8 to <16	150	300
26 to <31	8 to <18	150	300
31 to <41	8 to <18	185	370
41 to <51	8 to <18	220	440
51 to <61	8 to <18	260	520
61 to <71	8 to <18	300	600
71 to <81	8 to <18	300	600
>81	10 to <18	300	600

Single doses requiring combinations of more than one capsule:
300 mg: two 150 mg capsules or
four 75 mg capsules
260 mg: one 110 mg plus one 150 mg capsule or
one 110 mg plus two 75 mg capsules
220 mg: two 110 mg capsules
185 mg: one 75 mg plus one 110 mg capsule
150 mg: one 150 mg capsule or
two 75 mg capsules

Assessment of renal function prior to and during treatment
Prior to the initiation of treatment, the estimated glomerular filtration rate (eGFR) should be estimated using the Schwartz formula (method used for creatinine assessment to be checked with local lab).

Treatment with dabigatran etexilate in paediatric patients with eGFR <50 mL/min/1.73m^2 is contraindicated (see section 4.3).

Patients with an eGFR ≥50 mL/min/1.73m^2 should be treated with the dose according to table 4.

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 co-medications, etc).

Duration of use
The duration of therapy should be individualised based on the benefit risk assessment.

Missed dose
A forgotten dabigatran etexilate dose may still be taken up to 6 hours prior to the next scheduled dose.

From 6 hours prior to the next scheduled dose onwards, the missed dose should be omitted.

A double dose to make up for missed individual doses must never be taken.

Discontinuation of dabigatran etexilate
Dabigatran etexilate treatment should not be discontinued without medical advice. Patients or their caregivers should be instructed to contact the treating physician if the patient develops gastrointestinal symptoms such as dyspepsia (see section 4.8).

Switching

Dabigatran etexilate treatment to parenteral anticoagulant:
It is recommended to wait 12 hours after the last dose before switching from dabigatran etexilate to a parenteral anticoagulant (see section 4.5).

Parenteral anticoagulants to dabigatran etexilate:
The parenteral anticoagulant should be discontinued and dabigatran etexilate should be started 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous Unfractionated Heparin (UFH)) (see section 4.5).

Dabigatran etexilate treatment to Vitamin K antagonists (VKA):
Patients should start VKA 3 days before discontinuing dabigatran etexilate.

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

VKA to dabigatran etexilate:
The VKA should be stopped. Dabigatran etexilate can be given as soon as the INR is < 2.0.

Method of administration
This medicinal product is for oral use.

The capsules can be taken with or without food. The capsules 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 (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Severe renal impairment (CrCL < 30 mL/min) in adult patients
- eGFR <50 mL/min/1.73m^2 in paediatric patients
- 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), 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)
- 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, dronedarone and the fixed-dose combination glecaprevir/pibrentasvir (see section 4.5)
- Prosthetic heart valves requiring anticoagulant treatment (see section 5.1).

4.4 Special warnings and precautions for use

Haemorrhagic risk
Dabigatran etexilate should be used with caution in conditions with an increased risk of bleeding or with concomitant use of medicinal products affecting haemostasis by inhibition of platelet aggregation. Bleeding can occur at any site during therapy. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site.

For adult patients in situations of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effect of dabigatran is required, the specific reversal agent idarucizumab is available. The efficacy and safety of idarucizumab have not been established in paediatric patients.
Haemodialysis can remove dabigatran. For adult patients, fresh whole blood or fresh frozen plasma, coagulation factor concentration (activated or non-activated), recombinant factor VIIa or platelet concentrates are other possible options (see also section 4.9).

In clinical trials, dabigatran etexilate was associated with higher rates of major gastrointestinal (GI) bleeding. An increased risk was seen in the elderly (≥ 75 years) for the 150 mg twice daily dose regimen. Further risk factors (see also table 5) comprise co-medication with platelet aggregation inhibitors such as clopidogrel and acetylsalicylic acid (ASA) or non steroidal antiinflammatory drugs (NSAID), as well as the presence of esophagitis, gastritis or gastroesophageal reflux.

Risk factors
Table 5 summarises factors which may increase the haemorrhagic risk.

Table 5: Factors which may increase the haemorrhagic risk

	Risk factor
Pharmacodynamic and kinetic factors	Age ≥ 75 years
Factors increasing dabigatran plasma levels	Major: • Moderate renal impairment in adult patients (30-50 mL/min CrCL) • Strong P-gp inhibitors (see section 4.3 and 4.5) • Mild to moderate P-gp inhibitorco-medication (e.g. amiodarone, verapamil, quinidine and ticagrelor; see section 4.5) Minor: • Low body weight (< 50 kg) in adult patients
Pharmacodynamic interactions (see section 4.5)	• ASA and other platelet aggregation inhibitors such as clopidogrel • NSAIDs • SSRIs or SNRIs • Other medicinal products which may impair haemostasis
Diseases / procedures with special haemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Recent biopsy, major trauma

	• Bacterial endocarditis • Esophagitis, gastritis or gastroesophageal reflux

Limited data is available in adult patients < 50 kg (see section 5.2).

The concomitant use of dabigatran etexilate with P-gp-inhibitors has not been studied in paediatric patients but may increase the risk of bleeding (see section 4.5).

Precautions and management of the haemorrhagic risk
For the management of bleeding complications, see also section 4.9.

Benefit-risk assessment
The presence of lesions, conditions, procedures and/or pharmacological treatment (such as NSAIDs, antiplatelets, SSRIs and SNRIs, see section 4.5), which significantly increase the risk of major bleeding requires a careful benefit-risk assessment. Dabigatran etexilate should only be given if the benefit outweighs bleeding risks.

Limited clinical data are available for paediatric patients with risk factors, including patients with active meningitis, encephalitis and intracranial abscess (see section 5.1). In these patients, dabigatran etexilate should only be given if the expected benefit outweighs bleeding risks.

Close clinical surveillance
Close observation for signs of bleeding or anaemia is recommended throughout the treatment period, especially if risk factors are combined (see table 5 above). Particular caution should be exercised when dabigatran etexilate is co-administered with verapamil, amiodarone, quinidine or clarithromycin (P-gp inhibitors) and particularly in the occurrence of bleeding, notably in patients having a reduced renal function (see section 4.5).
Close observation for signs of bleeding is recommended in patients concomitantly treated with NSAIDs (see section 4.5).

Discontinuation of dabigatran etexilate
Patients who develop acute renal failure must discontinue dabigatran etexilate (see also section 4.3).

When severe bleedings occur, treatment must be discontinued, the source of bleeding investigated and use of the specific reversal agent (idarucizumab) may be considered in adult patients. The efficacy and safety of idarucizumab have not been established in paediatric patients. Haemodialysis can remove dabigatran.

Use of proton-pump inhibitors
The administration of a proton-pump inhibitor (PPI) can be considered to prevent GI bleeding. In case of paediatric patients local labeling recommendations for proton pump inhibitors have to be followed.

Laboratory coagulation parameters
Although this medicinal product does not in general require routine anticoagulant monitoring, the measurement of dabigatran related anticoagulation may be helpful to detect excessive high exposure to dabigatran in the presence of additional risk factors.

Diluted thrombin time (dTT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information, but results should be interpreted with caution due to inter-test variability (see section 5.1). The International Normalised Ratio (INR) test is unreliable in patients on dabigatran etexilate and false positive INR elevations have been reported. Therefore, INR tests should not be performed.

Table 6 shows coagulation test thresholds at trough for adult patients that may be associated with an increased risk of bleeding. Respective thresholds for paediatric patients are not known (see section 5.1)

Table 6 : Coagulation test thresholds at trough for adult patients that may be associated with an increased risk of bleeding

Test (trough value)	Indication	
	Primary prevention of VTE in orthopaedic surgery	SPAF and DVT/PE

dTT [ng/mL]	> 67	> 200
ECT [x-fold upper limit of normal]	No data	> 3
aPTT [x-fold upper limit of normal]	> 1.3	> 2
INR	Should not be performed	Should not be performed

Use of fibrinolytic medicinal products for the treatment of acute ischemic stroke
The use of fibrinolytic medicinal products for the treatment of acute ischemic stroke may be considered if the patient presents with a dTT, ECT or aPTT not exceeding the upper limit of normal (ULN) according to the local reference range.

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

Patients can stay on dabigatran etexilate while being cardioverted. There are no data available for 110 mg twice daily dabigatran etexilate treatment in patients undergoing catheter ablation for atrial fibrillation (see section 4.2).

Caution should be exercised when treatment is temporarily discontinued for interventions and anticoagulant monitoring is warranted. Clearance of dabigatran in patients with renal insufficiency may take longer (see section 5.2). This should be considered in advance of any procedures. In such cases a coagulation test (see sections 4.4 and 5.1) may help to determine whether haemostasis is still impaired.

Emergency surgery or urgent procedures
Dabigatran etexilate should be temporarily discontinued. When rapid reversal of the anticoagulation effect is required the specific reversal agent (idarucizumab) to dabigatran etexilate is available for adult patients. The efficacy and safety of idarucizumab have not been established in paediatric patients. Haemodialysis can remove dabigatran.

