

PRADAXA[®] Capsules 75 mg, 110 mg, 150 mg

Composition

1 Capsule contains 86.48 mg, 126.83 mg or 172.95 mg of
beta-alanine, N-[[[2-[[[4(hexyloxy)carbonyl]amino]iminomethyl] phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-,ethyl ester, methane-sulfonate, being the methane sulfonic acid salt
(corresponding to dabigatran etexilate base form 75 mg, 110 mg or 150 mg)

Excipients:

Tartaric acid, acacia, hypromellose, dimeticone, talc, hydroxypropylcellulose.

HPMC capsule shell: Carrageenan, potassium chloride, titanium dioxide, Sunset Yellow, Indigo Carmin, hypromellose.

Printing ink: Shellac, butyl alcohol, isopropyl alcohol, Iron oxide black, purified water, propylene glycol, ethanol anhydrous, potassium hydroxide, strong ammonia solution.

Indications

Pradaxa Capsules 75 mg:

1. Prevention of venous thromboembolic events (VTE) following major orthopedic surgery of the lower limbs in patients with a high risk for VTE

Pradaxa Capsules 110 mg:

1. Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
2. Prevention of venous thromboembolic events (VTE) following major orthopedic surgery of the lower limbs in patients with a high risk for VTE

Pradaxa Capsules 150 mg:

1. Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Dosage and administration

The drug should be taken under description.

Method of administration

Pradaxa should be swallowed as a whole with water, with or without food.

Patients should be instructed not to open the capsule as this may increase the risk of bleeding.

Prevention of venous thromboembolic events (VTE) following major orthopedic surgery of the lower limbs in patients with a high risk for VTE:

Patients following elective knee replacement surgery

The recommended dose of Pradaxa is 150 mg once daily taken as 2 capsules of 75 mg or 220 mg once daily taken as 2 capsules of 110mg. Treatment should be initiated orally within 1-4hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 10 days.

Patients following elective hip replacement surgery

The recommended dose of Pradaxa is 150 mg once daily taken as 2 capsules of 75 mg or 220 mg once daily taken as 2 capsules of 110 mg. Treatment should be initiated orally within 1-4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 28-35 days.

For the following groups the recommended daily dose of Pradaxa is 150 mg taken once daily as 2 capsules of 75 mg:

- Patients with moderate renal impairment (creatinine clearance (CrCL) 30-50 mL/min) [see Renal impairment (prevention of VTE)]
- Patients who receive concomitant verapamil, amiodarone, quinidine [see Concomitant use of Pradaxa with moderate P-glycoprotein (P-gp) inhibitors, i.e. amiodarone, quinidine or verapamil (prevention of VTE)]
- Patients aged 75 or above [see Elderly (prevention of VTE)]

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 (prevention of VTE):

In all patients:

- Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 mL/min). Pradaxa is contraindicated in patients with severe renal impairment
- 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 used to estimate renal function (CrCL in mL/min) during the clinical development of Pradaxa was the Cockcroft-Gault method. The formula is as follows:

- For creatinine in µmol/L:

$$\frac{1.23 \times (140 - \text{age [years]}) \times \text{weight [kg]} (\times 0.85 \text{ if female})}{\text{serum creatinine } [\mu\text{mol/L}]}$$

- For creatinine in mg/dL:

$$\frac{(140 - \text{age [years]}) \times \text{weight [kg]} (\times 0.85 \text{ if female})}{72 \times \text{serum creatinine [mg/dL]}}$$

This method is recommended when assessing patients' CrCL prior to and during Pradaxa treatment.

Special populations

Renal impairment (prevention of VTE)

Treatment with Pradaxa in patients with severe renal impairment (CrCL < 30 mL/min) is contraindicated.

In patients with moderate renal impairment (CrCL 30-50 mL/min), there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg.

Concomitant use of PRADAXA with moderate P-glycoprotein inhibitors, i.e. amiodarone, quinidine or verapamil:

Prevention of venous thromboembolic events (VTE) following major orthopedic surgery of the lower limbs in patients with a high risk for VTE:

Dosing should be reduced to PRADAXA 150 mg taken once daily as 2 capsules of 75 mg in patients who concomitantly receive PRADAXA and amiodarone, quinidine or verapamil (see “Interactions”).

Treatment initiation with verapamil should be avoided in patients who have undergone major orthopaedic surgery who are already treated with PRADAXA. Simultaneous initiation of treatment with PRADAXA and verapamil should also be avoided.

Elderly (prevention of VTE)

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

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 Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 mL/min). While on treatment the renal function should also be assessed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc).

Hepatic impairment (prevention of VTE)

Patients with elevated liver enzymes > 2 upper limit of normal (ULN) were excluded in clinical trials investigating the VTE prevention following elective hip or knee replacement surgery. No treatment experience is available for this subpopulation of patients, and therefore the use of Pradaxa is not recommended in this population. Hepatic impairment or liver disease expected to have any impact on survival is contraindicated.

Weight (prevention of VTE)

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, but close clinical surveillance is recommended .

Gender (prevention of VTE)

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

Switching (prevention of VTE)

Pradaxa treatment to parenteral anticoagulant

It is recommended to wait 24 hours after the last dose before switching from Pradaxa to a parenteral anticoagulant.

Parenteral anticoagulants to Pradaxa

Dabigatran etexilate should be given 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous Unfractionated Heparin (UFH)).

Paediatric population (prevention of VTE)

There is no relevant use of Pradaxa in the paediatric population in the indication: Prevention of venous thromboembolic events (VTE) following major orthopedic surgery of the lower limbs in patients with a high risk for VTE.

Missed dose (prevention of VTE)

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.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Recommended Dose

The recommended daily dose of PRADAXA is 110-150 mg taken orally, twice daily, with or without food, depending on the individual condition and clinical situation.

For patients with a higher risk of bleeding, e.g. age ≥ 75 years, CHADS₂ score of ≥ 3 , body weight < 50 kg, previous gastro-intestinal bleed or moderate renal impairment (30-50 ml CrCL/min), the dose of 110 mg taken orally, twice daily, may be considered.

