

New Zealand Datasheet

Name of Medicine

PRADAXA[®]

Dabigatran etexilate

Presentation

75 mg hard capsules: Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 2 filled with yellowish pellets. The cap is imprinted in black ink with the Boehringer Ingelheim company symbol, the body with R75.

110 mg hard capsules: Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 1 filled with yellowish pellets. The cap is imprinted in black ink with the Boehringer Ingelheim company symbol, the body with R110.

150 mg hard capsules: Imprinted hypromellose capsules with light blue, opaque cap and cream-coloured, opaque body of size 0 filled with yellowish pellets. The cap is imprinted in black ink with the Boehringer Ingelheim company symbol, the body with R150.

Indications

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with nonvalvular atrial fibrillation with one or more of the following risk factors:

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

Prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.

Dosage and Administration

PRADAXA hard capsules should be taken with water, with or without food. The capsule should not be chewed broken or opened as this may increase the bioavailability of dabigatran.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation

Adults:

The recommended daily dose of PRADAXA is 300 mg taken orally as 150 mg hard capsules twice daily, unless otherwise stated. Therapy should be continued life-long. In case of intolerability, patients should be instructed to contact their doctor.

Children:

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

Elderly:

Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure in those patients with age-related decline of renal function. As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the creatinine clearance (CrCl) prior to initiation of treatment with PRADAXA to exclude patients for treatment with severe renal impairment (i.e. CrCl < 30 ml/min). The renal function should also be assessed at least once a year in patients treated with PRADAXA or more frequently as needed in certain

clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc), see also Dosage and Administration - Renal Impairment.

Patients aged 80 years or above should be treated with a daily dose of 220 mg taken orally as 110 mg hard capsules twice daily. Patients aged 75 to 80 years may take the lower dose of 110mg capsule twice daily if their thromboembolic risk is low and bleeding risk is high.

Renal impairment:

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). There are no data to support use in patients with severe renal impairment (< 30 ml/min creatinine clearance); treatment in this population with dabigatran etexilate is not recommended (see 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). In patients with moderate renal impairment (CrCl 30-50 ml/min) the renal function should be assessed at least once a year.

In patients with adequate renal function (CrCl > 50 ml/min) no dose adjustment is necessary. Patients should be treated with a daily dose of 300 mg taken orally as 150 mg hard capsules twice daily.

In patients with moderate renal impairment (30 to 50 ml/min creatine clearance) a reduced dose of 220 mg given as 110 mg capsule twice daily may be considered if the bleeding risk is high and the throboembolic risk is low.

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

Weight:

There is little clinical experience in patients <50 kg or >110 kg. Given the available data no dose adjustment is necessary.

Concomitant use of PRADAXA with strong P-glycoprotein inhibitors e.g. 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.

Concomitant use of PRADAXA with strong P-glycoprotein inducers

The concomitant use of PRADAXA with the strong P-gp inducer rifampicin reduces dabigatran plasma concentrations. Other P-gp inducers such as St. John`s Wort or carbamazepine are also expected to reduce dabigatran plasma concentrations, and should be co-administered with caution. No dose adjustment is required when dabigatran etexilate is co-administered with atorvastatin, diclofenac, P-gp substrates and gastric pH elevating agents such as PPIs or H2-blockers (see Pharmacokinetics).

Patients at risk of bleeding:

The presence of the following factors may increase the risk of bleeding: e.g. age ≥ 75 years, moderate renal impairment (CrCL 30-50 ml /min), concomitant treatment with strong P-gp inhibitors (see Pharmacokinetics - special populations), or previous gastro-intestinal bleed (see Warnings and Precautions). For patients with one or more than one of these risk factors, a reduced daily dose of 220 mg given as 110 mg twice daily may be considered at the discretion of the physician.

Switching from 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 Vitamin K antagonists to PRADAXA:

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

Switching from PRADAXA to Vitamin K antagonists:

The starting time of the warfarin should be adjusted according to the patient's creatinine clearance as follows:

- For CrCl \geq 50 ml/min, start warfarin 3 days before discontinuing PRADAXA.
- For CrCl 30-<50 ml/min, start warfarin 2 days before discontinuing PRADAXA.

Cardioversion

Patients can stay on dabigatran etexilate 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.

VTE prevention following major orthopaedic surgery**Adults:***VTE prevention following major orthopaedic surgery:*

The recommended dose of PRADAXA is 220 mg once daily taken as 2 capsules of 110 mg. Patients with moderate renal impairment have an increased risk for bleeding. For those patients the recommended dose of PRADAXA is 150 mg once daily, taken as 2 capsules of 75 mg.