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

Subacute surgery/interventions
Dabigatran etexilate should be temporarily discontinued. A surgery / intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed the risk of bleeding may be increased. This risk of bleeding should be weighed against the urgency of intervention.

Elective surgery
If possible, dabigatran etexilate should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete haemostasis may be required consider stopping dabigatran etexilate 2-4 days before surgery.

Table 7 summarises discontinuation rules before invasive or surgical procedures for adult patients.

Table 7: Discontinuation rules before invasive or surgical procedures for adult patients

Renal function (CrCL in mL/min)	Estimated half-life (hours)	Dabigatran etexilate should be stopped 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)

Discontinuation rules before invasive or surgical procedures for paediatric patients are summarised in table 8.

Table 8: Discontinuation rules before invasive or surgical procedures for paediatric patients

Renal function	Stop dabigatran before elective surgery

(eGFR in mL/min/1.73m^2)	
> 80	24 hours before
50 – 80	2 days before
< 50	These patients have not been studied (see section 4.3).

Spinal anaesthesia/epidural anaesthesia/lumbar puncture
Procedures such as spinal anaesthesia may require complete haemostatic function.

The risk of spinal or epidural haematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 2 hours should elapse before the administration of the first dose of dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

Postoperative phase
Dabigatran etexilate treatment should be resumed / started after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established.

Patients at risk for bleeding or patients at risk of overexposure, notably patients with reduced renal function (see also table 5), should be treated with caution (see sections 4.4 and 5.1).

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

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

Hepatic impairment

Patients with elevated liver enzymes > 2 ULN were excluded in the main trials. No treatment experience is available for this subpopulation of patients, and therefore the use of dabigatran etexilate is not recommended in this population. Hepatic impairment or liver disease expected to have any impact on survival is contraindicated (see section 4.3).

Interaction with P-gp inducers
Concomitant administration of P-gp inducers is expected to result in decreased dabigatran plasma concentrations, and should be avoided (see sections 4.5 and 5.2).

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

Myocardial Infarction (MI)
In the phase III study RE-LY (SPAF, see section 5.1) the overall rate of MI was 0.82, 0.81, and 0.64% / year for dabigatran etexilate 110 mg twice daily, dabigatran etexilate 150 mg twice daily and warfarin, respectively, an increase in relative risk for dabigatran of 29% and 27% compared to warfarin. Irrespective of therapy, the highest absolute risk of MI was seen in the following subgroups, with similar relative risk: patients with previous MI, patients ≥ 65 years with either diabetes or coronary artery disease, patients with left ventricular ejection fraction < 40%, and patients with moderate renal dysfunction. Furthermore a higher risk of MI was seen in patients concomitantly taking ASA plus clopidogrel or clopidogrel alone.

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

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

Active cancer patients (DVT/PE, paediatric VTE)
The efficacy and safety have not been established for DVT/PE patients with active cancer. There is limited data on efficacy and safety for paediatric patients with active cancer.

Paediatric population
For some very specific paediatric patients, e.g. patients with small bowel disease where absorption may be affected, use of an anticoagulant with parenteral route of administration should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Transporter interactions

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors (see table 9) is expected to result in increased dabigatran plasma concentrations.

If not otherwise specifically described, close clinical surveillance (looking for signs of bleeding or anaemia) is required when dabigatran is co-administered with strong P-gp inhibitors. Dose reductions may be required in combination with some P-gp inhibitors (see sections 4.2, 4.3, 4.4 and 5.1).

Table 9: Transporter interactions

P-gp inhibitors	
Concomitant use contraindicated (see section 4.3)	
Ketoconazole	Ketoconazole increased total dabigatran $AUC_{0-\infty}$ and C_{max} values by 2.38-fold and 2.35-fold, respectively, after a single oral dose of 400 mg, and by 2.53-fold and 2.49-fold, respectively, after multiple oral dosing of 400 mg ketoconazole once daily.
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, respectively, after multiple dosing of 400 mg dronedarone bid, and about 2.1-fold and 1.9-fold, respectively, after a single dose of 400 mg.
Itraconazole, cyclosporine	Based on *in vitro* results a similar effect as with ketoconazole may be expected.
Glecaprevir / pibrentasvir	The concomitant use of dabigatran etexilate with the fixed-dose combination of the P-gp inhibitors glecaprevir/pibrentasvir has been shown to increase exposure of dabigatran and may increase the risk of bleeding.
Concomitant use not recommended	
Tacrolimus	Tacrolimus has been found *in vitro* to have a similar level of inhibitory effect on P- gp as that seen with itraconazole and cyclosporine. Dabigatran etexilate has not been clinically studied together with tacrolimus. However, limited clinical data with another P-gp substrate (everolimus) suggest that the inhibition of P-gp with tacrolimus is weaker than that observed with strong P-gp inhibitors.

Cautions to be exercised in case concomitant use (see sections 4.2 and 4.4)	
Verapamil	When dabigatran etexilate (150 mg) was co-administered 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 sections 4.2 and 4.4). The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to the dabigatran etexilate intake (increase of C_{max} by about 2.8-fold and AUC by about 2.5-fold). The effect was progressively decreased with administration of an extended release formulation (increase of C_{max} by about 1.9-fold and AUC by about 1.7-fold) or administration of multiple doses of verapamil (increase of C_{max} by about 1.6-fold and AUC by about 1.5-fold). There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increase of C_{max} by about 1.1-fold and AUC by about 1.2-fold). This is explained by completed dabigatran absorption after 2 hours.
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, respectively. In view of the long half-life of amiodarone the potential for an interaction may exist for weeks after discontinuation of amiodarone (see sections 4.2 and 4.4).
Quinidine	Quinidine was given as 200 mg dose every 2nd hour up to a total dose of 1,000 mg. Dabigatran etexilate was given twice daily 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 1.53-fold and 1.56-fold, respectively with concomitant quinidine (see sections 4.2 and 4.4).
Clarithromycin	When clarithromycin (500 mg twice daily) was administered together with dabigatran etexilate in healthy volunteers, increase of AUC by about 1.19-fold and C_{max} by about 1.15-fold was observed.
Ticagrelor	When a single dose of 75 mg 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, respectively. After multiple doses of ticagrelor 90 mg b.i.d. the increase of dabigatran exposure is 1.56-fold and 1.46- fold 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 $C_{max,ss}$ by 1.49-fold and 1.65-fold, 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, respectively, compared with dabigatran etexilate given alone. This staggered intake is

	the recommended administration for start of ticagrelor with a loading dose. Concomitant administration of 90 mg ticagrelor b.i.d. (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.
Posaconazole	Posaconazole also inhibits P-gp to some extent but has not been clinically studied. Caution should be exercised when dabigatran etexilate is co-administered with posaconazole.
P-gp inducers	
Concomitant use should be avoided.	
e.g. rifampicin, St. John´s wort (Hypericum perforatum), carbamazepine, or phenytoin	Concomitant administration is expected to result in decreased dabigatran concentrations. Pre-dosing of the probe inducer rifampicin at a dose of 600 mg once daily for 7 days decreased total dabigatran peak and total exposure by 65.5% and 67%, respectively. The inducing effect was diminished resulting in dabigatran exposure close to the reference by day 7 after cessation of rifampicin treatment. No further increase in bioavailability was observed after another 7 days.
Protease inhibitors such as ritonavir	
Concomitant use not recommended	
e.g. ritonavir and its combinations with other protease inhibitors	These affect P-gp (either as inhibitor or as inducer). They have not been studied and are therefore not recommended for concomitant treatment with dabigatran etexilate.
P-gp substrate	
Digoxin	In a study performed with 24 healthy subjects, when dabigatran etexilate was co-administered with digoxin, no changes on digoxin and no clinically relevant changes on dabigatran exposure have been observed.

Anticoagulants and antiplatelet aggregation medicinal products

There is no or only limited experience with the following treatments which may increase the risk of bleeding when used concomitantly with dabigatran etexilate: anticoagulants such as unfractionated heparin (UFH), low molecular weight heparins (LMWH), and heparin derivatives (fondaparinux, desirudin), thrombolytic medicinal products, and vitamin K antagonists, rivaroxaban or other oral anticoagulants (see section 4.3), and antiplatelet aggregation medicinal products such as GPIIb/IIIa receptor antagonists, ticlopidine, prasugrel, ticagrelor, dextran, and sulfinpyrazone (see section 4.4).

From the data collected in the phase III study RE-LY (see section 5.1) it was observed that the concomitant use of other oral or parenteral anticoagulants increases major bleeding rates with both dabigatran etexilate and warfarin by approximately 2.5-fold, mainly related to situations when switching from one anticoagulant to another (see section 4.3). Furthermore, concomitant use of antiplatelets, ASA or clopidogrel approximately doubled major bleeding rates with both dabigatran etexilate and warfarin (see section 4.4).