Instruct patients to swallow the capsules whole. Breaking, chewing, or emptying the contents of the capsule can result in increased exposure [see *Clinical Pharmacology*].

If a dose of PRADAXA is not taken at the scheduled time, the dose should be taken as soon as possible on the same day; the missed dose should be skipped if it cannot be taken at least 6 hours before the next scheduled dose. The dose of PRADAXA should not be doubled to make up for a missed dose.

Elderly

In geriatric patients over the age of 75, the administration of a dose of 220 mg of PRADAXA daily, taken orally as one 110 mg capsule twice a day, may be considered. As with any anticoagulant, caution is required when prescribing PRADAXA to the elderly.

As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCl < 30 ml/min). The renal function should also be assessed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc).

Patients at risk of bleeding:

Patients with an increased risk of bleeding should be closely monitored clinically (looking for signs of bleeding or anaemia). In such patients, a dose of 220 mg, given as 110 mg twice daily may be considered. A coagulation test, such as aPTT (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory

Tests), may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure.

As for any anticoagulant, PRADAXA is NOT indicated in patients at excessive risk of bleeding.

Hepatic insufficiency:

Patients with active liver disease including but not limited to the persistent elevation of liver enzymes ≥ 2 Upper Limit Normal (ULN), or hepatitis A, B or C were excluded in clinical trials. Treatment in this population with dabigatran is not recommended. In case the use of dabigatran in this population is necessary, administration with cautious and regular monitoring on the liver function are required.

Children:

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

Renal impairment:

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

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

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

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

Concomitant use of PRADAXA with moderate P-glycoprotein inhibitors, i.e. amiodarone, quinidine or verapamil:

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

Switching from PRADAXA treatment to parenteral anticoagulant:

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

Switching from parenteral anticoagulants treatment to PRADAXA:

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

Switching from Vit. K antagonists to PRADAXA

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

Switching from PRADAXA to Vit. K antagonists (VKA)

The starting time of the VKA should be adjusted according to the patient's CrCL as follows:

- CrCL $\geq$ 50 ml/min, start VKA 3 days before discontinuing dabigatran etexilate
- CrCL $\geq$ 30- < 50 ml/min, start VKA 2 days before discontinuing dabigatran etexilate.
- CrCL < 30 ml/min: contraindicated in this population.

Because Pradaxa can increase INR, the INR will better reflect warfarin's effect only after Pradaxa has been stopped for at least 2 days.

Cardioversion

Patients can stay on PRADAXA while being cardioverted.

Missed dose

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

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

Do not take a double dose to make up for missed individual doses.

Contraindications

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

Special warnings and precautions

Hepatic impairment

Patients with elevated liver enzymes > 2 ULN were excluded in clinical trials, and therefore the use of Pradaxa is not recommended in this population.

Haemorrhagic risk:

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

Table 1: Factors which increase haemorrhagic risk, as identified in clinical studies

Factors increasing dabigatran plasma levels	Moderate renal impairment (30-50ml/min CrCl)
	P-glycoprotein-inhibitor comedication
Pharmacodynamic interactions	Acetylsalicylic acid
	NSAID
	Clopidogrel
Diseases / procedures with special	Congenital or acquired coagulation disorders

haemorrhagic risks	Thrombocytopenia or functional platelet defects
	Active ulcerative gastrointestinal disease
	Recent gastro-intestinal bleeding
	Recent biopsy or major trauma
	Recent intracranial hemorrhage
	Brain, spinal or ophthalmic surgery
	Bacterial endocarditis
Others	Age $\geq$ 75 years

Pradaxa 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 Pradaxa 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

Test (trough value)	Indication	
	Prevention of VTE	Prevention of stroke and SEE
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

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

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

Patients who develop acute renal failure should discontinue PRADAXA.

Factors, such as decreased renal function (30 - 50mL/min CrCL), age $\geq$ 75 years, body weight < 50 kg, or moderate P-gp-inhibitor comedication are associated with increased dabigatran plasma levels. The presence of one or more than one of these factors may increase the risk of bleeding (see dosing and administration).

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

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

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

Use of fibrinolytic agents for the treatment of acute ischemic stroke:

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

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

Prevention of venous thromboembolic events (VTE) following major orthopedic surgery of the lower limbs in patients with a high risk for VTE:

NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with PRADAXA. If use NSAID with half-lives > 12 hours during treatment with PRADAXA, close observation for signs of bleeding is recommended.

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:

In patients with atrial fibrillation treated for the prevention of stroke and systemic embolism, the co-administration of oral anti-platelets (including aspirin and clopidogrel) increases the risk of bleeding by about two-fold while NSAID therapies increase the risk of bleeding by 50%. If necessary, co-administration of low-dose ASA, i.e. ≤ 100 mg daily with PRADAXA may be considered for other indications than stroke prevention in atrial fibrillation. Note that in the RELY trial, there is no evidence that the addition of ASA or clopidogrel to dabigatran, or its comparator warfarin, improved outcomes in respect of stroke.

Specifically, with concomitant intake of antiplatelets or strong P-gp inhibitors in patients aged ≥ 75 years, the risk of major bleeding, including gastrointestinal bleeding, increases. If bleeding is clinically suspected, appropriate measures such as testing for occult blood in stool, or testing for a drop in hemoglobin is suggested.

Patients with a body weight < 50 kg or BMI < 25 have a significantly higher risk of bleeding.

Myocardial Infarction

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). A causal relationship of myocardial infarction and treatment with dabigatran etexilate has not been established.

Interaction with P-gp inducers:

The concomitant use of PRADAXA with the P-gp inducer rifampicin reduces dabigatran plasma concentrations. Other P-gp inducers such as St. John's Wort, carbamazepine or phenytoin are

also expected to reduce dabigatran plasma concentrations, and should be avoided (see “Interactions” and “Special populations”).

Surgery and Interventions:

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

Preoperative Phase

Due to an increased risk of bleeding PRADAXA may be stopped temporarily in advance of invasive or surgical procedures. If possible, PRADAXA should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete hemostasis may be required consider stopping PRADAXA 2-4 days before surgery. Clearance of dabigatran in patients with renal insufficiency may take longer. This should be considered in advance of any procedures (see Table 3 and also “Pharmacokinetics”).

