For the use of a Cardiologist, Orthopaedic Surgeon, Neurologist, Intensive Care Specialist, Surgeon and Haematologist only

AFOGATRAN 75/110/150

(Dabigatran Etexilate Mesilate Capsules 75 mg/110 mg/150 mg)

COMPOSITION

AFOGATRAN 75

Each capsule contains:
Dabigatran etexilate mesilate 86.48 mg
equivalent to Dabigatran etexilate…….75 mg
Excipients……. q.s.
Approved colours (Indigo Carmine, Yellow oxide of Iron, Titanium dioxide I.P.) are used in capsule shell.

AFOGATRAN 110

Each capsule contains:
Dabigatran etexilate mesilate 126.83 mg
equivalent to Dabigatran etexilate…….110 mg
Excipients……. q.s.
Approved colours (Indigo Carmine, Yellow oxide of Iron, Titanium dioxide I.P.) are used in capsule shell**.**

AFOGATRAN 150

Each capsule contains:
Dabigatran etexilate mesilate 172.95 mg
equivalent to Dabigatran etexilate…….150 mg
Excipients……. q.s.
Approved colours (Indigo Carmine, Yellow oxide of Iron, Titanium dioxide I.P.) are used in capsule shell.

INDICATIONS

- For prevention of stroke, systemic embolism and reduction of vascular mortality in adult patients with atrial fibrillation.
- For the prevention of venous thromboembolic events in patients who have undergone orthopaedic surgery.

DOSAGES AND ADMINISTRATION

Posology (SPAF, DVT/PE)

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

The recommended daily dose of Afogatran is 300 mg taken as one 150 mg capsule twice daily. Therapy should be continued long term.

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

The recommended daily dose of Afogatran is 300 mg taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days. The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.

SPAF, DVT/PE

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

• Patients aged 80 years or above

• Patients who receive concomitant verapamil

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

• Patients between 75-80 years

• Patients with moderate renal impairment

• Patients with gastritis, esophagitis or gastroesophageal reflux

• Other patients at increased risk of bleeding

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

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

Elderly (SPAF, DVT/PE)

Patients between 75-80 years should be treated with a daily dose of 300 mg taken as one 150 mg capsule twice daily. A dose of 220 mg taken as one 110 mg capsule twice daily can

be individually considered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high.

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

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

Patients at risk of bleeding (SPAF, DVT/PE)

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

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

Assessment of renal function (SPAF, DVT/PE)

In all patients:

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

- For patients with creatinine clearance (CrCl) >30 mL/min, the recommended dose of Afogatran is 150 mg taken orally, twice daily, with or without food. For patients with CrCl 15-30 mL/min, the recommended dose is 75 mg twice daily.

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

The method used to estimate renal function (CrCL in mL/min) during the clinical development of Afogatran was the Cockcroft-Gault method.

Special populations

Renal impairment (SPAF, DVT/PE)
Treatment with Afogatran in patients with severe renal impairment (CrCL < 30 mL/min) is contraindicated.

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

Concomitant use of Afogatran with mild to moderate P-glycoprotein (P-gp) inhibitors, i.e. amiodarone, quinidine or verapamil (SPAF, DVT/PE)

No dose adjustment is necessary for concomitant use of amiodarone or quinidine.

Dosing should be reduced to 220 mg taken as one 110 mg capsule twice daily in patients who receive concomitantly dabigatran etexilate and verapamil. In this situation Afogatran and verapamil should be taken at the same time.

Weight (SPAF, DVT/PE)

Given the available clinical and kinetic data, no dose adjustment is necessary, but close clinical surveillance is recommended in patients with a body weight < 50 kg.

Gender (SPAF, DVT/PE)

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

Hepatic impairment (SPAF, DVT/PE)

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

Switching (SPAF, DVT/PE)

Afogatran treatment to parenteral anticoagulant

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

Parenteral anticoagulants to Afogatran

Discontinue the parenteral anticoagulant and start dabigatran etexilate 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)).