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

VTE prevention following knee replacement surgery:

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

VTE prevention following hip replacement surgery:

Treatment with PRADAXA should be initiated orally within 1 - 4 hours of completed surgery with a single capsule (110 mg) and continuing with 2 capsules once daily thereafter for a total of 28 – 35 days. If haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

Children:

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

Elderly:

Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure in those patients with age-related decline of renal function. As renal impairment may be frequent in the

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

No dose adjustment is necessary, patients should be treated with 220 mg dabigatran etexilate taken once daily as 2 capsules of 110 mg.

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 (CrCl <30 ml/min); 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).

Dosing should be reduced to 150 mg PRADAXA taken once daily as 2 capsules of 75 mg in patients with moderate renal impairment (30-50 ml/min creatinine clearance).

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

Weight:

There is little clinical experience in patients <50 kg or >110 kg. Given the available data no dose adjustment is necessary.

Concomitant use of dabigatran etexilate with strong P-glycoprotein inhibitors e.g. amiodarone, quinidine or verapamil:

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 following major orthopaedic surgery who are already treated with dabigatran etexilate. Simultaneous initiation of treatment with PRADAXA and verapamil should also be avoided.

The concomitant use of PRADAXA with the strong P-gp inducer rifampicin reduces dabigatran plasma concentrations. Other P-gp inducers such as St. John`s Wort or carbamazepine are also expected to reduce dabigatran plasma concentrations, and should be co-administered with caution. No dose adjustment is required when PRADAXA is co-administered with atorvastatin, diclofenac, P-gp substrates and gastric pH elevating agents such as PPIs or H2-blockers (see Pharmacokinetics).

Switching from PRADAXA treatment to parenteral anticoagulant:

Wait 24 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 Vitamin K antagonists to PRADAXA:

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

Missed dose

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

Contraindications

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

Warnings and Precautions

Haemorrhagic risk:

As with all anticoagulants, dabigatran etexilate should be used with caution in conditions with an increased risk of bleeding. Bleeding can occur at any site during therapy with dabigatran. An unexplained fall in hemoglobin and/or hematocrit or blood pressure should lead to a search for a bleeding site. Fatal bleeding may occur as with any anticoagulant, but there were fewer fatal bleeds with dabigatran etexilate than with warfarin in the RE-LY study. In this study of prevention of stroke and SEE in adult patients with nonvalvular atrial fibrillation, 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) (see Table 3 in Adverse Effects).

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

The following table summarises factors which may increase the haemorrhagic risk as identified in clinical studies.

Table 1

Factors increasing dabigatran plasma levels	<ul style="list-style-type: none">• Moderate renal impairment (30-50 ml/min CrCl)• P-glycoprotein-inhibitor co-medication
Pharmacodynamic interactions	<ul style="list-style-type: none">• Acetylsalicylic acid• NSAID• Clopidogrel
Diseases / procedures with special haemorrhagic risks	<ul style="list-style-type: none">• Congenital or acquired coagulation disorders• Thrombocytopenia or functional platelet defects• Active ulcerative gastrointestinal disease• Recent gastrointestinal bleeding• Recent biopsy or major trauma• Recent intracranial haemorrhage• Brain, spinal or ophthalmic surgery• Bacterial endocarditis
Others	<ul style="list-style-type: none">• Age ≥ 75 years

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

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

In atrial fibrillation patients in RE-LY 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 must discontinue PRADAXA.

Factors, such as decreased renal function (30 - 50ml/min CrCL), age ≥ 75 years, or strong P-gp-inhibitor comedication are associated with increased dabigatran plasma levels. The presence of one or more than one of these factors may increase the risk of bleeding (see Dosage 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, sulfipyrazone, rivaroxaban, prasugrel, ticagrelor, vitamin K antagonists, and the P-gp inhibitors dronedarone, itraconazole, tacrolimus, cyclosporine, ritonavir, tipranavir, nelfinavir and saquinavir.

The concomitant use of dronedarone increases exposure of dabigatran and is not recommended (see Pharmacokinetics - Special Populations).

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

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 stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

Co-administration of oral anti-platelet (including aspirin and clopidogrel) and NSAID therapies increase the risk of bleeding.

VTE prevention following major orthopaedic surgery:

NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. There is limited

evidence regarding the use of regular NSAID medication with half-lives of less than 12 hours during treatment with dabigatran etexilate and this has not suggested additional bleeding risk.

Hepatic impairment:

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 as well as in RE-LY study investigating the prevention of stroke and systemic emboli associated with atrial fibrillation. No treatment experience is available for this subpopulation of patients, and therefore the use of PRADAXA is not recommended in this population (see Pharmacokinetics).

Interaction with P-gp inducers:

The concomitant use of dabigatran etexilate with the strong P-gp inducer rifampicin reduces dabigatran plasma concentrations. Other P-gp inducers such as St. John`s Wort or carbamazepine are also expected to reduce dabigatran plasma concentrations, and should be co-administered with caution (see Interactions and Pharmacokinetics - Special Populations).

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 PRADAXA.