Table 3 summarizes discontinuation rules before invasive or surgical procedures.

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

*for more details see “Pharmakokinetics”

PRADAXA is contraindicated in patients with severe renal dysfunction (CrCl <30 mL/min) but should this occur then PRADAXA should be stopped at least 5 days before major surgery. If an acute intervention is required, PRADAXA 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 there may be an increase in the risk of bleeding. This risk of bleeding should be weighed together with the urgency of intervention (for cardioversion see “Dosage and administration”).

Spinal Anesthesia/Epidural Anesthesia/Lumbar Puncture:

Procedures such as spinal anesthesia may require complete hemostatic function.

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

Post Procedural Period

Resume treatment after complete haemostasis is achieved.

Excipients:

The product contains the excipient sunset yellow (E 110), which may cause allergic reactions.

Interactions

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

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

P-gp interactions:

P-glycoprotein inhibitors:

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors (such as amiodarone, verapamil, quinidine, systemic ketoconazole, dronedarone, ticagrelor and clarithromycin) is expected to result in increased dabigatran plasma concentrations. Concomitant administration of strong P-gp inhibitors, systemic ketoconazole, cyclosporine, itraconazole, are contraindicated.

Caution should be exercised with moderate P-gp inhibitors (e.g. amiodarone, quinidine, verapamil and ticagrelor).

For the concomitant use of P-gp inhibitors and dosing of PRADAXA in the indication “Prevention of venous thromboembolic events (VTE) following major orthopedic surgery of the lower limbs in patients with a high risk for VTE” please see “Dosing and administration” and “Special populations”.

Amiodarone:

In patients in the RE-LY trial concentrations were increased by no more than 14% and no increased risk of bleeding was observed. Dabigatran exposure in healthy subjects was increased by 1.6 fold (+ 60 %) in the presence of amiodarone (see special population).

Patients treated for prevention of VTEs after hip or knee replacement surgery, dosing should be reduced to 150 mg taken once daily as 2 capsules of 75 mg Pradaxa if they receive concomitantly dabigatran etexilate and 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.

Verapamil:

When PRADAXA (150 mg) was coadministered with oral verapamil, the C_{max} and AUC of dabigatran were increased but the magnitude of this change differs, depending on timing of administration and formulation of verapamil.

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

The greatest elevation of dabigatran exposure was observed with the first dose of an immediate

release formulation of verapamil administered one hour prior to dabigatran etexilate intake (increase of C_{max} by about 180 % and AUC by about 150 %). The effect was progressively decreased with administration of an extended release formulation (increased of C_{max} by about 90 % and AUC by about 70 %) or administration of multiple doses of verapamil (increased of C_{max} by about 60 % and AUC by about 50 %).

Therefore, close clinical surveillance (looking for signs of bleeding or anaemia) is required when dabigatran is co-administered with verapamil. In patients with normal renal function after hip or knee replacement surgery, receiving dabigatran etexilate and verapamil concomitantly, the dose of Pradaxa should be reduced to 150 mg taken once daily as 2 capsules of 75 mg. In patients with moderate renal impairment and concomitantly treated with dabigatran etexilate and verapamil, a dose reduction of Pradaxa to 75 mg daily should be considered (see “special populations”).

For patients with atrial nonvalvular fibrillation treated for prevention of stroke and SEE, concomitantly receiving dabigatran etexilate and verapamil, the dose of Pradaxa 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 (increase of C_{max} by about 10% and AUC by about 20%). This is explained by completed dabigatran absorption after 2 hours. (See Dosage and Administration).

Quinidine:

Dabigatran exposure in healthy subjects was increased by 1.5 fold (+53 %) in the presence of quinidine (see “special populations”).

Patients treated for prevention of VTEs after hip or knee replacement surgery, dosing should be reduced to 150 mg taken once daily as 2 capsules of 75 mg Pradaxa if they receive concomitantly dabigatran etexilate and 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.

Clarithromycin

Dabigatran exposure in healthy subjects was increased by about 19 % in the presence of clarithromycin without any clinical safety concern (see “special populations”).

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.

Ketoconazole:

Dabigatran exposure was increased by 2.5 fold (+150%) after single and multiple doses of systemic ketoconazole (see “Contraindications” and “Special populations”). Concomitant treatment with systemic ketoconazole is contraindicated.

Dronedarone:

Dabigatran exposure was increased by 2.1 fold (+114%) after single or 2.4 fold (+136%) after multiple doses of dronedarone, respectively (see “Special populations”). Concomitant treatment with dronedarone is not recommended.

Ticagrelor:

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

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.

Neither clinical nor *in vitro* test results are available for posaconazole which is not recommended for concomitant treatment with Pradaxa.

P- glycoprotein substrate:

Digoxin: In a study performed with 24 healthy subjects, when PRADAXA was coadministered with digoxin, no changes on digoxin and no clinical relevant changes on dabigatran exposure have been observed (see “Special populations”).

P-glycoprotein inducers:

After 7 days of treatment with 600 mg rifampicin qd total dabigatran AUC_{0-∞} and C_{max} were reduced by 67% and 66% compared to the reference treatment, respectively.

The concomitant use with P-gp inducers (e.g., rifampicin, St. John’s wort (*Hypericum perforatum*), carbamazepine, or phenytoin) reduces exposure to dabigatran and should be avoided (see “Special warnings and precautions” and “Special population”).

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 Pradaxa.

Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category C

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

Lactation

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

Fertility

No clinical data available.

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

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

Side effects

Summary of the safety profile

A total of 10,795 patients were treated in 6 actively controlled VTE prevention trials with at least one dose of the medicinal product. Of these 6,684 were treated with 150 mg or 220 mg daily of Pradaxa.

In the RE-LY trial investigating the prevention of stroke and systemic embolism in patients with atrial fibrillation a total of 12,042 patients were treated with 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 total, about 9% of patients treated for elective hip or knee surgery (short-term treatment for up to 42 days) and 22% of patient with atrial fibrillation treated for the prevention of stroke and SEE (long-term treatment for up to 3 years) experienced adverse reactions.