UFH can be administered at doses necessary to maintain a patent central venous or arterial catheter or during catheter ablation for atrial fibrillation (see section 4.3).

Table 10: Interactions with anticoagulants and antiplatelet aggregation medicinal products

NSAIDs	NSAIDs given for short-term analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use in the RE-LY study, NSAIDs increased the risk of bleeding by approximately 50% on both dabigatran etexilate and warfarin.
Clopidogrel	In young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times compared to clopidogrel monotherapy. In addition, dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ and the coagulation measures for dabigatran effect or the inhibition of platelet aggregation as measure of clopidogrel effect remained essentially unchanged comparing combined treatment and the respective mono-treatments. With a loading dose of 300 mg or 600 mg clopidogrel, dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ were increased by about 30-40% (see section 4.4) .
ASA	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 (see section 4.4).
LMWH	The concomitant use of LMWHs, such as enoxaparin and dabigatran etexilate has not been specifically investigated. After switching from 3-day treatment of once daily 40 mg enoxaparin s.c., 24 hours after the last dose of enoxaparin the exposure to dabigatran was slightly lower than that after administration of dabigatran etexilate (single dose of 220 mg) alone. A higher anti-FXa/FIIa activity was observed after dabigatran etexilate administration with enoxaparin pre-treatment compared to that after treatment with dabigatran etexilate alone. This is considered to be due to the carry-over effect of enoxaparin treatment, and regarded as not clinically relevant. Other dabigatran related anti-coagulation tests were not changed significantly by the pre-treatment of enoxaparin.

Other interactions

Table 11: Other interactions

Selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs)	
SSRIs, SNRIs	SSRIs and SNRIs increased the risk of bleeding in RE-LY in all treatment groups
Substances influencing gastric pH	
Pantoprazole	When dabigatran etexilate was co-administered with pantoprazole, a decrease in the dabigatran AUC of approximately 30% was observed. Pantoprazole and other proton-pump inhibitors (PPI) were co-administered with dabigatran etexilate in clinical trials, and concomitant PPI treatment did not appear to reduce the efficacy of dabigatran.
Ranitidine	Ranitidine administration together with dabigatran etexilate had no clinically relevant effect on the extent of absorption of dabigatran.

Interactions linked to dabigatran etexilate and dabigatran metabolic profile

Dabigatran etexilate and dabigatran are not metabolised by the cytochrome P450 system and have no *in vitro* effects on human cytochrome P450 enzymes. Therefore, related medicinal product interactions are not expected with dabigatran.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should avoid pregnancy during treatment with dabigatran.

Pregnancy

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

Dabigatran should not be used during pregnancy unless clearly necessary.

Breast-feeding

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

Fertility

No human data available.

In animal studies an effect on female fertility was observed in the form of a decrease in implantations and an increase in pre-implantation loss at 70 mg/kg (representing a 5-fold higher plasma exposure level compared to patients). No other effects on female fertility were observed. There was no influence on male fertility. At doses that were toxic to the mothers (representing a 5- to 10-fold higher plasma exposure level to patients), a decrease in foetal body weight and embryofoetal viability along with an increase in foetal variations were observed in rats and rabbits. In the pre- and post-natal study, an increase in foetal mortality was observed at doses that were toxic to the dams (a dose corresponding to a plasma exposure level 4-fold higher than observed in patients).

4.7 Effects on ability to drive and use machines

Dabigatran etexilate has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Dabigatran etexilate has been evaluated in clinical trials overall in approximately 64,000 patients; thereof approximately 35,000 patients were treated with dabigatran etexilate.

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

The most commonly reported events are bleedings occurring in approximately 14% of patients treated short-term for elective hip or knee replacement surgery, 16.6% in patients with atrial fibrillation treated long-term for the prevention of stroke and systemic embolism, and in 14.4% of adult patients treated for DVT/PE. Furthermore, bleeding occurred in 19.4% of patients in the DVT/PE prevention trial RE- MEDY (adult patients) and in 10.5% of patients in the DVT/PE prevention trial RE-SONATE (adult patients).

Since the patient populations treated in the three indications are not comparable and bleeding events are distributed over several System Organ Classes (SOC), a summary description of major and any bleeding are broken down by indication and provided in tables 13-17 below.

Although low 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.

Tabulated list of adverse reactions

Table 12 shows the adverse reactions identified from studies and post-marketing data in the indications primary VTE prevention after hip or knee replacement surgery, prevention of thromboembolic stroke and systemic embolism in patients with atrial fibrillation, DVT/PE treatment and DVT/PE prevention. They are ranked under headings of System Organ Class (SOC) and frequency using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 12: Adverse reactions

	Frequency		
SOC / Preferred term.	Primary VTE prevention after hip or knee replacement surgery	Stroke and systemic embolism prevention in patients with atrial fibrillation	DVT/PE treatment and DVT/PE prevention
Blood and lymphatic system disorders			
Anaemia	Uncommon	Common	Uncommon
Haemoglobin decreased	Common	Uncommon	Not known
Thrombocytopenia	Rare	Uncommon	Rare
Haematocrit decreased	Uncommon	Rare	Not known
Neutropenia	Not known	Not known	Not known
Agranulocytosis	Not known	Not known	Not known
Immune system disorder			
Drug hypersensitivity	Uncommon	Uncommon	Uncommon
Rash	Rare	Uncommon	Uncommon
Pruritus	Rare	Uncommon	Uncommon
Anaphylactic reaction	Rare	Rare	Rare
Angioedema	Rare	Rare	Rare
Urticaria	Rare	Rare	Rare
Bronchospasm	Not known	Not known	Not known
Nervous system disorders			
Intracranial haemorrhage	Rare	Uncommon	Rare
Vascular disorders			
Haematoma	Uncommon	Uncommon	Uncommon
Haemorrhage	Rare	Uncommon	Uncommon
Wound haemorrhage	Uncommon	-	
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Uncommon	Common	Common
Haemoptysis	Rare	Uncommon	Uncommon
Gastrointestinal disorders			
Gastrointestinal haemorrhage	Uncommon	Common	Common
Abdominal pain	Rare	Common	Uncommon
Diarrhoea	Uncommon	Common	Uncommon
Dyspepsia	Rare	Common	Common
Nausea	Uncommon	Common	Uncommon
Rectal haemorrhage	Uncommon	Uncommon	Common
Haemorrhoidal haemorrhage	Uncommon	Uncommon	Uncommon
Gastrointestinal ulcer, including oesophageal ulcer	Rare	Uncommon	Uncommon
Gastroesophagitis	Rare	Uncommon	Uncommon
Gastroesophageal reflux disease	Rare	Uncommon	Uncommon
Vomiting	Uncommon	Uncommon	Uncommon
Dysphagia	Rare	Uncommon	Rare
Hepatobiliary disorders			
Hepatic function abnormal/ Liver function Test abnormal	Common	Uncommon	Uncommon
Alanine aminotransferase increased	Uncommon	Uncommon	Uncrommon
Aspartate aminotransferase increased	Uncommon	Uncommon	Uncommon

Hepatic enzyme increased	Uncommon	Rare	Uncommon
Hyperbilirubinaemia	Uncommon	Rare	Not known
Skin and subcutaneous tissue disorder			
Skin haemorrhage	Uncommon	Common	Common
Alopecia	Not known	Not known	Not known
Musculoskeletal and connective tissue disorders			
Haemarthrosis	Uncommon	Rare	Uncommon
Renal and urinary disorders			
Genitourological haemorrhage, including haematuria	Uncommon	Common	Common
General disorders and administration site conditions			
Injection site haemorrhage	Rare	Rare	Rare
Catheter site haemorrhage	Rare	Rare	Rare
Bloody discharge	Rare	-	
Injury, poisoning and procedural complications			
Traumatic haemorrhage	Uncommon	Rare	Uncommon
Incision site haemorrhage	Rare	Rare	Rare
Post procedural haematoma	Uncommon	-	-
Post procedural haemorrhage	Uncommon	-	
Anaemia postoperative	Rare	-	-
Post procedural discharge	Uncommon	-	-
Wound secretion	Uncommon	-	-
Surgical and medical procedures			
Wound drainage	Rare	-	-
Post procedural drainage	Rare	-	-

Description of selected adverse reactions

Bleeding reactions

Due to the pharmacological mode of action, the use of dabigatran etexilate may be associated with an increased risk of occult or overt bleeding from any tissue or organ. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia. In the clinical studies mucosal bleedings (e.g. gastrointestinal, genitourinary) were seen more frequently during long term dabigatran etexilate treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit is of value to detect occult bleeding. The risk of bleedings may be increased in certain patient groups e.g. those patients with moderate renal impairment and/or on concomitant treatment affecting haemostasis or strong P-gp inhibitors (see section 4.4 Haemorrhagic risk). Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock.

Known bleeding complications such as compartment syndrome and acute renal failure due to hypoperfusion and anticoagulant-related nephropathy (ARN) in patients with predisposing risk factors have been reported for dabigatran etexilate. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient. For adult patients, a specific reversal agent for dabigatran, idarucizumab, is available in case of uncontrollable bleeding (see section 4.9).