Afogatran treatment to Vitamin K antagonists (VKA)

Adjust the starting time of the VKA based on CrCL as follows:

• CrCL ≥ 50 mL/min, start VKA 3 days before discontinuing dabigatran etexilate

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

Because Afogatran can increase INR, the INR will better reflect VKA's effect only after Dabigatran has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.

VKA to Afogatran

The VKA should be stopped. Dabigatran etexilate can be given as soon as the International Normalized Ratio (INR) is < 2.0.

Cardioversion (SPAF, DVT/PE)

Patients can stay on dabigatran etexilate while being cardioverted.

Catheter ablation for atrial fibrillation (SPAF)

Catheter ablation can be conducted in patients on 150 mg twice daily Afogatran treatment. Afogatran treatment does not need to be interrupted.

Paediatric population (SPAF)

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

Missed dose (SPAF, DVT/PE)

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.

Method of administration (SPAF, DVT/PE)

Afogatran can be taken with or without food. Afogatran 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.

CONTRAINDICATIONS

• Hypersensitivity to the active substance or to any of the excipients.

• Patients with severe renal impairment (CrCL < 30 mL/min).

• Active clinically significant bleeding

• Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices,

arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities

• Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under specific circumstances of switching anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.

• Hepatic impairment or liver disease expected to have any impact on survival

• Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and dronedarone.
• Prosthetic heart valves requiring anticoagulant treatment

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

- **Hepatic impairment**

Patients with elevated liver enzymes > 2 ULN were excluded from the main trials. No treatment experience is available for this subpopulation of patients, and therefore the use of Dabigatran is not recommended in this population.

- **Haemorrhagic risk**

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

For 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.

Factors, such as decreased renal function (30-50 mL/min CrCL), age ≥ 75 years, low body weight < 50 kg, or mild to moderate P-gp inhibitor co-medication (e.g. amiodarone, quinidine or verapamil) are associated with increased dabigatran plasma levels.

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

In a study of prevention of stroke and SEE in adult patients with NVAF, dabigatran etexilate was associated with higher rates of major gastrointestinal (GI) bleeding which was

statistically significant for dabigatran etexilate 150 mg twice daily. This increased risk was seen in the elderly (≥ 75 years). Use of acetylsalicylic acid (ASA), clopidogrel or non-steroidal anti-inflammatory drug (NSAID), as well as the presence of esophagitis, gastritis or gastroesophageal reflux increase the risk of GI bleeding. In these atrial fibrillation patients, a dosage of 220 mg dabigatran given as 110 mg capsule twice daily should be considered and posology recommendations in dosage and administration section be followed. The administration of a PPI can be considered to prevent GI bleeding.

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

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

Table 1 summarises factors which may increase the haemorrhagic risk.

Table 1: Factors which may increase the haemorrhagic risk.

Pharmacodynamic and kinetic factors	Age ≥ 75 years
Factors increasing dabigatran plasma levels	Major: • Moderate renal impairment (30-50 mL/min CrCL) • P-gp inhibitor co-medication (some P-gp inhibitors are contraindicated Minor: • Low body weight (< 50 kg)
Pharmacodynamic interactions	• ASA • NSAID • Clopidogrel • SSRIs or SNRIs • Other drugs 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

The presence of lesions, conditions, procedures and/or pharmacological treatment (such as NSAIDs, antiplatelets, SSRIs and SNRIs), which significantly increase the risk of major

bleeding requires a careful benefit-risk assessment. Dabigatran should only be given if the benefit outweighs bleeding risks.

Dabigatran does not in general require routine anticoagulant monitoring. However, the measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. The INR test is unreliable in patients on Dabigatran and false positive INR elevations have been reported. Therefore, INR tests should not be performed. Diluted thrombin time (dTT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information, but the tests are not standardised, and results should be interpreted with caution.

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

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

Test (trough value)	Indication
	SPAF and DVT/PE
dTT [ng/mL]	> 200
ECT [x-fold upper limit of normal]	> 3
aPTT [x-fold upper limit of normal]	> 2
INR	Should not be performed

Patients who develop acute renal failure must discontinue Dabigatran.