Bleeding is the most relevant side effect of PRADAXA; dependant of the indication bleeding of any type or severity occurred in approximately 14 % of patients treated short-term for elective hip or knee replacement surgery and in long-term treatment in yearly 16.5 % of patient with atrial fibrillation treated for the prevention of stroke and systemic embolism.

Since the patient populations treated in the 2 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 given in tables 5 and 6 below.

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

Tabulated list of adverse reactions

Table 4 shows the adverse reactions identified from the primary VTE prevention studies after hip or knee replacement surgery and the prevention of thromboembolic stroke and SEE in patients with atrial fibrillation program ranked under headings of SOC and frequency using the following

convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

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

Aspartate aminotransferase increased	Uncommon	Uncommon
Hepatic enzyme increased	Uncommon	Rare
Hyperbilirubinaemia	Uncommon	Rare
Skin and subcutaneous tissue disorder		
Skin haemorrhage	Uncommon	Common
Musculoskeletal and connective tissue disorders		
Haemarthrosis	Uncommon	Rare
Renal and urinary disorders		
Genitourological haemorrhage, including haematuria	Uncommon	Common
General disorders and administration site conditions		
Injection site haemorrhage	Rare	Rare
Catheter site haemorrhage	Rare	Rare
Bloody discharge	Rare	-
Injury, poisoning and procedural complications		
Traumatic haemorrhage	Uncommon	Rare
Incision site haemorrhage	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	-

Prevention of VTE

The table 5 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.

	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)

The definition of the adverse reaction major bleeding in the RE-NOVATE and RE-MODEL studies were as follows:

- fatal bleeding
- clinically overt bleeding in excess of what was expected and associated with $\geq 20\text{g/L}$ (corresponds to 1.24mmol/L ; 2g/dl) fall in haemoglobin in excess of what was expected
- clinically overt bleeding in excess of what was expected and leading to transfusion of ≥ 2 units packed cells or whole blood in excess of what was expected
- symptomatic retroperitoneal, intracranial, intraocular or intraspinal bleeding
- bleeding requiring treatment cessation

- bleeding leading to re-operation

Objective testing was required for a retroperitoneal bleed (ultrasound or Computer Tomography (CT) scan) and for an intracranial and intraspinal bleed (CT scan or Magnetic Resonance Imaging).

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

Bleeding [see Warnings and Precautions]

Table 6 shows the number of patients experiencing serious bleeding during the treatment period in the RE-LY study.

Table 6: Frequency and annualized event rate (%) of bleeding events from the RELY trial

	Dabigatran etexilate 110 mg bid N (%)	Dabigatran etexilate 150 mg bid N (%)	Warfarin** N (%)
Patients randomised	6,015	6,076	6,022
Patient-years	11,899	12,033	11,794
Major bleeding event (MBE)*	342 (2.87)	399 (3.32)	421 (3.57)
Hazard ratio vs. warfarin (95% CI)	0.80 (0.70, 0.93)	0.93 (0.81, 1.07)	
p-value	0.0026	0.3146	
Life-threatening MBE	147 (1.24)	179 (1.49)	218 (1.85)
Hazard ratio vs. warfarin (95% CI)	0.67 (0.54, 0.82)	0.80 (0.66, 0.98)	
p-value	0.0001	0.0305	
Intra-cranial hemorrhage (ICH)⁺	27 (0.23)	38 (0.32)	90 (0.76)
Hazard ratio vs. warfarin (95% CI)	0.30 (0.19, 0.45)	0.41 (0.28, 0.60)	
p-value	< 0.0001	< 0.0001	
Any bleeding event ^a	1,754 (14.74)	1,993 (16.56)	2,166 (18.37)
Hazard ratio vs. warfarin (95% CI)	0.78 (0.73, 0.83)	0.91 (0.85, 0.96)	
p-value	< 0.0001	0.0016	

* Adjudicated Bleeds

** Dose-adjusted warfarin to an INR of 2.0 – 3.0

⁺ICH consists of adjudicated hemorrhagic stroke and subdural and/or subarachnoid hemorrhage.

^a Investigator-reported bleeding events

Major bleeding fulfilled one or more of the following criteria:

- Bleeding associated with a reduction in hemoglobin of at least 20 grams per litre (2 g/dl) or leading to a transfusion of at least 2 units of blood or packed cells;
- Symptomatic bleeding in a critical area or organ: intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or

pericardial bleeding.

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

- Fatal bleed; symptomatic intracranial bleed; reduction in hemoglobin of at least 50 grams per litre (5 g/dl); transfusion of at least 4 units of blood or packed cells; a bleed associated with hypotension requiring the use of intravenous inotropic agents; a bleed that necessitated surgical intervention.

The risk of major bleeds was similar with PRADAXA 150 mg and warfarin across major subgroups defined by baseline characteristics, with the exception of age, where there was a trend towards a higher incidence of major bleeding on PRADAXA (hazard ratio 1.2, 95% CI: 1.0 to 1.4) for patients ≥ 75 years of age.

Gastrointestinal Adverse Reactions

Gastrointestinal adverse reactions occurred more often with dabigatran etexilate than warfarin. These were related to dyspepsia (including upper abdominal pain, abdominal pain, abdominal discomfort, epigastric discomfort), or gastritis-like symptoms (including GERD, esophagitis, erosive gastritis, gastric hemorrhage, hemorrhagic gastritis, hemorrhagic erosive gastritis, gastrointestinal ulcer).

Gastrointestinal (GI) hemorrhage occurred at a higher frequency with PRADAXA compared to warfarin (see Table 7). GI adjudicated major bleeds were reported at 1.14%, 1.57%, and 1.07% (annualized rates) in the DE 110 mg, DE 150 mg and warfarin groups, respectively. GI life-threatening bleeds occurred with a frequency of 0.57%, 0.79% and 0.49% in the DE 110 mg, DE 150 mg and warfarin groups, respectively. Any GI bleeds occurred with frequency of 5.41%, 6.13% and 4.02% in the DE 110 mg, DE 150 mg and warfarin groups, respectively. The underlying mechanism of the increased rate of GI bleeding has not been established.