Preoperative Phase

Due to an increased risk of bleeding PRADAXA may be stopped temporarily in advance of invasive or surgical procedures. If possible, dabigatran etexilate should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete hemostasis may be required consider stopping dabigatran etexilate 2-4 days before surgery. Clearance of dabigatran in patients with renal insufficiency may take longer. This should be considered in advance of any procedures (see Table 2 and also Table 7 in Pharmacokinetics).

Table 2 summarizes discontinuation rules before invasive or surgical procedures.

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

*for more details see Table 7 Pharmacokinetics

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

If an acute intervention is required, 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 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 1 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.

The product contains the excipient sunset yellow, which may cause allergic reactions.

Use in Pregnancy

No clinical data on exposed pregnancies are available. The potential risk for humans is unknown.

Women of child-bearing potential should avoid pregnancy during treatment with dabigatran etexilate and when pregnant, women should not be treated with dabigatran etexilate unless the expected benefit is greater than the risk.

Use in Lactation

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

Fertility

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

Effects on Ability to Drive and Use Machines

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

Paediatric Use

There is no experience in children. PRADAXA has not been investigated in patients <18 years of age. Treatment of children with PRADAXA is not recommended.

Adverse Effects

The safety of PRADAXA has been evaluated overall in 22,687 patients.

In the primary VTE prevention trials after major orthopaedic surgery a total of 10,596 patients were treated in 5 controlled studies with at least one dose of study medication. Of these 5,674 were treated with 150 or 220 mg once daily of PRADAXA, while 522 received doses less than 150 mg once daily and 1168 received doses in excess of 220 mg once daily.

In the RE-LY trial investigating the prevention of stroke and systemic embolism in patients with atrial fibrillation a total of 12,091 patients were randomised. Of these 6,076 were treated with 150 mg twice daily of PRADAXA, while 6,015 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 systemic embolism (long-term treatment for up to 3 years) experienced adverse reactions.

Bleeding

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

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

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

Major bleeding fulfilled one or more of the following criteria:

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

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

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

Subjects randomized to dabigatran etexilate 110 mg twice daily and 150mg twice daily had a significantly lower risk for life-threatening bleeds, haemorrhagic stroke and intracranial bleeding compared to warfarin (p < 0.05). Both dose strengths of dabigatran etexilate had also a statistically significant lower total bleed rate. Subjects randomised to dabigatran etexilate 110mg twice daily had a significantly lower risk for major bleeds compared with warfarin (hazard ratio 0.80, p= 0.0026)

Table 3: Bleeding events broken down to major and any bleeding in the pivotal study testing the prevention of thromboembolic SSE in patients with atrial fibrillation.

	Dabigatran etexilate 110 mg twice daily	Dabigatran etexilate 150 mg twice daily	Warfarin
Subjects randomized	6,015	6,076	6,022
Major Bleeding	342 (2.87 %)	399 (3.32 %)	421 (3.57 %)
Intracranial bleeding	27 (0.23 %)	38 (0.32 %)	90 (0.76 %)
Gastrointestinal bleeding	134 (1.14 %)	186 (1.57 %)	125 (1.07 %)
Fatal bleeding	23 (0.19 %)	28 (0.23 %)	39 (0.33 %)
Minor bleeding	1,566 (13.16 %)	1,787 (14.85%)	1,931 (16.37%)
Any bleeding	1,754 (14.74 %)	1,993 (16.56 %)	2,166 (18.37 %)

% refers to yearly event rate

VTE prevention following major orthopaedic surgery.

Overall bleeding rates were similar between treatment groups and not significantly different.

Table 4, below, shows the number (%) of patients experiencing bleeding events during the treatment period in the VTE prevention in the two pivotal clinical trials, according to dose.

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

Side effects

Adverse reactions classified by SOC and MedDRA preferred terms reported from any treatment group per population of all controlled studies are shown in the listings below. Table 5 lists identified side effects applicable to both indications. Table 6 lists indication specific side effects identified.

Side effects are generally associated to the pharmacological mode of action of dabigatran etexilate and represent bleeding associated events that may occur in different anatomical regions and organs.

In patients treated for VTE prevention after hip or knee replacement surgery the observed incidences of side effects of dabigatran etexilate were in the range of enoxaparin.

The observed incidences of side effects of dabigatran etexilate in patients treated for stroke prevention after atrial fibrillation were in the range of warfarin except gastrointestinal disorders which appeared at a higher rate in the dabigatran etexilate arms.

Table 5: Side effects identified from the Primary VTE prevention studies after major orthopaedic surgery program and the Prevention of thromboembolic stroke and systemic embolism in patients with atrial fibrillation at moderate to high risk of stroke program. Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1000$); very rare ($< 1/10,000$).