Limited data is available in patients < 50 kg.

When severe bleedings occur treatment must be discontinued and the source of bleedinginvestigated.

Medicinal products that may enhance the risk of haemorrhage should not be administered concomitantly or should be administered with caution with Dabigatran.

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 ULN according to the local reference range.

Interaction with P-gp inducers

Concomitant administration of P-gp inducers (such as rifampicin, St. John`s wort (Hypericum perforatum), carbamazepine, or phenytoin) is expected to result in decreased dabigatran plasma concentrations, and should be avoided.

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 while being cardioverted. Dabigatran treatment (150 mg twice daily) does not need to be interrupted in patients undergoing catheter ablation for atrial fibrillation.

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. This should be considered in advance of any procedures. In such cases a coagulation test 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 agen (Praxbind, idarucizumab) to Dabigatran is available.

Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Dabigatran treatment can be re-initiated 24 hours after administration of Praxabind (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 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 2-4 days before surgery. Clearance of dabigatran in patients with renal insufficiency may take longer. This should be considered in advance of any procedures.

Table 3 summarises discontinuation rules before invasive or surgical procedures.

Table 3: Discontinuation rules before invasive or surgical procedures

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

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 should be restarted 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 moderate renal impairment (CrCL 30-50 mL/min), should be treated with caution.

Patients at high surgical mortality risk and with intrinsic risk factors for thromboembolic events

There are limited efficacy and safety data for dabigatran available in these patients and therefore they should be treated with caution.

Myocardial Infarction (SPAF)

In the phase III study RE-LY the overall rate of myocardial infarction (MI) was 0.82, 0.81, and 0.64 % / year for dabigatran etexilate 110 mg twice daily, dabigatran etexilate 150 mg twice daily and warfarin, respectively, an increase in relative risk for dabigatran of 29 % and 27 % compared to warfarin. Irrespective of therapy, the highest absolute risk of MI was seen in the following subgroups, with similar relative risk: patients with previous MI, patients ≥ 65 years with either diabetes or coronary artery disease, patients with left

ventricular ejection fraction < 40 %, and patients with moderate renal dysfunction. Furthermore, a higher risk of MI was seen in patients concomitantly taking ASA plus clopidogrel or clopidogrel alone.

Myocardial Infarction (DVT/PE)

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

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

Active Cancer Patients (DVT/PE)

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

DRUG INTERACTIONS

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: 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, and platelet aggregation medicinal products such as GPIIb/IIIa receptor antagonists, ticlopidine, prasugrel, ticagrelor, dextran and sulfinpyrazone.

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

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

From the data collected in the phase III study RE-LY in patients with atrial fibrillation, it was observed that the concomitant use of antiplatelets ASA or clopidogrel approximately doubles major bleeding rates with both dabigatran etexilate and warfarin.

Clopidogrel: In a phase I study in young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times compared to clopidogrel monotherapy. In addition, dabigatran AUC, ss and Cmax,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, ss and Cmax,ss were increased by about 30-40 % (see also subsection on ASA below).

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

NSAIDs: NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use in the RE-LY study, NSAIDs increased the risk of bleeding by approximately 50% on both dabigatran etexilate and warfarin. Therefore, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives > 12 hours, close observation for signs of bleeding is recommended.

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.

<u>Interactions linked to dabigatran etexilate and dabigatran metabolic profile</u>
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.

<u>Transporter interactions</u>

P-gp inhibitors

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors (such as amiodarone, verapamil, quinidine, ketoconazole,

dronedarone, clarithromycin and ticagrelor) 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. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure.

The following strong P-gp inhibitors are contraindicated: systemic ketoconazole, cyclosporine, itraconazole and dronedarone. Concomitant treatment with tacrolimus is not recommended. Caution should be exercised with mild to moderate P-gp inhibitors (e.g. amiodarone, posaconazole, quinidine, verapamil and ticagrelor).