Table 7: Common Adverse Reactions observed in $\geq 1\%$ of dabigatran-treated patients with atrial fibrillation in the active- controlled trial, RELY

	Dabigatran etexilate 110 mg N (%)	Dabigatran etexilate 150 mg N (%)	Warfarin N (%)
	5,983 (100)	6,059 (100)	5,998 (100)
Bleeding and anemia*	599 (10.0)	747 (12.3)	825 (13.8)
Anemia	73 (1.22)	97 (1.60)	74 (1.23)
Epistaxis	66 (1.10)	67 (1.11)	107 (1.78)
Gastrointestinal hemorrhage	196 (3.28)	277 (4.57)	155 (2.58)
Urogenital hemorrhage	66 (1.10)	84 (1.39)	96 (1.60)
Gastrointestinal disorders*	735 (12.3)	772 (12.7)	220 (3.7)
Abdominal pain	135 (2.25)	134 (2.21)	15 (0.25)
Diarrhoea	75 (1.25)	71 (1.17)	11 (0.18)
Dyspepsia	250 (4.18)	234 (3.90)	13 (0.22)
Nausea	58 (0.97)	73 (1.20)	12 (0.20)

*Aggregate incidence presented for all adverse reactions within the body system, including those reactions occurring < 1% and not listed in the Table above.

Hypersensitivity Reactions

In the RE-LY study, drug hypersensitivity (including urticaria, rash, and pruritus), allergic edema, anaphylactic reaction, and anaphylactic shock were reported in <0.1% of patients receiving PRADAXA.

Liver Function Tests

In the long-term RELY study, observed abnormalities of liver function tests (LFT) are presented below in Table 8.

Table 8: Liver Function Tests in the RELY trial

	Dabigatran etexilate 110 mg twice daily N (%)	Dabigatran etexilate 150 mg twice daily N (%)	Warfarin N (%)
Total treated	5,983 (100.0)	6,059 (100.0)	5,998 (100.0)
ALT or AST > 3xULN	118 (2.0)	106 (1.7)	125 (2.1)
ALT or AST > 5xULN	36 (0.7)	45 (0.7)	50 (0.8)
ALT or AST > 3xULN + Bilirubin >2xULN	11 (0.2)	14 (0.2)	21 (0.4)

Overdose

Overdose following administration of PRADAXA may lead to haemorrhagic complications due to its pharmacodynamic properties. A specific antidote antagonising the pharmacodynamic effect of PRADAXA is not available. Doses of PRADAXA beyond those recommended expose the patient to increased risk of bleeding. Excessive anticoagulation may require discontinuation of PRADAXA. 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.

Appropriate standard treatment, e.g. surgical haemostasis as indicated and blood volume replacement, should be undertaken. In addition, consideration may be given to the use of fresh whole blood or fresh frozen plasma. As protein binding is low, dabigatran is dialysable, however there is limited clinical experience in using dialysis in this setting (see “Special populations”). Activated prothrombin complex concentrates (e.g., FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX or X may be considered. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatran but their usefulness in clinical settings and also on the possible risk of rebound thromboembolism have not yet been systematically demonstrated. Coagulation tests may become unreliable following administration of suggested reversing medicinal products.

Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet drugs have been used. All symptomatic treatment has to be given according to the physician's judgement.

Pharmacological properties

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

General

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.

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

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

Prevention of VTE

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 (25th-75th 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 (25th-75th percentile range).

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

- the 90th percentile of dabigatran plasma concentrations was 67 ng/mL, measured at trough (20-28 hours after the previous dose),
- the 90th 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.

Clinical trials in Venous Thromboembolism (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 Pradaxa 75 mg or 110 mg within 1-4 hours of surgery followed by 150 mg (2 capsules of 75 mg) or 220 mg (2 capsules of 110 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 PE, proximal and distal DVT, whatever symptomatic or asymptomatic) 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) 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 Pradaxa 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 9). Better results were seen with the 220 mg dose where the point estimate of Major VTE was slightly better than enoxaparin (table 9).

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 9.

Data for the total VTE and all cause mortality endpoint are shown in table 10.

Data for adjudicated major bleeding endpoints are shown in table 11 below.

Table 9: 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 10: 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 11: 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)

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

The clinical evidence for the efficacy of PRADAXA was derived from RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy), a multi-center, multi-national, randomized parallel group trial comparing two blinded doses of PRADAXA (110 mg twice daily and 150 mg twice daily) with open-label warfarin (dosed to target INR of 2 to 3) in patients with non-valvular, persistent, paroxysmal, or permanent atrial fibrillation and one or more of the following additional risk factors:

- Previous stroke, transient ischemic attack (TIA), or systemic embolism
- Left ventricular ejection fraction <40%
- Symptomatic heart failure, $\geq$ New York Heart Association Class 2
- Age $\geq$ 75 years
- Age $\geq$ 65 years and one of the following: diabetes mellitus, coronary artery disease (CAD), or hypertension

The primary objective of this study was to determine if PRADAXA was non-inferior to warfarin in reducing the occurrence of the composite endpoint, stroke (ischemic and hemorrhagic) and

systemic embolism. The study was designed to ensure that PRADAXA preserved more than 50% of warfarin's effect as established by previous randomized, placebo-controlled trials of warfarin in atrial fibrillation. Statistical superiority was also analyzed.

A total of 18,113 patients were randomized and followed for a median of 2 years. The patient's mean age was 71.5 years and the mean CHADS₂ score was 2.1. The patient population was 64% male, 70% Caucasian, 16% Asian, and 1% black. Twenty percent of patients had a history of a stroke or TIA and 50% were Vitamin K antagonist (VKA) naïve, defined as less than 2 months total lifetime exposure to a VKA. Thirty-two percent of the population had never been exposed to a VKA. Concomitant diseases of patients in this trial included hypertension 79%, diabetes 23%, and CAD 28%. At baseline, 40% of patients were on aspirin and 6% were on clopidogrel. For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2 to 3) was 64%; the mean percentages of time INR measurements were greater than 4 or less than 1.5 were 2% and 5%, respectively.