Blood and lymphatic system disorders	
Common	Anaemia
Uncommon	Thrombocytopenia
Immune system disorders	
Uncommon	Drug hypersensitivity, rash, pruritus,
Rare	Urticaria
Unknown	Bronchospasm
Nervous system disorders	
Uncommon	Intracranial haemorrhage
Vascular disorders	
Uncommon	Haematoma, haemorrhage
Respiratory, thoracic and mediastinal disorders	
Common	Epistaxis
Uncommon	Haemoptysis
Gastrointestinal disorders	
Common	Gastrointestinal haemorrhage, abdominal pain, diarrhoea, dyspepsia, nausea
Uncommon	Gastrointestinal ulcer, gastroesophagitis, gastroesophageal reflux disease, vomiting, dysphagia
Hepatobiliary disorders	
Common	Hepatic function abnormal
Skin and subcutaneous tissue disorders	
Uncommon	Skin haemorrhage
Musculoskeletal, connective tissue and bone disorders	
Uncommon	Haemarthrosis
Renal and urinary disorders	
Common	Urogenital haemorrhage
Uncommon	Haematuria
General disorders and administration site conditions	
Rare	Injection site haemorrhage, catheter site haemorrhage

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

Table 6: Additional specific side effects identified per indication

<i>VTE prevention following major orthopaedic surgery.</i>	
Vascular disorders	
Uncommon	Wound haemorrhage
General disorders and administration site conditions	
Rare	Bloody discharge
Injury, poisoning and procedural complications	
Uncommon	Post-procedural haematoma, Post-procedural haemorrhage, Anaemia post-operative, Post-procedural discharge, Wound secretion,
Surgical and medical procedures	
Rare	Wound drainage, Post-procedural drainage,
<i>Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:</i>	
None	

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 (refer to Dosage and Administration and 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).

Anticoagulants and platelet aggregation agents:

The following treatments should not be administered concomitantly with dabigatran etexilate: unfractionated heparins and heparin derivatives low molecular weight heparins (LMWH), except for bridging situations when switching from dabigatran etexilate treatment to parenteral anticoagulant or vice versa, factor Xa inhibitors like fondaparinux, other thrombin inhibitors like desirudin, thrombolytic agents, GpIIb/IIIa receptor antagonists, anti-thrombotic agents like ticlopidine, dextran, sulfinpyrazone and vitamin K antagonists except for converting patients from dabigatran etexilate to vitamin K antagonists. It should be noted that unfractionated heparin 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 it was observed that ASA or clopidogrel co-medication with dabigatran etexilate at dosages of 110 mg or 150 mg twice daily may increase the risk of major bleeding. The higher rate of bleeding events by ASA or clopidogrel co-medication was also observed for warfarin.

The co-administration of low-dose aspirin and / or clopidogrel with dabigatran etexilate should be accompanied by clinical observation for bleeding.

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 and clarithromycin) is expected to result in increased dabigatran plasma concentrations.

Concomitant administration of systemic ketoconazole is contraindicated.

For the other P-gp inhibitors listed above no dose adjustments are required for PRADAXA in the indication "prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation".

For the concomitant use of P-gp inhibitors and dosing of PRADAXA in the indication "Prevention of Venous Thromboembolism (VTE) in patients who have undergone major orthopaedic surgery" please see Dosage and Administration and Pharmacokinetics - Special Populations.

Amiodarone: Dabigatran exposure in healthy subjects was increased by 1.6 fold (+60%) in the presence of amiodarone (see Pharmacokinetics - special populations).

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

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

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

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

Clarithromycin: Dabigatran exposure in healthy subjects was increased by 19% in the presence of clarithromycin without any clinical safety concern (see Pharmacokinetics - special populations).

Ketoconazole: Dabigatran exposure was increased by 2.5-fold (+150%) after single and multiple doses of systemic ketoconazole (see Contraindications and Pharmacokinetics - Special Populations).

Dronedarone: Dabigatran exposure was increased by 2.1 fold (+114%) after single or 2.4 fold (+136%) after multiple doses of dronedarone, respectively (see Pharmacokinetics - Special Populations).

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 Pharmacokinetics - Special Populations).

P-glycoprotein inducers:

After 7 days of treatment with 600 mg rifampicin once daily 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) reduces exposure to dabigatran and should be avoided (see Warnings and Precautions and Pharmacokinetics - special population).

Overdosage

Overdose following administration of dabigatran etexilate may lead to haemorrhagic complications due to its pharmacodynamic properties. A specific antidote antagonising the pharmacodynamic effect of dabigatran etexilate is not available. Doses of dabigatran etexilate beyond those recommended expose the patient to increased risk of bleeding. Excessive anticoagulation may require discontinuation of dabigatran etexilate. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained.

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 Pharmacokinetics - 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 has not yet been systematically demonstrated. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet drugs have been used. All symptomatic treatment has to be given according to the physician's judgement.

Pharmaceutical Precautions

CAPSULES (blister packs): Store below 30°C. Protect from moisture.

CAPSULES (bottle): Store below 30°C. Protect from moisture. Once opened, the bottle must be used within 4 months. Keep the bottle tightly closed.