Ketoconazole: Ketoconazole increased total dabigatran AUC0-∞ and Cmax values by 138 % and 135 %, respectively, after a single oral dose of 400 mg, and 153 % and 149 %, respectively, after multiple oral dosing of 400 mg ketoconazole once daily. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole. Concomitant treatment with systemic ketoconazole is contraindicated.

Dronedarone: When dabigatran etexilate and dronedarone were given at the same time total dabigatran AUC0-∞ and Cmax values increased by about 2.4-fold and 2.3-fold (+136 % and 125 %), respectively, after multiple dosing of 400 mg dronedarone bid, and about 2.1-fold and 1.9-fold (+114 % and 87 %), respectively, after a single dose of 400 mg. The terminal half-life and renal clearance of dabigatran were not affected by dronedarone. When single and multiple doses of dronedarone were given 2 h after dabigatran etexilate, the increases in dabigatran AUC0-∞ were 1.3-fold and 1.6-fold, respectively. Concomitant treatment with dronedarone is contraindicated.

Amiodarone: When Dabigatran 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 Cmax were increased by about 60 % and 50 %, respectively. The mechanism of the interaction has not been completely clarified. In view of the long half-life of amiodarone the potential for drug interaction may exist for weeks after discontinuation of amiodarone. Close clinical surveillance is recommended when dabigatran etexilate is combined with amiodarone and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.

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,ss and Cmax,ss were increased on average by 53 % and 56 %, respectively with concomitant quinidine. Close clinical surveillance is recommended when dabigatran etexilate is combined with quinidine and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.

Verapamil: When dabigatran etexilate (150 mg) was co-administered with oral verapamil, the Cmax and AUC of dabigatran were increased but magnitude of this change differs depending on timing of administration and formulation of verapamil.

The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to dabigatran etexilate intake (increase of Cmax by about 180 % and AUC by about 150 %). The effect was progressively decreased with administration of an extended release formulation (increased of Cmax by about 90 % and AUC by about 70 %) or administration of multiple doses of verapamil (increased of Cmax by about 60 % and AUC by about 50 %).

Patients concomitantly receiving dabigatran etexilate and verapamil, the dose of Dabigatran should be reduced to 220 mg taken as one 110 mg capsule twice daily. Close clinical surveillance is recommended when dabigatran etexilate is combined with verapamil and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.

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

Clarithromycin: When clarithromycin (500 mg twice daily) was administered together with dabigatran etexilate in healthy volunteers, increase of AUC by about 19 % and Cmax by about 15 % was observed without any clinical safety concern. However, in patients receiving dabigatran, a clinically relevant interaction cannot be excluded when combined with clarithromycin. Therefore, a close monitoring should be exercised when dabigatran etexilate is combined with clarithromycin and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.

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

Concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg dabigatran etexilate (in steady state) increased the dabigatran AUC,ss and Cmax,ss by 1.49-fold and 1.65-fold (+49% and 65%), respectively, compared with dabigatran etexilate given alone. When a loading dose of 180 mg ticagrelor was given 2 hours after 110 mg dabigatran etexilate (in steady state), the increase of dabigatran AUC,ss and Cmax,ss was reduced to 1.27-fold and 1.23-fold (+27% and 23%), respectively, compared with dabigatran etexilate given alone. This staggered intake is the recommended administration for start of ticagrelor with a loading dose.

Concomitant administration of 90 mg ticagrelor BID (maintenance dose) with 110 mg dabigatran etexilate increased the adjusted dabigatran AUC,ss and Cmax,ss 1.26-fold and 1.29-fold, respectively, compared with dabigatran etexilate given alone.

The following potent P-gp inhibitors have not been clinically studied but from in vitro results a similar effect as with ketoconazole may be expected:

Itraconazole and cyclosporine, which are contra-indicated.

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. Based on these data concomitant treatments with tacrolimus is not recommended.

Posaconazole also inhibits P-gp to some extent but has not been clinically studied. Caution should be exercised when Dabigatran is co-administered with posaconazole.