Relative to warfarin and to PRADAXA 110 mg twice daily, PRADAXA 150 mg twice daily significantly reduced the primary composite endpoint of stroke and systemic embolism (see Table 12 and Figure 1). PRADAXA 110 mg (twice daily) was non-inferior to warfarin in preventing stroke and systemic embolism.

Table 12: Analysis of first occurrence of stroke or systemic embolism (primary endpoint) during the study period in the RELY study

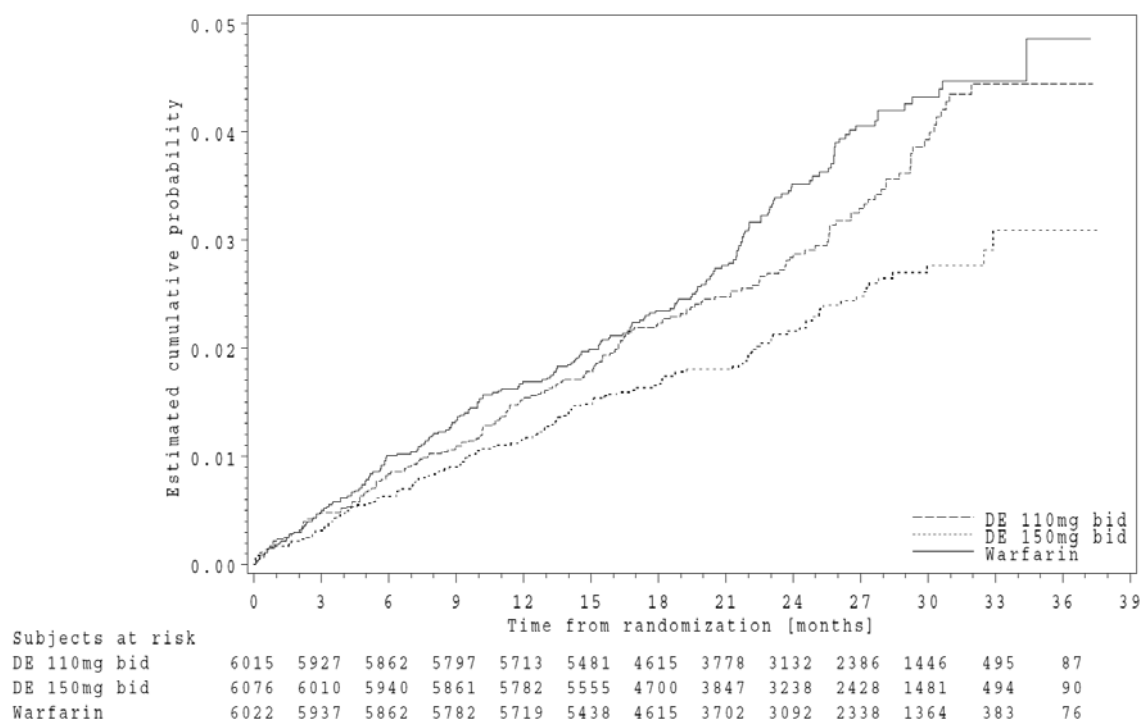
	Dabigatran etexilate 110 mg bid	Dabigatran etexilate 150 mg bid	Warfarin⁺
Patients randomised	6,015	6,076	6,022
Total Stroke and/or SEE **			
No. of events (%) *	183 (1.54)	134 (1.11)	202 (1.71)
Hazard ratio over warfarin (95% CI)	0.90 (0.74, 1.10)	0.65 (0.52, 0.81)	
p-value, superiority	p = 0.2943	p = 0.0001	
p-value, non- inferiority	p < 0.0001	p < 0.0001	

* % refers to yearly event rate

** SEE: systemic embolic event

⁺ dose adjusted, INR 2.0- 3.0

Figure 1: Kaplan-Mayer curve of time to first stroke or systemic embolism in the RELY trial



The contributions of the components of the composite endpoint, including stroke by subtype, are shown in Table 13. The treatment effect was primarily a reduction in stroke. PRADAXA 150 mg twice daily significantly reduced both ischemic and hemorrhagic strokes relative to warfarin.

Table 13: Analysis of first occurrence of ischemic or haemorrhagic strokes during the study period in the RELY study

	Dabigatran etexilate 110 mg bid	Dabigatran etexilate 150 mg bid	Warfarin ⁺
Patients randomised	6,015	6,076	6,022
Total Stroke			
No. of events (%)	171 (1.44)	122 (1.01)	186 (1.58)
Hazard ratio vs. warfarin (95% CI)	0.92 (0.75, 1.14)	0.64 (0.51, 0.81)	
p-value, superiority	0.443	<0.001	
SEE			
No. of events (%)	15 (0.13)	13 (0.11)	21 (0.18)
Hazard ratio vs. warfarin (95% CI)	0.73 (0.37, 1.46)	0.67 (0.33, 1.36)	
p-value, superiority	0.378	0.271	
Ischemic stroke			
No. of events (%)	152 (1.28)	103 (0.86)	134 (1.14)
Hazard ratio vs.	1.14 (0.91, 1.44)	0.76 (0.58, 0.98)	

warfarin (95% CI)			
p-value, superiority	0.258	0.034	
Hemorrhagic stroke			
No. of events (%)	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, superiority	<0.001	<0.001	

⁺ dose adjusted, INR 2.0- 3.0

% refers to yearly event rate

Table 14: Analysis of all cause mortality and cardiovascular mortality during the study period in the RELY study

	Dabigatran etexilate 110 mg bid	Dabigatran etexilate 150 mg bid	Warfarin+
Patients randomised	6,015	6,076	6,022
All-cause mortality			
No. of events (%)	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	0.0516	
Vascular mortality *			
No. of events (%)	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	0.2093	0.0430	

⁺ dose adjusted, INR 2.0- 3.0

% refers to yearly event rate

* vascular mortality: cardiac death (includes sudden and non-sudden cardiac death, e.g. pump failure), and mortality due to stroke, pulmonary embolus, peripheral embolus, aortic dissection/rupture, hemorrhage and deaths of unknown cause

For the randomised set, there was an imbalance in adjudicated MI with an increased frequency observed in the dabigatran etexilate (DE) treatment groups compared to the warfarin treatment group.