Medicine Classification

Prescription Medicine

Package Quantities

Capsules 75 mg: Blister packs: 10, 30, 60 capsules.
Bottle: 60 capsules.

Capsules 110mg : Blister packs: 10, 30, 60 capsules.
Bottle: 60 capsules.

Capsules 150mg : Blister packs: 10, 30, 60 capsules.
Bottle: 60 capsules.

Not all pack sizes may be marketed.

Further Information

PRADAXA[®] is a registered Trademark

Excipients

Capsule fill: Tartaric acid, acacia, hypromellose, dimethicone 350, talc, hydroxypropylcellulose

HPMC capsule shell: Sodium carragenan, potassium chloride, titanium dioxide, sunset yellow FCF (E110), indigo carmine (E132), hypromellose, water - purified

Printing ink: Shellac, tert-butyl alcohol, isopropyl alcohol, methylated spirit - industrial, iron oxide black (E172), water - purified, propylene glycol.

Actions

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

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 concentration and degree of anticoagulant effect. Dabigatran prolongs the aPTT, ECT and TT.

Pharmacokinetics

After oral administration of dabigatran etexilate in healthy volunteers, the pharmacokinetic profile of dabigatran in plasma is characterised by a rapid increase in plasma concentrations with C_{max} attained within 0.5 and 2.0 hours post administration. C_{max} and the area under the plasma concentration-time curve were dose proportional. After C_{max}, plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of 11 hours in healthy elderly subjects. After multiple dose a terminal half-life of about 12-14 hours was observed. The half-life was independent of dose. However, half-life is prolonged if renal function is impaired as shown below, in Table 7.

Table 7: 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)

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

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

The oral bioavailability may be increased by about 1.8-fold (+75%) compared to the reference capsule formulation when the pellets are taken without the HPMC capsule shell. Hence, the integrity of the HPMC capsules should always be preserved in clinical use to avoid unintentionally increased bioavailability of dabigatran etexilate. Therefore, patients should be advised not to open the capsules and taking the pellets alone (e.g. sprinkled over food or into beverages) (see Dosage and Administration).

A study evaluating post-operative absorption of dabigatran etexilate, 1-3 hours following surgery, demonstrated relatively slow absorption compared with that in healthy volunteers, showing a smooth plasma concentration-time profile without high peak plasma concentrations. Peak plasma concentrations are reached at 6 hours following administration, or at 7 to 9 hours following surgery

(BISTRO Ib). It is noted however that contributing factors such as anaesthesia, gastrointestinal paresis, and surgical effects will mean that a proportion of patients will experience absorption delay independent of the oral drug formulation. Although this study did not predict whether impaired absorption persists with subsequent doses, it was demonstrated in a further study that slow and delayed absorption is usually only present on the day of surgery. On subsequent days absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after drug administration.

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

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

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

Special populations

Renal impairment:

The exposure (AUC) of dabigatran after the oral administration of dabigatran etexilate in a phase I study was approximately 2.7 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 Dosage and Administration and Contraindications sections).

Clearance of dabigatran by hemodialysis was investigated in 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 free- or total dabigatran concentrations, respectively. The amount of drug cleared by dialysis is proportional to the blood flow rate. The anticoagulant activity of dabigatran decreased with decreasing plasma concentrations and the PK/PD relationship was not affected by the procedure

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 patients:

Specific pharmacokinetic studies with elderly subjects in phase 1 studies showed an increase of 1.4- to 1.6-fold (+40 to 60%) in the AUC and of more than 1.25-fold (+25%) in C_{max} compared to young subjects. The AUC_{T,ss} and C_{max,ss} in male and female elderly subjects (>65 years) were

approximately 1.9 fold and 1.6-fold higher for elderly females compared to young females and 2.2 and 2.0 fold higher for elderly males than in male subjects of 18 - 40 years of age. The observed increase of dabigatran exposure correlated with the age-related reduction in creatinine clearance.

The effect by age on exposure to dabigatran was confirmed in the RE-LY 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 of age between 65 and 75 years.

Hepatic insufficiency:

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

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation.

Patients with active liver disease including but not limited to the persistent elevation of liver enzymes ≥ 2 Upper Limit Normal (ULN), or hepatitis A, B or C were excluded in clinical trials.

VTE prevention following major orthopaedic surgery.

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

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:

Drug exposure in the primary VTE prevention studies was about 1.4- to 1.5-fold (+40% to 50%) higher in female patients. In atrial fibrillation patients females had on average 1.3-fold (+30%) higher trough and post-dose concentrations. This finding had no clinical relevance.

Ethnic origin:

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

Pharmacokinetic interactions:

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

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

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

P-gp inhibitor / inducer interactions

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

Co-medication with P-gp inhibitors

Amiodarone: When dabigatran etexilate was 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 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.

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 once daily.. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole.