P-gp inducers

Concomitant administration of a P-gp inducer (such as rifampicin, St. John´s wort (Hypericum perforatum), carbamazepine, or phenytoin) is expected to result in decreased dabigatran concentrations and should be avoided.

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

Other medicinal products affecting P-gp

Protease inhibitors including ritonavir and its combinations with other protease inhibitors affect P-gp (either as inhibitor or as inducer). They have not been studied and are therefore not recommended for concomitant treatment with Dabigatran.

P-gp substrate

Digoxin: In a study performed with 24 healthy subjects, when Dabigatran was co-administered with digoxin, no changes on digoxin and no clinical relevant changes on dabigatran exposure have been observed.

Co-medication with selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs)

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

Gastric pH

Pantoprazole: When Dabigatran was co-administered with pantoprazole, a decrease in the dabigatran area under the plasma concentration-time curve of approximately 30 % was observed. Pantoprazole and other proton-pump inhibitors (PPI) were co-administered with Dabigatran in clinical trials, and concomitant PPI treatment did not appear to reduce the efficacy of Dabigatran.

Ranitidine: Ranitidine administration together with Dabigatran had no clinically relevant effect on the extent of absorption of dabigatran.

FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential / Contraception in males and females

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

Pregnancy

There are limited amount of data from the use of dabigatran etexilate in pregnant women.

Studies in animals have shown reproductive toxicity. 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).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

UNDESIRABLE EFFECTS

Summary of the safety profile

In the pivotal study investigating the prevention of stroke and SEE in patients with atrial fibrillation, a total of 12,042 patients were treated with dabigatran etexilate. Of these 6,059 were treated with 150 mg twice daily of dabigatran etexilate, while 5,983 received doses of 110 mg twice daily.

In the 2 active controlled DVT/PE treatment trials, RE-COVER and RE-COVER II, a total of 2,553 patients were included in the safety analysis for dabigatran etexilate. All patients received doses of 150 mg twice daily of dabigatran etexilate. Adverse drug reactions for both treatments, dabigatran etexilate and warfarin, 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 adverse drug reactions which occurred during dabigatran therapy. All adverse drug reactions, which occurred during warfarin therapy, are included except for those during the overlap period between warfarin and parenteral therapy.

A total of 2,114 patients were treated in the active controlled DVT/PE prevention trial, RE-MEDY, and in the placebo-controlled DVT/PE prevention trial, RE-SONATE. All patients received doses of 150 mg twice daily of dabigatran etexilate.

In total, 22 % of patient with atrial fibrillation treated for the prevention of stroke and SEE (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 adverse reactions are bleedings occurring in total in approximately 16.6 % in patients with atrial fibrillation treated long-term for the prevention of stroke and SEE and in 14.4 % of patients treated for DVT/PE. Furthermore, bleedings occurred in 19.4 % of patients in the DVT/PE prevention trial RE-MEDY and in 10.5 % of patients in the DVT/PE trial RE-SONATE.

Since the patient population 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 are provided in tables 5, 6, 7 and 8 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 4 shows the adverse reactions identified from the study in prevention of thromboembolic stroke and SEE in patients with atrial fibrillation, the studies in DVT/PE treatment and in 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 4: Adverse reactions

	Stroke and SEE prevention in patients with atrial fibrillation	DVT/PE treatment and DVT/PE prevention
SOC / Preferred term.		
Blood and lymphatic system disorders		
Anaemia	Common	Uncommon
Haemoglobin decreased	Uncommon	Not known
Thrombocytopenia	Uncommon	Rare
Haematocrit decreased	Rare	Not known
Immune system disorder		
Drug hypersensitivity	Uncommon	Uncommon
Rash	Uncommon	Uncommon
Pruritus	Uncommon	Uncommon
Anaphylactic reaction	Rare	Rare
Angioedema	Rare	Rare
Urticaria	Rare	Rare