Primary prevention of VTE in orthopaedic surgery

The table 13 shows the number (%) of patients experiencing the adverse reaction bleeding during the treatment period in the VTE prevention in the two pivotal clinical trials, according to dose.

Table 13: Number (%) of patients experiencing the adverse reaction bleeding

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

Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors

The table 14 shows bleeding events broken down to major and any bleeding in the pivotal study testing the prevention of thromboembolic stroke and systemic embolism in patients with atrial fibrillation.

Table 14: Bleeding events in a study testing the prevention of thromboembolic stroke and systemic embolism in patients with atrial fibrillation

	Dabigatran etexilate 110 mg twice daily	Dabigatran etexilate 150 mg twice daily	Warfarin
Subjects randomized	6,015	6,076	6,022
Major bleeding	347 (2.92%)	409 (3.40%)	426 (3.61%)
Intracranial bleeding	27 (0.23%)	39 (0.32%)	91 (0.77%)
GI bleeding	134 (1.13%)	192 (1.60%)	128 (1.09%)
Fatal bleeding	26 (0.22%)	30 (0.25%)	42 (0.36%)
Minor bleeding	1,566 (13.16%)	1,787 (14.85%)	1,931 (16.37%)
Any bleeding	1,759 (14.78%)	1,997 (16.60%)	2,169 (18.39%)

Subjects randomized to dabigatran etexilate 110 mg twice daily or 150 mg twice daily had a significantly lower risk for life-threatening bleeds 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 110 mg dabigatran etexilate twice daily had a significantly lower risk for major bleeds compared with warfarin (hazard ratio 0.81 [p=0.0027]). Subjects randomized to 150 mg dabigatran etexilate twice daily had a significantly higher risk for major GI bleeds compared with warfarin (hazard ratio 1.48 [p=0.0005]. This effect was seen primarily in patients ≥ 75 years.
The clinical benefit of dabigatran with regard to stroke and systemic embolism prevention and decreased risk of ICH compared to warfarin is preserved across individual subgroups, e.g. renal impairment, age, concomitant medicinal product use such as anti-platelets or P-gp inhibitors. While certain patient subgroups are at an increased risk of major bleeding when treated with an anticoagulant, the excess bleeding risk for dabigatran is due to GI bleeding, typically seen within the first 3-6 months following initiation of dabigatran etexilate therapy.

Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults (DVT/PE treatment)

Table 15 shows bleeding events in the pooled pivotal studies RE-COVER and RE-COVER II testing the treatment of DVT and PE. In the pooled studies the primary safety endpoints of major bleeding, major or clinically relevant bleeding and any bleeding were significantly lower than warfarin at a nominal alpha level of 5%.

Table 15: Bleeding events in the studies RE-COVER and RE-COVER II testing the treatment of DVT and PE

	Dabigatran etexilate 150 mg twice daily	Warfarin	Hazard ratio vs. warfarin (95% confidence interval)
Patients included in safety analysis	2,456	2,462	
Major bleeding events	24 (1.0%)	40 (1.6%)	0.60 (0.36, 0.99)
Intracranial Bleeding	2 (0.1%)	4 (0.2%)	0.50 (0.09, 2.74)
Major GI bleeding	10 (0.4%)	12 (0.5%)	0.83 (0.36, 1.93)
Life-threatening bleed	4 (0.2%)	6 (0.2%)	0.66 (0.19, 2.36)
Major bleeding events/clinically relevant bleeds	109 (4.4%)	189 (7.7%)	0.56 (0.45, 0.71)
Any bleeding	354 (14.4%)	503 (20.4%)	0.67 (0.59, 0.77)
Any GI bleeding	70 (2.9%)	55 (2.2%)	1.27 (0.90, 1.82)

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 etexilate therapy. All bleeding events which occurred during warfarin therapy are included except for those during the overlap period between warfarin and parenteral therapy.

Table 16 shows bleeding events in pivotal study RE-MEDY testing prevention of DVT and PE. Some bleeding events (MBEs/CRBEs; any bleeding) were significantly lower at a nominal alpha level of 5% in patients receiving dabigatran etexilate as compared with those receiving warfarin.

Table 16: Bleeding events in study RE-MEDY testing prevention of DVT and PE

	Dabigatran etexilate 150 mg twice daily	Warfarin	Hazard ratio vs warfarin (95% Confidence Interval)
Treated patients	1,430	1,426	
Majory bleeding events	13 (0.9%)	25 (1.8%)	0.54 (0.25, 1.16)
Intracranial bleeding	2 (0.1%)	4 (0.3%)	Not calculable*
Major GI bleeding	4 (0.3%)	8 (0.5%)	Not calculable*
Life-threatening bleed	1 (0.1%)	3 (0.2%))	Not calculable*
Major bleeding event /clinically relevant bleeds	80 (5.6%)	145 (10.2%)	0.55 (0.41, 0.72)
Any bleeding	278 (19.4%)	373 (26.2%)	0.71 (0.61, 0.83)
Any GI bleeds	45 (3.1%)	32 (2.2%)	1.39 (0.87, 2.20)

*HR not estimable as there is no event in either one cohort/treatment

Table 17 shows bleeding events in pivotal study RE-SONATE testing prevention of DVT and PE. The rate of the combination of MBEs/CRBEs and the rate of any bleeding was significantly lower at a nominal alpha level of 5% in patients receiving placebo as compared with those receiving dabigatran etexilate.

Table 17: Bleeding events in study RE-SONATE testing prevention of DVT and PE

	Dabigatran etexilate 150 mg twice daily	Placebo	Hazard ratio vs placebo (95% confidence interval)
Treated patients	684	659	
Major bleeding events	2 (0.3%)	0	Not calculable*
Intracranial bleeding	0	0	Not calculable*
Major GI bleeding	2 (0.3%)	0	Not calculable*
Life-threatening bleeds	0	0	Not calculable*
Major bleeding event/clinical relevant bleeds	36 (5.3%)	13 (2.0%)	2.69 (1.43, 5.07)
Any bleeding	72 (10.5%)	40 (6.1%)	1.77 (1.20, 2.61)
Any GI bleeds	5 (0.7%)	2 (0.3%)	2.38 (0.46, 12.27)

*HR not estimable as there is no event in either one treatment.

Agranulocytosis and neutropenia

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Agranulocytosis and neutropenia have been reported very rarely during post approval use of dabigatran etexilate. Because adverse reactions are reported in the postmarketing surveillance setting from a population of uncertain size, it is not possible to reliably determine their frequency. The reporting rate was estimated as 7 events per 1 million patient years for agranulocytosis and as 5 events per 1 million patient years for neutropenia.

Paediatric population

The safety of dabigatran etexilate in the treatment of VTE and prevention of recurrent VTE in paediatric patients was studied in two phase III trials (DIVERSITY and 1160.108). In total, 328 paediatric patients had been treated with dabigatran etexilate. The patients received age and weight adjusted doses of an age-appropriate formulation of dabigatran etexilate.
Overall, the safety profile in children is expected to be the same as in adults.
In total, 26% of paediatric patients treated with dabigatran etexilate for VTE and for prevention of recurrent VTE experienced adverse reactions.

Tabulated list of adverse reactions

Table 18 shows the adverse reactions identified from the studies in the treatment of VTE and prevention of recurrent VTE in paediatric patients. They are ranked under headings of System Organ Class (SOC) and frequency using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 18: Adverse reactions

	Frequency
SOC / Preferred term.	treatment of VTE and prevention of recurrent VTE in paediatric patients
Blood and lymphatic system disorders	
Anaemia	Common
Haemoglobin decreased	Uncommon
Thrombocytopenia	Common
Haematocrit decreased	Uncommon
Neutropenia	Uncommon
Agranulocytosis	Not known
Immune system disorder	
Drug hypersensitivity	Uncommon
Rash	Common
Pruritus	Uncommon
Anaphylactic reaction	Not known
Angioedema	Not known
Urticaria	Common
Bronchospasm	Not known
Nervous system disorders	
Intracranial haemorrhage	Uncommon
Vascular disorders	
Haematoma	Common
Haemorrhage	Not known
Respiratory, thoracic and mediastinal disorders	
Epistaxis	Common
Haemoptysis	Uncommon
Gastrointestinal disorders	
Gastrointestinal haemorrhage	Uncommon
Abdominal pain	Uncommon
Diarrhoea	Common
Dyspepsia	Common
Nausea	Common
Rectal haemorrhage	Uncommon
Haemorrhoidal haemorrhage	Not known
Gastrointestinal ulcer, including oesophageal ulcer	Not known
Gastroesophagitis	Uncommon
Gastroesophageal reflux disease	Common
Vomiting	Common
Dysphagia	Uncommon
Hepatobiliary disorders	
Hepatic function abnormal/ Liver function Test abnormal	Not known
Alanine aminotransferase increased	Uncommon
Aspartate aminotransferase increased	Uncommon
Hepatic enzyme increased	Common
Hyperbilirubinaemia	Uncommon
Skin and subcutaneous tissue disorder	

Skin haemorrhage	Uncommon
Alopecia	Common
Musculoskeletal and connective tissue disorders	
Haemarthrosis	Not known
Renal and urinary disorders	
Genitourological haemorrhage, including haematuria	Uncommon
General disorders and administration site conditions	
Injection site haemorrhage	Not known
Catheter site haemorrhage	Not known
Injury, poisoning and procedural complications	
Traumatic haemorrhage	Uncommon
Incision site haemorrhage	Not known

Bleeding reactions

In the two phase III trials in the indication treatment of VTE and prevention of recurrent VTE in paediatric patients, a total of 7 patients (2.1%) had a major bleeding event, 5 patients (1.5%) a clinically relevant non-major bleeding event and 75 patients (22.9%) a minor bleeding event. The frequency of bleeding events was overall higher in the oldest age group (12 to <18 years: 28.6%) than in the younger age groups (birth to <2 years: 23.3%; 2 to <12 years: 16.2%). Major or severe bleeding, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Dabigatran etexilate doses beyond those recommended expose the patient to increased risk of bleeding.