Table 15: Other Measures Evaluated in the RELY study

	Dabigatran etexilate 110 mg bid N(%)	Dabigatran etexilate 150 mg bid N(%)	Warfarin N(%)
Patients randomised	6,015	6,076	6,022
Myocardial infarction*			
No. of events (%)	98 (0.82)	97 (0.81)	75 (0.64)
Hazard ratio vs. Warfarin (95%CI)	1.29 (0.96, 1.75)	1.27 (0.94, 1.71)	
p-value	0.0929	0.1240	

% refers to yearly event rate

*myocardial infarction including silent MI

Table 16: Yearly event rates and hazard ratios for stroke/SEE by age groups in the RELY trial

	Dabigatran etexilate 110 mg bid	Dabigatran etexilate 150 mg bid	Warfarin⁺
Patients < 65 years , N = 2,981			
Annual event rate (%/ year)	1.47	0.69	1.35
Hazard ratio vs. warfarin (95% CI)	1.10 (0.64, 1.87)	0.51 (0.26, 0.98)	
Patients ≥65 - <75 years, N = 7,894			
Annual event rate (%/ year)	1.26	0.98	1.45
Hazard ratio vs. warfarin (95% CI)	0.87 (0.62, 1.20)	0.68 (0.47,0.96)	
Patients ≥ 75 years, N = 7,238			
Annual event rate (%/ year)	1.89	1.43	2.15
Hazard ratio vs. warfarin (95% CI)	0.88 (0.66, 1.17)	0.67 (0.49, 0.90)	

⁺ dose adjusted, INR 2.0 – 3.0

Table 17: Yearly event rates and hazard ratios for major bleeding events by age groups in the RELY trial

	Dabigatran etexilate 110 mg bid	Dabigatran etexilate 150 mg bid	Warfarin⁺
Patients < 65 years , N= 2,981			
Annual event rate (%/ year)	0.81	0.88	2.43
Hazard ratio vs. warfarin (95% CI)	0.33 (0.19, 0.59)	0.36 (0.21, 0.62)	
Patients ≥65 - <75 years, N = 7,894			
Annual event rate (%/ year)	2.29	2.60	3.24
Hazard ratio vs. warfarin (95% CI)	0.70 (0.56, 0.89)	0.80 (0.64,1.00)	
Patients ≥ 75 years, N = 7,238			
Annual event rate (%/ year)	4.44	5.12	4.39
Hazard ratio vs. warfarin (95% CI)	1.01 (0.83, 1.23)	1.18 (0.98, 1.43)	

⁺ dose adjusted, INR 2.0 – 3.0

Centers were ranked post hoc by the percentage of time that warfarin-treated patients were in therapeutic range (INR 2 to 3). Findings for stroke/systemic embolism, all-cause mortality, and major bleeds are shown for centers above and below the median level of INR control in Table 18. The benefits of PRADAXA 150 mg relative to warfarin were most apparent in patients enrolled at centers with INR control below the median.

Table 18 Center INR Control in the RE-LY Study

	Centers with INR control below the median of 67%	Centers with INR control above the median of 67%
Stroke/systemic embolism	0.57 (0.42, 0.76)	0.76 (0.55, 1.05)
All-cause mortality	0.78 (0.66, 0.93)	1.01 (0.84, 1.23)
Major bleed	0.82 (0.68, 0.99)	1.08 (0.89, 1.31)

For patients with age ≥ 75 years, the major bleeding rates on DE 110, DE 150, and warfarin were 4.44, 5.12, and 4.39% / year, respectively. For this age class, the ICH (intracranial hemorrhage) rates were 0.37, 0.40 and 1.00% / year, respectively.

The major bleeding rates by CHADS score on DE 110, DE 150, and warfarin were 1.59, 1.00, and 2.17% / year for CHADS score=0, 1.88, 2.20, and 2.90% / year, respectively, for CHADS score=1, 2.98, 3.04 and 3.31% / year, respectively, for CHADS score=2, and 3.80, 4.86 and 4.61% / year for CHADS score ≥ 3 .

The data for the efficacy and safety of East Asian sub-population.

Table 19 Yearly event rate (%) for composite endpoint of stroke/SEE in all East Asian subjects

	DE 110 N (%)	DE 150 N (%)	Warfarin N (%)
Subjects randomized	545	552	551
Subject-years	1071	1076	1055
Subjects with stroke/SEE	20 (1.87)	19 (1.77)	24 (2.28)
Stroke	19 (1.77)	19 (1.77)	22 (2.09)
Ischemic stroke	15 (1.40)	16 (1.49)	16 (1.52)
Haemorrhagic stroke	1 (0.09)	3 (0.28)	6 (0.57)
Stroke of uncertain classifications	3 (0.28)	2 (0.19)	1 (0.09)
SEE	1 (0.09)	0 (0.00)	3 (0.28)

Each subject with an event was counted once for the composite endpoint and once for each component of the composite endpoint. Subject-years = sum (date of study termination – date of randomization +1) of all randomized subjects / 365.25.

Yearly event rate (%) = # of subjects with event / subject-years * 100

Table 20 Frequency and yearly event rate (%) of major bleeding events in the East Asian population

	DE 110 N (%)	DE 150 N (%)	Warfarin N (%)
Number of subjects adjudicated as bleeding events	545	552	551
Subject-years	1071	1076	1055
Major bleeds	26 (2.43)	21 (1.95)	34 (3.22)
Life threatening MBEs	11 (1.03)	14 (1.3)	19 (1.80)
Other MBEs	15 (1.40)	10 (0.93)	17 (1.61)

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

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

Pharmacokinetics

Dabigatran etexilate mesylate is absorbed as the dabigatran etexilate ester. The ester is then hydrolyzed, forming dabigatran, the active moiety. Dabigatran is metabolized to four different acyl glucuronides and both the glucuronides and dabigatran have similar pharmacological activity. Pharmacokinetics described here refer to the sum of dabigatran and its glucuronides. Dabigatran displays dose-proportional pharmacokinetics in healthy subjects and patients in the range of doses from 10 to 400 mg.