Bronchospasm	Not known	Not known
Nervous system disorders		
Intracranial haemorrhage	Uncommon	Rare
Vascular disorders		
Haematoma	Uncommon	Uncommon
Haemorrhage	Uncommon	Uncommon
Respiratory, thoracic and mediastinal disorders		
Epistaxis	Common	Common
Haemoptysis	Uncommon	Uncommon
Gastrointestinal disorders		
Gastrointestinal haemorrhage	Common	Common
Abdominal pain	Common	Uncommon
Diarrhoea	Common	Uncommon
Dyspepsia	Common	Common
Nausea	Common	Uncommon
Rectal haemorrhage	Uncommon	Common
Haemorrhoidal haemorrhage	Uncommon	Uncommon
Gastrointestinal ulcer	Uncommon	Uncommon
Gastroesophagitis	Uncommon	Uncommon
Gastroesophageal reflux disease	Uncommon	Uncommon
Vomiting	Uncommon	Uncommon
Dysphagia	Uncommon	Rare
Hepatobiliary disorders		
Hepatic function abnormal/ Liver function Test abnormal	Uncommon	Uncommon
Alanine aminotransferase increased	Uncommon	Uncommon
Aspartate aminotransferase increased	Uncommon	Uncommon
Hepatic enzyme increased	Rare	Uncommon
Hyperbilirubinaemia	Rare	Not known
Skin and subcutaneous tissue disorder		
Skin haemorrhage	Common	Common
Musculoskeletal and connective tissue disorders		
Haemarthrosis	Rare	Uncommon
Renal and urinary disorders		

Genitourological haemorrhage, including haematuria	Common	Common
General disorders and administration site conditions		
Injection site haemorrhage	Rare	Rare
Catheter site haemorrhage	Rare	Rare
Injury, poisoning and procedural complications		
Traumatic haemorrhage	Rare	Uncommon
Incision site haemorrhage	Rare	Rare

Bleeding

Prevention of stroke and SEE in adult patients with nonvalvular atrial fibrillation with one or more risk factors (SPAF)

The table 5 shows bleeding events broken down to major and any bleeding in the pivotal study testing the prevention of thromboembolic stroke and SEE in patients with atrial fibrillation.

Table 5: Bleeding events in a study testing the prevention of thromboembolic stroke and SEE 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 %)

Major bleeding was defined to fulfil one or more of the following criteria:

Bleeding associated with a reduction in haemoglobin of at least 20 g/L or leading to a transfusion of at least 2 units of blood or packed cells.

Symptomatic bleeding in a critical area or organ: intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding.

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

Fatal bleed; symptomatic intracranial bleed; reduction in haemoglobin of at least 50 g/L; transfusion of at least 4 units of blood or packed cells; a bleed associated with hypotension requiring the use of intravenous inotropic medicinal products; a bleed that necessitated surgical intervention.

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 dabigatran etexilate 110 mg twice daily had a significantly lower risk for major bleeds compared with warfarin (hazard ratio 0.81 [p=0.0027]). Subjects randomized to dabigatran etexilate 150 mg 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 SEE prevention and decreased risk of ICH compared to warfarin is preserved across individual subgroups, e.g. renal impairment, age, concomitant medication 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 deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (DVT/PE) treatment

Table 6 shows bleeding events in the pooled pivotal studies RE-COVER and RE-COVER II testing the treatment of deep vein thrombosis (DVT) and pulmonary embolism (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 6: Bleeding events in the studies RE-COVER and RE-COVER II testing the treatment of deep vein thrombosis (DVT) and pulmonary embolism (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.

The definition of major bleeding events (MBEs) followed the recommendations of the International Society on Thrombosis and Haemostasis. A bleeding event was categorised as an MBE if it fulfilled at least one of the following criteria:

• Fatal bleeding

• Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial, or intramuscular with compartment syndrome. In order for bleeding in a critical area or organ to be classified as a MBE it had to be associated with a symptomatic clinical presentation

• Bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or red cells

Table 7 shows bleeding events in pivotal study RE-MEDY testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (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 7: Bleeding events in study RE-MEDY testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE)

	Dabigatran etexilate 150 mg twice daily	Warfarin	Hazard ratio vs warfarin (95% Confidence Interval)

Treated patients	1,430	1,426	
Major 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

The definition of MBEs followed the recommendations of the International Society on Thrombosis and Haemostasis as described under RE-COVER and RE-COVER II.