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

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

Co-medication with P-gp substrates

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

Co-medication with P-gp inducers

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.

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 bd 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. There is limited evidence regarding the use of regular NSAID medication with half-lives of less than 12 hours during treatment with dabigatran etexilate and this has not suggested additional bleeding risk.

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

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

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

Co-medication with selective serotonin re-uptake inhibitors:

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

Co-medication with gastric pH-elevating agents:

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

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.

Clinical Trials

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

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

In the RE-LY study, a total of 18,113 patients were randomised, with a mean age of 71.5 years and a mean CHADS₂ score of 2.1. The population had approximately equal proportions of patients with CHADS₂ score 1, 2 and ≥ 3. The patient population was 64% male, 70% Caucasian and 16% Asian. RE-LY had a median treatment of 20 months with dabigatran etexilate given as fixed dose without coagulation monitoring. In addition to documented non-valvular atrial fibrillation (AF) e.g., persistent AF or paroxysmal, patients had one of the following additional risk factors for stroke:

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

The concomitant diseases of patients in this trial included hypertension 79%, diabetes 23% and CAD 28%. 50% of the patient population was VKA naïve defined as less than 2 months total life time exposure. 32% of the population had never been exposed to a VKA. For those patients randomised to warfarin, the time in therapeutic range (INR 2 to 3) for the trial was a median of 67%. Concomitant medications included aspirin (25% of subjects used at least 50% of the time in study), clopidogrel (3.6%), ASA+clopidogrel (2%), NSAIDs (6.3%), beta-blockers (63.4%), diuretics (53.9%), statins (46.4%), ACE-inhibitors (44.6%), angiotensin receptor blockers (26.1%), oral hypoglycemics (17.5%), insulin (5.2%), digoxin (29.4%), amiodarone (11.3%), diltiazem (8.9%), verapamil (5.4%), and proton pump inhibitors (17.8%).

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

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

Figure 1 and tables 8 - 12 display details of key results:

Table 8: Analysis of first occurrence of stroke or systemic embolism (primary endpoint) during the study period in the RE-LY

	Dabigatran etexilate 150 mg bid	Dabigatran etexilate 110 mg bid	Warfarin
Subjects randomized	6076	6015	6022
Stroke and/or SEE			
Incidences (%)	134 (1.11)	183 (1.54)	202 (1.71)
Hazard ratio over warfarin (95% CI)	0.65 (0.52, 0.81)	0.90 (0.74, 1.10)	
p value superiority	p < 0.0001	p = 0.2943	