In case of an overdose suspicion, coagulation tests can help to determine a bleeding risk (see sections 4.4 and 5.1). A calibrated quantitative dTT test or repetitive dTT measurements allow prediction of the time by when certain dabigatran levels will be reached (see section 5.1), also in case additional measures e.g. dialysis have been initiated.

Excessive anticoagulation may require interruption of dabigatran etexilate treatment. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. As protein binding is low, dabigatran can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies (see section 5.2).

Management of bleeding complications

In the event of haemorrhagic complications, dabigatran etexilate treatment must be discontinued and the source of bleeding investigated. Depending on the clinical situation appropriate supportive treatment, such as surgical haemostasis and blood volume replacement, should be undertaken at the prescriber's discretion.
For adult patients in situations when rapid reversal of the anticoagulant effect of dabigatran etexilate is required the specific reversal agent (idarucizumab) antagonizing the pharmacodynamic effect of dabigatran etexilate is available. The efficacy and safety of idarucizumab have not been established in paediatric patients (see section 4.4).

Coagulation factor concentrates (activated or non-activated) or recombinant Factor VIIa may be taken into account. There is some experimental evidence to support the role of these medicinal products in reversing the anticoagulant effect of dabigatran, but data on their usefulness in clinical settings and also on the possible risk of rebound thromboembolism is very limited. Coagulation tests may become unreliable following administration of suggested coagulation factor concentrates. Caution should be exercised when interpreting these tests. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet medicinal products have been used. All symptomatic treatment should be given according to the physician's judgement.

Depending on local availability, a consultation of a coagulation expert should be considered in case of major bleedings.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, direct thrombin inhibitors, ATC code: B01AE07.

Mechanism of action

Dabigatran etexilate is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma.
Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

Pharmacodynamic effects

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

There is a clear correlation between plasma dabigatran concentration and degree of anticoagulant effect based on phase II studies. Dabigatran prolongs the thrombin time (TT), ECT, and aPTT.

The calibrated quantitative diluted TT (dTT) test provides an estimation of dabigatran plasma concentration that can be compared to the expected dabigatran plasma concentrations. When the calibrated dTT assay delivers a dabigatran plasma concentration result at or below the limit of quantification, an additional coagulation assay such as TT, ECT or aPTT should be considered.

The ECT can provide a direct measure of the activity of direct thrombin inhibitors.

The aPTT test is widely available and provides an approximate indication of the anticoagulation intensity achieved with dabigatran. However, the aPTT test has limited sensitivity and is not suitable for precise quantification of anticoagulant effect, especially at high plasma concentrations of dabigatran. Although high aPTT values should be interpreted with caution, a high aPTT value indicates that the patient is anticoagulated.

In general, it can be assumed that these measures of anti-coagulant activity may reflect dabigatran levels and can provide guidance for the assessment of bleeding risk, i.e. exceeding the 90^{th} percentile of dabigatran trough levels or a coagulation assay such as aPTT measured at trough (for aPTT thresholds see section 4.4, table 6) is considered to be associated with an increased risk of bleeding.

Primary prevention of VTE in orthopaedic surgery

Steady state (after day 3) geometric mean dabigatran peak plasma concentration, measured around 2 hours after 220 mg dabigatran etexilate administration, was 70.8 ng/mL, with a range of 35.2-162 ng/mL (25^{th}–75^{th} percentile range).The dabigatran geometric mean trough concentration, measured at the end of the dosing interval (i.e. 24 hours after a 220 mg dabigatran dose), was on average 22.0 ng/mL, with a range of 13.0-35.7 ng/mL (25^{th}-75^{th} percentile range).

In a dedicated study exclusively in patients with moderate renal impairment (creatinine clearance, CrCL 30-50 mL/min) treated with dabigatran etexilate 150 mg QD, the dabigatran geometric mean trough concentration, measured at the end of the dosing interval, was on average 47.5 ng/mL, with a range of 29.6 - 72.2 ng/mL (25^{th}-75^{th} percentile range).

In patients treated for prevention of VTEs after hip or knee replacement surgery with 220 mg dabigatran etexilate once daily,

- the 90^{th} percentile of dabigatran plasma concentrations was 67 ng/mL, measured at trough (20-28 hours after the previous dose) (see section 4.4 and 4.9),
- the 90^{th} percentile of aPTT at trough (20-28 hours after the previous dose) was 51 seconds, which would be 1.3-fold upper limit of normal.

The ECT was not measured in patients treated for prevention of VTEs after hip or knee replacement surgery with 220 mg dabigatran etexilate once daily.

Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors (SPAF)

Steady state geometric mean dabigatran peak plasma concentration, measured around 2 hours after 150 mg dabigatran etexilate administration twice daily, was 175 ng/mL, with a range of 117-275 ng/mL (25^{th}-75^{th} percentile range). The dabigatran geometric mean trough concentration, measured at trough in the morning, at the end of the dosing interval (i.e. 12 hours after the 150 mg dabigatran evening dose), was on average 91.0 ng/mL, with a range of 61.0-143 ng/mL (25^{th}-75^{th} percentile range).

For patients with NVAF treated for prevention of stroke and systemic embolism with 150 mg dabigatran etexilate twice daily,

- the 90^{th} percentile of dabigatran plasma concentrations measured at trough (10-16 hours after the previous dose) was about 200 ng/mL,
- an ECT at trough (10-16 hours after the previous dose), elevated approximately 3-fold upper limit of normal refers to the observed 90^{th} percentile of ECT prolongation of 103 seconds,
- an aPTT ratio greater than 2-fold upper limit of normal (aPTT prolongation of about 80 seconds), at trough (10-16 hours after the previous dose) reflects the 90^{th} percentile of observations.

Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults (DVT/PE)

In patients treated for DVT and PE with 150 mg dabigatran etexilate twice daily, the dabigatran geometric mean trough concentration, measured within 10−16 hours after dose, at the end of the dosing interval (i.e. 12 hours after the 150 mg dabigatran evening dose), was 59.7 ng/ml, with a range of 38.6 - 94.5 ng/ml (25^{th}-75^{th} percentile range). For treatment of DVT and PE, with dabigatran etexilate 150 mg twice daily,

- the 90^{th} percentile of dabigatran plasma concentrations measured at trough (10-16 hours after the previous dose) was about 146 ng/ml,
- an ECT at trough (10-16 hours after the previous dose), elevated approximately 2.3-fold compared to baseline refers to the observed 90^{th} percentile of ECT prolongation of 74 seconds,
- the 90^{th} percentile of aPTT at trough (10-16 hours after the previous dose) was 62 seconds, which would be 1.8-fold compared to baseline.

In patients treated for prevention of recurrent of DVT and PE with 150 mg dabigatran etexilate twice daily no pharmacokinetic data are available.

Clinical efficacy and safety

Ethnic origin
No clinically relevant ethnic differences among Caucasians, African-American, Hispanic, Japanese or Chinese patients were observed.

Clinical trials in VTE prophylaxis following major joint replacement surgery

In 2 large randomized, parallel group, double-blind, dose-confirmatory trials, patients undergoing elective major orthopaedic surgery (one for knee replacement surgery and one for hip replacement surgery) received 75 mg or 110 mg dabigatran etexilate within 1-4 hours of surgery followed by 150 mg or 220 mg once daily thereafter, haemostasis having been secured, or enoxaparin 40 mg on the day prior to surgery and 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 2,076 patients (knee) and 3,494 (hip) were treated respectively.

Composite of total VTE (including pulmonary embolism (PE), proximal and distal deep vein thrombosis (DVT), whatever symptomatic or asymptomatic detected by routine venography) and all-cause mortality constituted the primary end-point for

both studies. Composite of major VTE (including PE and proximal DVT, whatever symptomatic or asymptomatic detected by routine venography) and VTE-related mortality constituted a secondary end-point and is considered of better clinical relevance.