Table 8 shows bleeding events in pivotal study RE-SONATE testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (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 8: Bleeding events in study RE-SONATE testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE)

	Dabigatran etexilate 150 mg twice daily	Placebo	Hazard ratio vs placebo (95% confidence interval)
Treated patients	684	659	
Major bleeding events	(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

The definition of MBEs followed the recommendations of the International Society on Thrombosis and Haemostasis as described under RE-COVER and RE-COVER II.

Myocardial infarction

Prevention of stroke and SEE in adult patients with nonvalvular atrial fibrillation with one or more risk factors (SPAF)

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

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

In the three active controlled studies, a higher rate of MI was reported in patients who received dabigatran etexilate than in those who received warfarin: 0.4% vs. 0.2% in the short-term RECOVER and RECOVER 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.

Paediatric population (DVT/PE)

In the clinical study 1160.88 in total, 9 adolescent patients (age 12 to < 18 years) with diagnosis of primary VTE received an initial oral dose of dabigatran etexilate of 1.71 (± 10 %) mg/kg bodyweight. Based on dabigatran concentrations as determined by the diluted thrombin time test and clinical assessment, the dose was adjusted to the target dose of 2.14 (± 10%) mg/kg bodyweight of dabigatran etexilate On treatment 2 (22.1 %) patients experienced mild related adverse events (gastrooesophageal reflux / abdominal pain; abdominal discomfort) and 1 (11.1 %) patient experienced a not related serious adverse event (recurrent VTE of the leg) in the post treatment period > 3 days after stop of dabigatran etexilate.

OVERDOSE

Doses of dabigatran etexilate 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. A calibrated quantitative (dTT) test or repetitive dTT measurements allow prediction of the time by when certain dabigatran levels will be reached, also in case additional measures e.g. dialysis have been initiated.

Excessive anticoagulation may require interruption of Dabigatran treatment. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding

investigated. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. Depending on the clinical situation appropriate supportive treatment, such as surgical haemostasis and blood volume replacement, should be undertaken at the prescriber's discretion.

For situations when rapid reversal of the anticoagulant effects of Dabigatran is required the specific reversal agent (Praxbind, idarucizumab) antagonizing the pharmacodynamics effect of Dabigatran is available.

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 drugs 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.

As protein binding is low, dabigatran can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic, 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 also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

Pharmacodynamic effects

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

There is a 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 90th percentile of dabigatran trough levels or a coagulation assay such as aPTT measured at trough is considered to be associated with an increased risk of bleeding.

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 (25th–75thpercentile 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 (25th–75th percentile range).

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

• the 90th 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 90th 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 90th percentile of observations.

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 (25th-75th percentile range). For treatment of DVT and PE, with dabigatran etexilate 150 mg twice daily,

• the 90th 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 90th percentile of ECT prolongation of 74 seconds,

• the 90th 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 (SPAF)

Prevention of stroke and SEE 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 SEE. 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 SEE. Statistical superiority was also analyzed.

In the RE-LY study, a total of 18,113 patients were randomized, with a mean age of 71.5 years and a mean CHADS2 score of 2.1. The patient population was 64 % male, 70 % Caucasian and 16 % Asian. For patients randomized to warfarin, the mean percentage within 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 SEE 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 9-11 display details of key results in the overall population.

Table 9: Analysis of first occurrence of stroke or SEE (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 SEE			
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 10: 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	
SEE			
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 11: 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 12-13 display results of the primary efficacy and safety endpoint in relevant sub-populations:

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

Table 12: Hazard Ratio and 95 % CI for stroke/SEE 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 and warfarin.

There was no significant interaction of treatment effects with the subgroups of renal function and CHADS2 score.

Table 13: Hazard Ratio and 95 % CI for major bleeds by subgroups

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.