% refers to yearly event rate

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

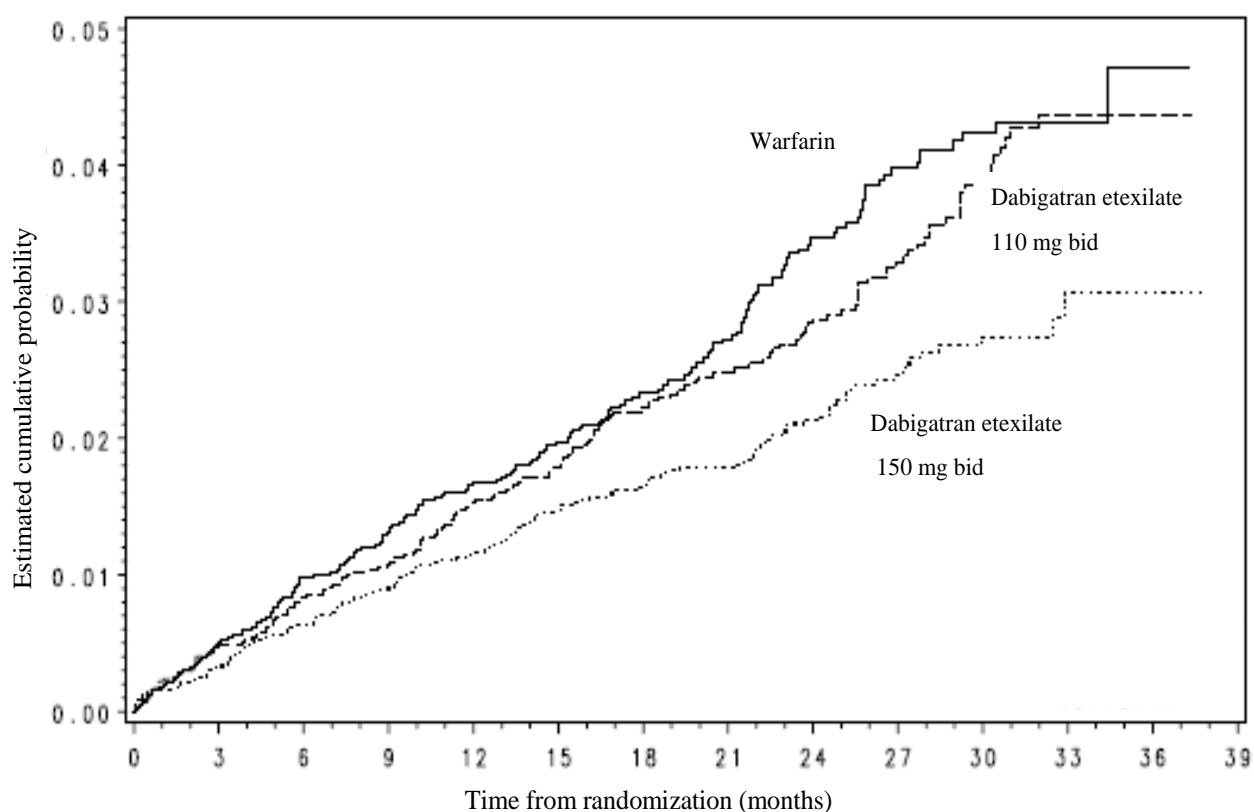


Table 9: Analysis of first occurrence of ischemic or haemorrhagic strokes during the study period in the RE-LY

	Dabigatran etexilate 150 mg bid	Dabigatran etexilate 110 mg bid	Warfarin
Subjects randomized	6076	6015	6022
Stroke			
Incidences (%)	122 (1.01)	171 (1.44)	186 (1.58)
Hazard ratio vs. warfarin (95% CI)	0.64 (0.51, 0.81)	0.91 (0.74, 1.12)	
p-value	<0.0001	0.3828	

SEE			
Incidences (%)	13 (0.11)	15 (0.13)	21 (0.18)
Hazard ratio vs. warfarin (95% CI)	0.61 (0.30, 1.21)	0.71 (0.37, 1.38)	
p-value	0.1582	0.3099	
Ischemic stroke			
Incidences (%)	103 (0.86)	152 (1.28)	134 (1.14)
Hazard ratio vs. warfarin (95% CI)	0.75 (0.58, 0.97)	1.13 (0.89, 1.42)	
p-value	0.0296	0.3139	
Hemorrhagic stroke			
Incidences (%)	12 (0.10)	14 (0.12)	45 (0.38)
Hazard ratio vs. warfarin (95% CI)	0.26 (0.14, 0.49)	0.31 (0.17, 0.56)	
p-value	<0.001	<0.001	

% refers to yearly event rate

Table 10: Analysis of all cause and cardiovascular survival during the study period in the RE-LY

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

% refers to yearly event rate

The net clinical benefit (NCB) as measured by the unweighted composite clinical endpoint of stroke, systemic embolism, pulmonary embolism, acute myocardial infarction, vascular deaths, and major bleeds was assessed and is presented as part of Table 9. The yearly event rates for the dabigatran etexilate groups were lower compared to the warfarin group. The risk reduction for this composite endpoint was 8% and 10% for the dabigatran etexilate 110 mg bd and 150 mg bd treatment groups. Other components evaluated included all hospitalisations which had statistically significant fewer hospitalizations at dabigatran etexilate 110 mg bd compared to warfarin (7% risk reduction, 95% CI 0.87, 0.99, p=0.021).

Table 11: Other Measures Evaluated

	Dabigatran etexilate 150 mg bid	Dabigatran etexilate 110 mg bid	Warfarin
Subjects randomized	6076	6015	6022
Stroke/SEE/death			
Incidences (%)	520 (4.32)	577 (4.85)	613 (5.20)
Hazard ratio vs. warfarin (95%CI)	0.83 (0.74, 0.93)	0.93 (0.83, 1.045)	
p-value	0.0015	0.2206	

Stroke/SEE/PE/MI/death/maj or bleed (net clinical benefit)			
Incidences (%)	848 (7.05)	863 (7.25)	925 (7.84)
Hazard ratio vs. Warfarin (95%CI)	0.90 (0.82, 0.99)	0.92 (0.84, 1.01)	
p-value	0.0254	0.0852	
Pulmonary embolism			
Incidences (%)	18 (0.15)	14 (0.12)	12 (0.10)
Hazard ratio vs. Warfarin (95%CI)	1.41 (0.71, 3.06)	1.16 (0.54, 2.51)	
p-value	0.2980	0.7076	
Myocardial infarction			
Incidences (%)	97 (0.81)	98 (0.82)	75 (0.64)
Hazard ratio vs. Warfarin (95%CI)	1.27 (0.94, 1.71)	1.29 (0.96, 1.75)	
p-value	0.1240	0.0929	

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). In the RE-LY AF patients, the modest imbalance in MI to the disfavor of dabigatran etexilate compared to warfarin is counterbalanced by dabigatran etexilate's larger beneficial effects on stroke reduction and lower observed rates of CV mortality and total mortality, compared to warfarin. The totality of the evaluated data with dabigatran etexilate allows the conclusion that MI is not an adverse consequence of the administration of dabigatran etexilate.