Results of both studies showed that the antithrombotic effect of dabigatran etexilate 220 mg and 150 mg were statistically non-inferior to that of enoxaparin on total VTE and all-cause mortality. The point estimate for incidence of Major VTE and VTE related mortality for the 150 mg dose was slightly worse than enoxaparin (table 19). Better results were seen with the 220 mg dose where the point estimate of Major VTE was slightly better than enoxaparin (table 19).

The clinical studies have been conducted in a patient population with a mean age > 65 years.

There were no differences in the phase 3 clinical studies for efficacy and safety data between men and women.

In the studied patient population of RE-MODEL and RE-NOVATE (5,539 patients treated), 51% suffered from concomitant hypertension, 9% from concomitant diabetes, 9% from concomitant coronary artery disease and 20% had a history of venous insufficiency. None of these diseases showed an impact on the effects of dabigatran on VTE-prevention or bleeding rates.

Data for the major VTE and VTE-related mortality endpoint were homogeneous with regards to the primary efficacy endpoint and are shown in table 19.

Data for the total VTE and all cause mortality endpoint are shown in table 20.

Data for adjudicated major bleeding endpoints are shown in table 21 below.

Table 19: 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 once daily	Dabigatran etexilate 150 mg once daily	Enoxaparin 40 mg
RE-NOVATE (hip)			
N	909	888	917
Incidences (%)	28 (3.1)	38 (4.3)	36 (3.9)
Risk ratio over enoxaparin	0.78	1.09	
95% CI	0.48, 1.27	0.70, 1.70	
RE-MODEL (knee)			
N	506	527	511
Incidences (%)	13 (2.6)	20 (3.8)	18 (3.5)
Risk ratio over enoxaparin	0.73	1.08	
95% CI	0.36, 1.47	0.58, 2.01	

Table 20: Analysis of total VTE and all cause mortality during the treatment period in the RE-NOVATE and the RE-MODEL orthopaedic surgery studies

Trial	Dabigatran etexilate 220 mg once daily	Dabigatran etexilate 150 mg once daily	Enoxaparin 40 mg
RE-NOVATE (hip)			
N	880	874	897
Incidences (%)	53 (6.0)	75 (8.6)	60 (6.7)
Risk ratio over enoxaparin	0.9	1.28	
95% CI	(0.63, 1.29)	(0.93, 1.78)	
RE-MODEL (knee)			
N	503	526	512
Incidences (%)	183 (36.4)	213 (40.5)	193 (37.7)
Risk ratio over enoxaparin	0.97	1.07	
95% CI	(0.82, 1.13)	(0.92, 1.25)	

Table 21: Major bleeding events by treatment in the individual RE-MODEL and the RE-NOVATE studies

Trial	Dabigatran etexilate 220 mg once daily	Dabigatran etexilate 150 mg once daily	Enoxaparin 40 mg
RE-NOVATE (hip)			
Treated patients N	1,146	1,163	1,154
Number of MBE N(%)	23 (2.0)	15 (1.3)	18 (1.6)
RE-MODEL (knee)			
Treated patients N	679	703	694
Number of MBE N(%)	10 (1.5)	9 (1.3)	9 (1.3)

Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors

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-centre, multi-national, randomized parallel group study of two blinded doses of dabigatran etexilate (110 mg and 150 mg twice daily) compared to open-label warfarin in patients with atrial fibrillation at moderate to high risk of stroke and systemic embolism. The primary objective in this study was to determine if dabigatran etexilate was non-inferior to warfarin in reducing the occurrence of the composite endpoint stroke and systemic embolism. Statistical superiority was also analysed.

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 patient population was 64% male, 70% Caucasian and 16% Asian.

For patients randomized to warfarin, the mean percentage of time in therapeutic range (TTR) (INR 2-3) was 64.4% (median TTR 67%).

The RE-LY 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 ICH, total bleeding and major bleeding. The dose of 150 mg twice daily reduces significantly the risk of ischemic and haemorrhagic stroke, vascular death, ICH and total bleeding compared to warfarin. Major bleeding rates with this dose were comparable to warfarin. Myocardial infarction rates were slightly increased with dabigatran etexilate 110 mg twice daily and 150 mg twice daily compared to warfarin (hazard ratio 1.29; p=0.0929 and hazard ratio 1.27; p=0.1240, respectively). With improving monitoring of INR the observed benefits of dabigatran etexilate compared to warfarin diminish.

Tables 22-24 display details of key results in the overall population:

Table 22: Analysis of first occurrence of stroke or systemic embolism (primary endpoint) during the study period in RE-LY

	Dabigatran etexilate 110 mg twice daily	Dabigatran etexilate 150 mg twice daily	Warfarin
Subjects randomized	6,015	6,076	6,022
Stroke and/or systemic embolism			
Incidences (%)	183 (1.54)	135 (1.12)	203 (1.72)
Hazard ratio over warfarin (95% CI)	0.89 (0.73, 1.09)	0.65 (0.52, 0.81)	
p value superiority	p=0.2721	p=0.0001	

% refers to yearly event rate

Table 23: Analysis of first occurrence of ischemic or haemorrhagic strokes during the study period in RE-LY

	Dabigatran etexilate 110 mg twice daily	Dabigatran etexilate 150 mg twice daily	Warfarin
Subjects randomized	6,015	6,076	6,022
Stroke			
Incidences (%)	171 (1.44)	123 (1.02)	187 (1.59)
Hazard ratio vs. warfarin (95% CI)	0.91 (0.74, 1.12)	0.64 (0.51, 0.81)	
p-value	0.3553	0.0001	
Systemic embolism			
Incidences (%)	15 (0.13)	13 (0.11)	21 (0.18)

Hazard ratio vs. warfarin (95% CI)	0.71 (0.37, 1.38)	0.61 (0.30, 1.21)	
p-value	0.3099	0.1582	
Ischemic stroke			
Incidences (%)	152 (1.28)	104 (0.86)	134 (1.14)
Hazard ratio vs. warfarin (95% CI)	1.13 (0.89, 1.42)	0.76 (0.59, 0.98)	
p-value	0.3138	0.0351	
Haemorrhagic stroke			
Incidences (%)	14 (0.12)	12 (0.10)	45 (0.38)
Hazard ratio vs. warfarin (95% CI)	0.31 (0.17, 0.56)	0.26 (0.14, 0.49)	
p-value	0.0001	< 0.0001	

% refers to yearly event rate

Table 24: Analysis of all cause and cardiovascular survival during the study period in RE-LY

	Dabigatran etexilate 110 mg twice daily	Dabigatran etexilate 150 mg twice daily	Warfarin
Subjects randomized	6,015	6,076	6,022
All-cause mortality			
Incidences (%)	446 (3.75)	438 (3.64)	487 (4.13)
Hazard ratio vs. warfarin (95% CI)	0.91 (0.80, 1.03)	0.88 (0.77, 1.00)	
p-value	0.1308	0.0517	
Vascular mortality			
Incidences (%)	289 (2.43)	274 (2.28)	317 (2.69)
Hazard ratio vs. warfarin (95% CI)	0.90 (0.77, 1.06)	0.85 (0.72, 0.99)	
p-value	0.2081	0.0430	

% refers to yearly event rate

Tables 25-26 display results of the primary efficacy and safety endpoint in relevant sub-populations:

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.

Table 25: Hazard Ratio and 95% CI for stroke/systemic embolism by subgroups

Endpoint	Dabigatran etexilate 110 mg twice daily vs. Warfarin	Dabigatran etexilate 150 mg twice daily vs. Warfarin
Age (years)		
< 65	1.10 (0.64, 1.87)	0.51 (0.26, 0.98)
65 ≤ and < 75	0.86 (0.62, 1.19)	0.67 (0.47, 0.95)
≥ 75	0.88 (0.66, 1.17)	0.68 (0.50, 0.92)
≥ 80	0.68 (0.44, 1.05)	0.67 (0.44, 1.02)
CrCL(mL/min)		
30 ≤ and < 50	0.89 (0.61, 1.31)	0.48 (0.31, 0.76)
50 ≤ and < 80	0.91 (0.68, 1.20)	0.65 (0.47, 0.88)
≥ 80	0.81 (0.51, 1.28)	0.69 (0.43, 1.12)

For the primary safety endpoint of major bleeding there was an interaction of treatment effect and age. The relative risk of bleeding with dabigatran compared to warfarin increased with age. Relative risk was highest in patients ≥ 75 years. The concomitant use of antiplatelets ASA or clopidogrel approximately doubles MBE rates with both dabigatran etexilate and warfarin. There was no significant interaction of treatment effects with the subgroups of renal function and $CHADS_2$ score.