Patients undergoing catheter ablation for atrial fibrillation

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

Paediatric population (SPAF)

The European Medicines Agency has waived the obligation to submit the results of studies with Dabigatran in all subsets of the paediatric population in prevention of thromboembolic events for the granted indication.

Ethnic origin (SPAF)

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

Clinical efficacy and safety (DVT/PE treatment)

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (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 randomized and 5,107 were treated.

The duration of treatment with fixed dose of dabigatran was 174.0 days without coagulation monitoring. For patients randomized to warfarin, the median time in therapeutic range (INR 2.0 to 3.0) was 60.6 %.

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

Ethnic orgin (DVT/PE treatment)

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

Paediatric population (DVT/PE treatment)

The European Medicines Agency has deferred the obligation to submit the results of studies with Dabigatran in all subsets of the paediatric population for DVT/PE treatment.

The pharmacokinetics and pharmacodynamics of dabigatran etexilate administered twice daily for three consecutive days (total 6 doses) at the end of standard anticoagulant therapy were assessed in an open-label safety and tolerability study in 9 stable adolescents (12 to < 18 years). All patients received an initial oral dose of 1.71 (± 10%) mg/kg of dabigatran etexilate (80 % of the adult dose of 150 mg/70 kg adjusted for the patient's weight). Based on dabigatran concentrations and clinical assessment, the dose was subsequently modified to a target dose of 2.14 (± 10 %) mg/kg of dabigatran etexilate (100 % of the adult dose adjusted for the patient's weight). In this small number of adolescents, dabigatran etexilate capsules were apparently tolerated with only three mild and transient gastrointestinal adverse events reported by two patients. According to the relatively low exposure, coagulation at 72 hrs (presumed dabigatran trough level at steady state or close to steady state conditions) was only slightly prolonged with aPTT at maximum 1.60 fold, ECT 1.86 fold, and Hemoclot® TT (Anti-FIIa) 1.36 fold, respectively. Dabigatran plasma concentrations observed at 72 hrs were relatively low, between 32.9 ng/mL and 97.2 ng/mL at final doses between 100 mg and 150 mg (gMean dose normalized total dabigatran plasma concentration of 0.493 ng/mL/mg).

Clinical efficacy and safety (DVT/PE prevention)

Prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (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 exilate treatment ranged from 6 to 36 months (median 534.0 days). For patients randomized to warfarin, the median time in therapeutic range (INR 2.0-3.0) was 64.9 %.

RE-MEDY demonstrated that treatment with dabigatran etexilate 150 mg twice daily was non-inferior to warfarin (non-inferiority margin 2.85 for hazard ratio and 2.8 for risk difference).

Table 15: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the 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 16: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the RE-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

Ethnic origin (DVT/PE prevention)

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

Paediatric population (DVT/PE prevention)

The European Medicines Agency has deferred the obligation to submit the results of studies with Dabigatran in all subsets of the paediatric population for DVT/PE prevention.

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.

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 was approximately 6.5 %.

After oral administration of Dabigatran in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterized by a rapid increase in plasma concentrations with Cmax 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.

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. Therefore, patients should be advised not to open the capsules and taking the pellets alone (e.g. sprinkled over food or into beverages).

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.

Cmax and the area under the plasma concentration-time curve were dose proportional. 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 17.

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.

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 volunteers with moderate renal insufficiency (CrCL between 30–50 mL/min) than in those without renal insufficiency.

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

Table 17: 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 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 drug 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 and 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-dosedabigatran 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 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 Cmax 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.

Hepatic impairment

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

Body weight

The dabigatran trough concentrations were about 20 % lower in 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. Limited clinical data in patients < 50 kg are available.

Gender

In atrial fibrillation patients females had on average 30 % higher trough and post-dose concentrations. No dose adjustment is recommended.

Ethnic origin

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

Pharmacokinetic interactions

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

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).

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 repeat-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 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.

EXPIRY DATE
Do not use later than the date of expiry.

STORAGE
Store below 25°C. Protect from light & moisture.

PRESENTATION
Blister pack of 10 Capsules.

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