Absorption

The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate is approximately 3 to 7%. Dabigatran etexilate is a substrate of the efflux transporter P-gp. After oral administration of dabigatran etexilate in healthy volunteers, C_{max} occurs at 1 hour post-administration in the fasted state. Coadministration of PRADAXA with a high-fat meal delays the time to C_{max} by approximately 2 hours but has no effect on the bioavailability of dabigatran; PRADAXA may be administered with or without food.

The oral bioavailability of dabigatran etexilate increases by 75% when the pellets are taken without the capsule shell compared to the intact capsule formulation. PRADAXA capsules should therefore not be broken, chewed, or opened before administration.

Distribution

Dabigatran is approximately 35% bound to human plasma proteins. The red blood cell to plasma partitioning of dabigatran measured as total radioactivity is less than 0.3. The volume of distribution of dabigatran is 50 to 70 L. Dabigatran pharmacokinetics are dose proportional after single doses of 10 to 400 mg. Given twice daily, dabigatran's accumulation factor is approximately two.

Elimination

Dabigatran is eliminated primarily in the urine. Renal clearance of dabigatran is 80% of total clearance after intravenous administration. After oral administration of radiolabeled dabigatran, 7% of radioactivity is recovered in urine and 86% in feces. The half-life of dabigatran in healthy subjects is 12 to 17 hours.

Metabolism

After oral administration, dabigatran etexilate is converted to dabigatran. The cleavage of the dabigatran etexilate by esterase-catalyzed hydrolysis to the active principal dabigatran is the predominant metabolic reaction. Dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes. Dabigatran is subject to conjugation forming pharmacologically active acyl glucuronides. Four positional isomers, 1-O, 2-O, 3-O, and 4-O-acylglucuronide exist, and each accounts for less than 10% of total dabigatran in plasma.

Special populations

Renal impairment:

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

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

Clearance of dabigatran by hemodialysis was investigated in 7 patients with end-stage renal disease (ESRD) without atrial fibrillation. Dialysis was conducted with 700ml/min dialysate flow rate, four hour duration, a blood flow rate of either 200ml/min or 350 - 390ml/min. This resulted in a removal of 50% or 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 30-50 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).

Elderly:

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

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

The observed increase of dabigatran exposure correlated with the age-related reduction in creatinine clearance.

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

Hepatic insufficiency:

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

Prevention of venous thromboembolic events (VTE) following major orthopedic surgery of the lower limbs in patients with a high risk for VTE.

Patients with moderate and severe hepatic impairment (Child-Pugh classification B and C) or liver disease expected to have any impact on survival or with elevated liver enzymes ≥ 2 Upper Limit Normal (ULN) were excluded in clinical trials.

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

Patients with active liver disease including but not limited to the persistent elevation of liver enzymes ≥ 2 Upper Limit Normal (ULN), or hepatitis A, B or C were excluded in clinical trials. Treatment experience is limited for patients with hepatic impairment, and therefore the use of Pradaxa is not recommended in this population.

Body weight:

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

Gender:

In atrial fibrillation patients females had on average 1.3-fold (+30 %) higher trough and post-dose concentrations.

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

This finding had no clinical relevance.

Ethnic origin:

The pharmacokinetics of dabigatran was investigated in Caucasian and Japanese volunteers after single and multiple doses. Ethnic origin does not affect the pharmacokinetics of dabigatran in a clinically relevant manner.

Limited pharmacokinetic data in black patients are available which suggest no relevant differences.

Pharmacokinetic interactions:

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

Atorvastatin: When dabigatran etexilate was coadministered with atorvastatin, a CYP3A4 substrate, exposure of atorvastatin, atorvastatin metabolites and of dabigatran were not changed clinically meaningful.

Diclofenac: When dabigatran etexilate was coadministered with diclofenac, a CYP2C9 substrate, pharmacokinetics of both drugs were not changed clinically meaningful indicating insignificant interaction between dabigatran etexilate and diclofenac.

P-gp inhibitor / inducer interactions

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

Co-medication with P-gp inhibitors

Amiodarone: When dabigatran etexilate was coadministered with a single oral dose of 600 mg amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The dabigatran AUC and $C_{\max}$ were increased by about 1.6-fold and 1.5-fold (+60 % and 50 %), respectively.

In the population pharmacokinetics study from RE-LY, no important changes in dabigatran trough levels were observed in patients who received amiodarone (see section on “interactions”).

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

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

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

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

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

In the population pharmacokinetics study from RE-LY, no important changes in dabigatran trough levels were observed in patients who received verapamil (see section on “interactions”).

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

systemic ketoconazole is contraindicated.

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

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

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

Co-medication with P-gp substrates

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

Co-medication with P-gp inducers

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

Co-medications with platelet-inhibitors:

Acetylsalicylic acid (ASA): The effect of concomitant administration of dabigatran etexilate and acetylsalicylic acid (ASA) on the risk of bleeds was studied in patients with atrial fibrillation in a phase II study in which a randomized ASA coadministration was applied. Based on logistic regression analysis, co-administration of ASA and 150 mg dabigatran etexilate twice daily may increase the risk for any bleeding from 12 % to 18 % and 24% with 81 mg and 325 mg ASA, respectively. From the data gathered in the phase III study RE-LY it was observed that ASA or clopidogrel co-medication with dabigatran etexilate at dosages of 110 or 150 mg bid may increase the risk of major bleeding. The higher rate of bleeding events by ASA or clopidogrel co-medication was, however, also observed for warfarin.

NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. If use NSAID with half-lives > 12 hours during treatment with dabigatran etexilate, close observation for signs of bleeding is recommended.

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

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

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

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.

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.

Co-medication with gastric pH-elevating agents:

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

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

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

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

Toxicology

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 pharmacodynamics 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.

Storage conditions

Blister:

Store below 30°C. Store in the original package in order to protect from moisture.

Bottle:

Store below 30°C. Once opened, the product must be used within 4 months.

Keep the bottle tightly closed. Store in the original package in order to protect from moisture.

Store in a safe place out of the reach of children!

Manufactured by

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