Table 26: Hazard Ratio and 95% CI for major bleeds by sub roups

Endpoint	Dabigatran etexilate 110 mg twice daily vs. Warfarin	Dabigatran etexilate 150 mg twice daily vs. Warfarin
Age (years)		

< 65	0.32 (0.18, 0.57)	0.35 (0.20, 0.61)
65 ≤ and < 75	0.71 (0.56, 0.89)	0.82 (0.66, 1.03)
≥ 75	1.01 (0.84, 1.23)	1.19 (0.99, 1.43)
≥ 80	1.14 (0.86, 1.51)	1.35 (1.03, 1.76)
CrCL(mL/min)		
30 ≤ and < 50	1.02 (0.79, 1.32)	0.94 (0.73, 1.22)
50 ≤ and < 80	0.75 (0.61, 0.92)	0.90 (0.74, 1.09)
≥ 80	0.59 (0.43, 0.82)	0.87 (0.65, 1.17)
ASA use	0.84 (0.69, 1.03)	0.97 (0.79, 1.18)
Clopidogrel use	0.89 (0.55, 1.45)	0.92 (0.57, 1.48)

RELY-ABLE (Long term multi-center extension of dabigatran treatment in patients with atrial fibrillation who completed the RE-LY trial)

The RE-LY extension study (RELY-ABLE) provided additional safety information for a 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 110 mg b.i.d. and 150 mg b.i.d.. 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.

Data from non-interventional studies

A non-interventional study (GLORIA-AF) prospectively collected (in its second phase) safety and effectiveness data in newly diagnosed NVAF patients on dabigatran etexilate in a real-world setting. The study included 4,859 patients on dabigatran etexilate (55% treated with 150 mg bid, 43% treated with 110 mg bid, 2% treated with 75 mg bid). Patients were followed-up for 2 years. The mean $CHADS_2$ and HAS-BLED scores were 1.9 and 1.2, respectively. Mean on-therapy follow-up time was 18.3 months. Major bleeding occurred in 0.97 per 100 patient-years. Life-threatening bleeding was reported in 0.46 per 100 patient-years, intracranial haemorrhage in 0.17 per 100 patient-years and gastrointestinal bleeding in 0.60 per 100 patient-years. Stroke occurred in 0.65 per 100 patient-years.

In addition, in a non-interventional study [Graham DJ et al., Circulation. 2015;131:157-164] in more than 134,000 elderly patients with NVAF in the United States (contributing more than 37,500 patient- years of on-therapy follow-up time) dabigatran etexilate (84% patients treated with 150 mg bid, 16% patients treated with 75 mg bid) was associated with a reduced risk of ischemic stroke (hazard ratio 0.80, 95% confidence interval [CI] 0.67 – 0.96), intracranial haemorrhage (hazard ratio 0.34, CI 0.26 – 0.46), and mortality (hazard ratio 0.86, CI 0.77 – 0.96) and increased risk of gastrointestinal bleeding (hazard ratio 1.28, CI 1.14 – 1.44) compared to warfarin. No difference was found for major bleeding (hazard ratio 0.97, CI 0.88 – 1.07).

These observations in real-world settings are consistent with the established safety and efficacy profile for dabigatran etexilate in the RE-LY study in this indication.

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 ASA 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 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.

Treatment of DVT and PE in adults (DVT/PE treatment)

The efficacy and safety was investigated 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 etexilate 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 treatment period.

In the pooled RE-COVER and RE-COVER II studies, a total of 5,153 patients were randomised and 5,107 were treated.

The duration of treatment with fixed dose of dabigatran etexilate 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%.

The trials, demonstrated that treatment with dabigatran etexilate 150 mg twice daily was non-inferior to the treatment with warfarin (non-inferiority margin for RE-COVER, and RE-COVER II: 3.6 for risk difference and 2.75 for hazard ratio).

Table 27: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the pooled studies RE-COVER and RE-COVER II

	Dabigatran etexilate 150 mg twice daily	Warfarin
Treated patients	2,553	2,554
Recurrent symptomatic VTE and VTE-related death	68 (2.7%)	62 (2.4%)
Hazard ratio vs warfarin (95% confidence interval)	1.09 (0.77, 1.54)	
Secondary efficacy endpoints		
Recurrent symptomatic VTE and all-cause deaths	109 (4.3%)	104 (4.1%)
95% confidence interval	3.52, 5.13	3.34, 4.91
Symptomatic DVT	45 (1.8%)	39 (1.5%)
95% confidence interval	1.29, 2.35	1.09, 2.08
Symptomatic PE	27 (1.1%)	26 (1.0%)
95% confidence interval	0.70, 1.54	0.67, 1.49
VTE-related deaths	4 (0.2%)	3 (0.1%)

95% confidence interval	0.04, 0.40	0.02, 0.34
All-cause deaths	51 (2.0%)	52 (2.0%)
95% confidence interval	1.49, 2.62	1.52, 2.66

Prevention of recurrent DVT and PE in adults (DVT/PE prevention)

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

The objective of the RE-MEDY study was to compare the safety and efficacy of oral dabigatran etexilate (150 mg bid) to warfarin (target INR 2.0-3.0) for the long-term treatment and prevention of recurrent, symptomatic DVT and/or PE. A total of 2,866 patients were randomized and 2,856 patients were treated. Duration of dabigatran etexilate 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 (non-inferiority margin: 2.85 for hazard ratio and 2.8 for risk difference).

Table 28: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the RE-MEDY study

	Dabigatran etexilate 150 mg twice daily	Warfarin
Treated patients	1430	1426
Recurrent symptomatic VTE and VTE- related death	26 (1.8%)	18 (1.3%)
Hazard ratio vs warfarin (95% confidence interval)	1.44 (0.78, 2.64)	
non-inferiority margin	2.85	
Patients with event at 18 months	22	17
Cumulative risk at 18 months (%)	1.7	1.4
Risk difference vs. warfarin (%)	0.4	
95% confidence interval		
non-inferiority margin	2.8	
Secondary efficacy endpoints		
Recurrent symptomatic VTE and all-cause deaths	42 (2.9%)	36 (2.5%)
95% confidence interval	2.12, 3.95	1.77, 3.48
Symptomatic DVT	17 (1.2%)	13 (0.9%)
95% confidence interval	0.69, 1.90	0.49, 1.55
Symptomatic PE	10 (0.7%)	5 (0.4%)
95% confidence interval	0.34, 1.28	0.11, 0.82
VTE-related deaths	1 (0.1%)	1 (0.1%)
95% confidence interval	0.00, 0.39	0.00, 0.39
All-cause deaths	17 (1.2%)	19 (1.3%)
95% confidence interval	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.

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 from 5.6% to 0.4% (relative risk reduction 92% based on hazard ratio) 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 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 (95% CI 0.42, 0.88), p=0.0082).

Table 29: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the RE-SONATE study

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

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 valve replacement surgery (i.e. within the current hospital stay) and in patients who received a mechanical heart valve replacement more than three months ago. More thromboembolic events (mainly strokes and symptomatic/asymptomatic prosthetic valve thrombosis) and more bleeding events were observed with dabigatran etexilate than with warfarin. In the early post-operative patients, major bleeding manifested predominantly as haemorrhagic pericardial effusions, specifically in patients who started dabigatran etexilate early (i.e. on Day 3) after heart valve replacement surgery (see section 4.3).

Paediatric population

Clinical trials in VTE prophylaxis following major joint replacement surgery
Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing dabigatran etexilate in all subsets of the paediatric population for the indication of primary prevention of VTE in patients who have undergone elective total hip replacement surgery or total knee replacement surgery and the indication of prevention of stroke and systemic embolism in patients with NVAF (see section 4.2 for information on paediatric use).

Treatment of VTE and prevention of recurrent VTE in paediatric patients

The DIVERSITY study was conducted to demonstrate the efficacy and safety of dabigatran etexilate compared to standard of care (SOC) for the treatment of VTE in paediatric patients from birth to less than 18 years of age. The study was designed as an

open-label, randomised, parallel-group, noninferiority study. Patients enrolled were randomised according to a 2:1 scheme to either an age-appropriate formulation (capsules, coated granules or oral solution) of dabigatran etexilate (doses adjusted for age and weight) or SOC comprised of low molecular weight heparins (LMWH) or vitamin K antagonists (VKA) or fondaparinux (1 patient 12 years old). The primary endpoint was a composite endpoint of patients with complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality related to VTE. Exclusion criteria included active meningitis, encephalitis and intracranial abscess.
In total, 267 patients had been randomised. Of those, 176 patients were treated with dabigatran etexilate and 90 patients according to SOC (1 randomised patient was not treated). 168 patients were 12 to less than 18 years old, 64 patients 2 to less than 12 years, and 35 patients were younger than 2 years.
Of the 267 randomised patients, 81 patients (45.8%) in the dabigatran etexilate group and 38 patients (42.2%) in the SOC group met the criteria for the composite primary endpoint (complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality-related VTE). The corresponding rate difference demonstrated non-inferiority of dabigatran etexilate to SOC. Consistent results were also generally observed across subgroups: there were no significant differences in the treatment effect for the subgroups by age, sex, region, and presence of certain risk factors. For the 3 different age strata, the proportions of patients that met the primary efficacy endpoint in the dabigatran etexilate and SOC groups, respectively, were 13/22 (59.1%) and 7/13 (53.8%) for patients from birth to <2 years, 21/43 (48.8%) and 12/21 (57.1%) for patients aged 2 to <12 years, and 47/112 (42.0%) and 19/56 (33.9%) for patients aged 12 to <18 years.
Adjudicated major bleeds were reported for 4 patients (2.3%) in the dabigatran etexilate group and 2 patients (2.2%) in the SOC group. There was no statistically significant difference in the time to first major bleeding event. Thirty-eight patients (21.6%) in the dabigatran etexilate arm and 22 patients (24.4%) in the SOC arm had any adjudicated bleeding event, most of them categorised as minor. The combined endpoint of adjudicated major bleeding event (MBE) or clinically relevant non-major (CRNM) bleeding (on treatment) was reported for 6 (3.4%) patients in the dabigatran etexilate group and 3 (3.3%) patients in the SOC group.