Table 12: Liver Function Tests

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

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

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

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

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

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

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

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

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

In RE-MODEL and RENOVATE the randomisation to the respective study medication was done pre-surgery, and in the RE-MOBILIZE and the Japanese placebo controlled trial the randomisation to the respective study medication was done post-surgery. This is of note especially in the safety evaluation of these trials. For this reason the trials are grouped in pre and post surgery randomised trials in Table 13.

Data for the major VTE and VTE-related mortality end-point and adjudicated major bleeding endpoints are shown in Table 13 below. VTE was defined as the composite incidence of deep vein thrombosis and Pulmonary Embolism.

Table 13 - Analysis of major VTE and VTE-related mortality during the treatment period in the RE-MODEL and the RE-NOVATE orthopaedic surgery studies

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

RE-MOBILIZE (knee) ²	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 60 mg
N	618	656	668
Incidences (%)	21 (3.4)	20 (3.0)	15 (2.2)
Risk differences vs. enoxaparin (%)	1.2	0.8	
95 % CI	(-0.7, 3.0)	(-0.9, 2.5)	
Risk ratio over enoxaparin	1.51	1.36	
95% CI	(0.79, 2.91)	(0.70, 2.63)	
Japanese knee study ²			
			Placebo
N	102	113	104
Incidences (%)	0	2 (1.8)	6 (5.8)
Risk differences vs. placebo (%)	-5.8	-4.0	
95 % CI	(-10.3, -1.3)	(-9.1, 1.1)	
¹	pre-operative randomisation studies		
²	post-operative randomisation studies		

Pre-clinical Toxicology

Acute oral toxicity studies were conducted in rats and mice. In both species, the approximate lethal dose after single oral administration was above 2000 mg/kg. In dogs and Rhesus monkeys, oral administration of 600 mg/kg dabigatran etexilate did not induce any toxicologically meaningful changes.

In repeat-dose toxicity studies over a maximum of 26 weeks in rats and 52 weeks in Rhesus monkeys, dosages up to 300 mg/kg (free base equivalent) were used. Generally, these doses were tolerated remarkably well by both, rats and Rhesus monkeys. Bleeding problems were observed in association with traumata (e.g. blood sampling) within the first 4 – 6 hours after administration and are directly related to the pharmacodynamic activity of dabigatran.

Teratology studies were performed with up to 200 mg/kg (free base equivalent) in rats and rabbits. A slight effect on the morphogenesis of foetuses was observed in rats at 200 mg/kg (free base equivalent). No teratogenic effects were noted in rabbits.

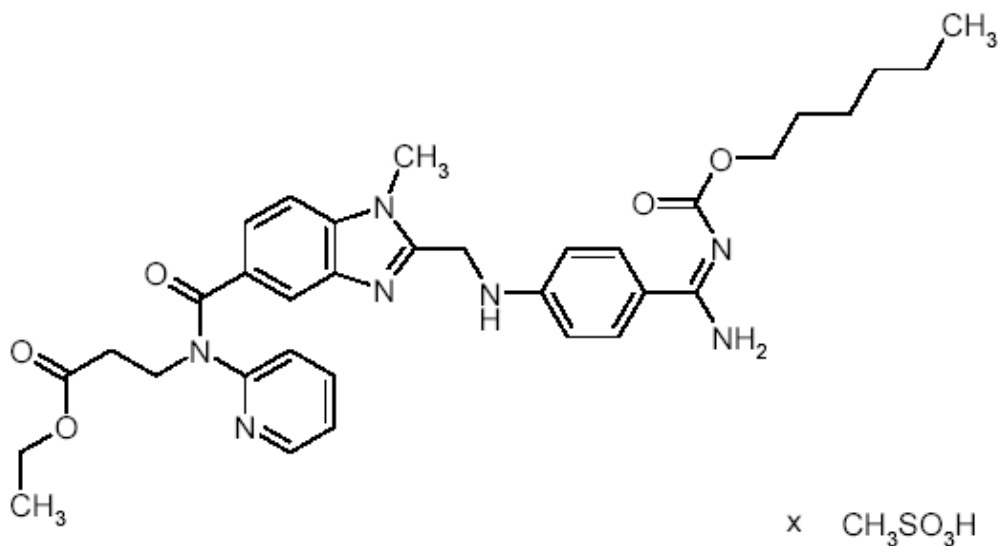
In the fertility study in rats, no toxicologically remarkable parental findings were noted. With respect to litter parameters, a slight decrease in corpora lutea and an increase in pre-implantation loss led to a decrease in the mean number of implantations in the 200 mg/kg (free base equivalent) dose group.

Comprehensive *in vitro* and *in vivo* studies revealed no evidence of a mutagenic potential.

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 (free base equivalent).

Chemical Structure

Dabigatran etexilate is 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.



Molecular Formula: C₃₅H₄₅N₇O₈S

CAS Registry Number: 211915-06-9 (free base)
593282-20-3 (mesilate)

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