An open label, single arm safety prospective cohort, multi-centre, phase III study (1160.108) was conducted to assess the safety of dabigatran etexilate for the prevention of recurrent VTE in paediatric patients from birth to less than 18 years. Patients who required further anticoagulation due to the presence of a clinical risk factor after completing the initial treatment for confirmed VTE (for at least 3 months) or after completing the DIVERSITY study were allowed to be included in the study. Eligible patients received age and weight adjusted doses of an age-appropriate formulation (capsules, coated granules or oral solution) of dabigatran etexilate until the clinical risk factor resolved, or up to a maximum of 12 months. The primary endpoints of the study included the recurrence of VTE, major and minor bleeding events and the mortality (overall and related to thrombotic or thromboembolic events) at 6 and 12 months. Outcome events were adjudicated by an independent blinded adjudication committee.
Overall, 214 patients entered the study; among them 162 patients in age stratum 1 (from 12 to less than 18 years of age), 43 patients in age stratum 2 (from 2 to less than 12 years of age) and 9 patients in age stratum 3 (from birth to less than 2 years of age). During the on-treatment period, 3 patients (1.4%) had an adjudication-confirmed recurrent VTE within the first 12 months after treatment start. Adjudication-confirmed bleeding events during the on-treatment period were reported for 48 patients (22.5%) within the first 12 months. The majority of the bleeding events were minor. In 3 patients (1.4%), an adjudication-confirmed major bleeding event occurred within the first 12 months. For 3 patients (1.4%), adjudication-confirmed CRNM bleeding was reported within the first 12 months. No on-treatment deaths occurred. During the on-treatment period, 3 patients (1.4%) developed postthrombotic syndrome (PTS) or had worsening of PTS within the first 12 months.

5.2 Pharmacokinetic properties

After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran, which is the active form in plasma. The cleavage of the prodrug dabigatran etexilate by esterase-catalysed hydrolysis to the active principle dabigatran is the predominant metabolic reaction. The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate was approximately 6.5%.

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

Absorption
A study evaluating post-operative absorption of dabigatran etexilate, 1-3 hours following surgery, demonstrated relatively slow absorption compared with that in healthy volunteers, showing a smooth plasma concentration-time profile without high peak plasma concentrations. Peak plasma concentrations are reached at 6 hours following administration in a postoperative period due to contributing factors such as anaesthesia, GI paresis, and surgical effects independent of the oral medicinal product formulation. 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 medicinal product administration.

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

C_{max} and AUC were dose proportional.

The oral bioavailability may be increased by 75% after a single dose and 37% at steady state compared to the reference capsule formulation when the pellets are taken without the Hydroxypropylmethylcellulose (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 (see section 4.2).

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
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.

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
Plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of 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. Half-life is prolonged if renal function is impaired as shown in table 30.

Special populations

Renal insufficiency
In phase I studies the exposure (AUC) of dabigatran after the oral administration of dabigatran is approximately 2.7-fold higher in adult volunteers with moderate renal insufficiency (CrCL between 30 and 50 mL/min) than in those without renal insufficiency.

In a small number of adult volunteers with severe renal insufficiency (CrCL 10-30 mL/min), the exposure (AUC) to dabigatran was approximately 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal insufficiency (see sections 4.2, 4.3 and 4.4).

Table 30: Half-life of total dabigatran in healthy subjects and subjects with impaired renal function

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

Additionally, dabigatran exposure (at trough and peak) was assessed in a prospective open label randomized pharmacokinetic study in NVAF patients with severe renal impairment (defined as creatinine clearance [CrCl] 15-30 mL/min) receiving dabigatran etexilate 75 mg twice daily. This regimen resulted in a geometric mean trough concentration of 155 ng/ml (gCV of

76.9%), measured immediately before administration of the next dose and in a geometric mean peak concentration of 202 ng/ml (gCV of 70.6%) measured two hours after the administration of the last dose.

Clearance of dabigatran by haemodialysis was investigated in 7 adult patients with end-stage renal disease (ESRD) without atrial fibrillation. Dialysis was conducted with 700 mL/min dialysate flow rate, four hour duration and a blood flow rate of either 200 mL/min or 350-390 mL/min. This resulted in a removal of 50% to 60% of dabigatran concentrations, respectively. The amount of substance cleared by dialysis is proportional to the blood flow rate up to a blood flow rate of 300 mL/min. The anticoagulant activity of dabigatran decreased with decreasing plasma concentrations and the PK/PD relationship was not affected by the procedure.

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).

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

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

Elderly patients
Specific pharmacokinetic phase I studies with elderly subjects showed an increase of 40 to 60% in the AUC and of more than 25% in C_{max} compared to young subjects.

The effect by age on exposure to dabigatran was confirmed in the RE-LY study with an about 31% higher trough concentration for subjects ≥ 75 years and by about 22% lower trough level for subjects < 65 years compared to subjects between 65 and 75 years (see sections 4.2 and 4.4).

Hepatic impairment
No change in dabigatran exposure was seen in 12 adult subjects with moderate hepatic insufficiency (Child Pugh B) compared to 12 controls (see sections 4.2 and 4.4).

Body weight
The dabigatran trough concentrations were about 20% lower in adult patients with a body weight > 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 (see sections 4.2 and 4.4). Limited clinical data in adult patients < 50 kg are available.

Gender
Active substance exposure in the primary VTE prevention studies was about 40% to 50% higher in female patients and no dose adjustment is recommended. In atrial fibrillation patients females had on average 30% higher trough and post-dose concentrations. No dose adjustment is required (see section 4.2).

Ethnic origin
No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding dabigatran pharmacokinetics and pharmacodynamics.

Paediatric population
Oral administration of dabigatran etexilate according to the protocol defined dosing algorithm resulted in exposure within the range observed in adults with DVT / PE. Based on the pooled analysis of pharmacokinetic data of studies DIVERSITY and 1160.108, the observed geometric mean trough exposures were 53.9 ng/mL, 63.0 ng/mL and 99.1 ng/mL in 0 to < 2-year-old, 2 to < 12-year-old and 12 to < 18-year-old paediatric VTE patients, respectively.

Pharmacokinetic interactions

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Effects observed in the repeated dose toxicity studies were due to the exaggerated pharmacodynamic effect of dabigatran.

An effect on female fertility was observed in the form of a decrease in implantations and an increase in pre-implantation loss at 70 mg/kg (5-fold the plasma exposure level in patients). At doses that were toxic to the mothers (5- to 10-fold the plasma exposure level in patients), a decrease in foetal body weight and viability along with an increase in foetal variations were observed in rats and rabbits. In the pre- and post-natal study, an increase in foetal mortality was observed at doses that were toxic to the dams (a dose corresponding to a plasma exposure level 4-fold higher than observed in patients).

In a juvenile toxicity study conducted in Han Wistar rats, mortality was associated with bleeding events at similar exposures, at which bleeding was seen in adult animals. In both adult and juvenile rats, mortality is considered to be related to the exaggerated pharmacological activity of dabigatran in association with the exertion of mechanical forces during dosing and handling. Data of the juvenile toxicity study did neither indicate an increased sensitivity in toxicity, nor any toxicity specific to juvenile animals.

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

Dabigatran, the active moiety of dabigatran etexilate mesilate, is persistent in the environment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Tartaric acid
Hypromellose
Hydroxypropylcellulose
Talc

Capsule shell
Titanium dioxide (E171)
Indigo carmine (E132)
Carrageenan
Potassium chloride
Hypromellose

Printing ink
Shellac
Iron oxide black (E172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Blister:
This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from light and moisture.

Container:
This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from light and moisture.
Keep the container tightly closed.

6.5 Nature and contents of container

Perforated unit dose blister OPA/Alu/PE+DES//Alu/PE peel-off blister: 10 x 1, 30 x 1, 60 x 1, 100 x 1 hard capsule or multipacks containing 100 (2 packs of 50 x 1) or 180 (3 packs of 60 x 1) hard capsules, in a box.

HDPE container, child resistant tamper evident polypropylene cap: 60 hard capsules or 3 containers of 60 hard capsules, in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

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