



Pradaxa[®]

dabigatran etexilate



Product Information

Second Edition

Marketed by:



Rafa Laboratories Ltd.

Under license from:



Boehringer
Ingelheim

PRADAXA® PRODUCT INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 75 hard capsules

Pradaxa 110 hard capsules

Pradaxa 150 hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Pradaxa 75 mg hard capsule contains 75 mg of dabigatran etexilate (as mesilate).

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

Each Pradaxa 150 mg hard capsule contains 150 mg of dabigatran etexilate (as mesilate).

Excipients:

Each Pradaxa 75 mg hard capsule contains 2 micrograms sunset yellow (E110).

Each Pradaxa 110 mg hard capsule contains 3 micrograms sunset yellow (E110).

Each Pradaxa 150 mg hard capsule contains 4 micrograms sunset yellow (E110).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pradaxa 75 mg hard capsules have a light blue, opaque cap and cream-coloured, opaque body of size 2 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with "R75".

Pradaxa 110 mg hard capsules have a light blue, opaque cap and cream-coloured, opaque body of size 1 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with "R110".

Pradaxa 150 mg hard capsules have a light blue, opaque cap and cream-coloured, opaque body of size 0 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with "R150".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pradaxa 75 mg and 110 mg: Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

Pradaxa 110 mg and 150 mg: Prevention of stroke and systemic embolism in adult patients with atrial fibrillation.

4.2 Posology and method of administration

Posology

Prevention of Venous Thromboembolism (VTE)

Patients following elective knee replacement surgery

The recommended dose of Pradaxa is 220 mg once daily taken as 2 capsules of 110 mg. Treatment should be initiated orally within 1-4 hours of completed surgery with a single

capsule 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 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 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.

Elderly

In elderly patients (> 75 years) there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg (see sections 4.4 and 5.1).

Renal impairment

Treatment with Pradaxa in patients with severe renal impairment (creatinine clearance (CrCL) < 30 ml/min) is contraindicated (see section 4.3).

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 (see sections 4.4 and 5.1).

Concomitant use of Pradaxa with strong P-glycoprotein (P-gp) inhibitors, i.e. amiodarone, quinidine or verapamil

Dosing should be reduced to 150 mg taken once daily as 2 capsules of 75 mg Pradaxa in patients who receive concomitantly dabigatran etexilate and amiodarone, quinidine or verapamil (see sections 4.4 and 4.5). In this situation Pradaxa and these medicinal products should be taken at the same time.

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 sections 4.4 and 4.5).

Hepatic impairment

Patients with elevated liver enzymes > 2 X 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 (see sections 4.4 and 5.2).

Weight

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

Gender

Given the available clinical and kinetic data, no dose adjustment is necessary (see section 5.2).

Switching

Pradaxa treatment to parenteral anticoagulant

It is recommended to wait 24 hours after the last dose before switching from Pradaxa to a parenteral anticoagulant (see section 4.5).

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)) (see section 4.5).

Paediatric population

There is no relevant use of Pradaxa in the paediatric population in the indication: primary prevention of venous thromboembolic events in patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

Pradaxa is not recommended for use in patients below 18 years due to lack of data on safety and efficacy.

Missed dose

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

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

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

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

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

Elderly

Patients between 75-80 years should be treated with a daily dose of 300 mg taken as one 150 mg capsule twice daily. A dose of 220 mg taken as one 110 mg capsule twice daily can be individually considered, at the discretion of the physician, when the thromboembolic risk is low and the bleeding risk is high (see section 4.4).

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

Patients at risk of bleeding

Patients with an increased bleeding risk (see sections 4.4, 4.5, 5.1 and 5.2) should be closely monitored clinically (looking for signs of bleeding or anaemia). Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient. A coagulation test (see section 4.4) may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. When excessive dabigatran exposure is identified in patients at high risk of bleeding, a dose of 220 mg taken as one 110 mg capsule twice daily is recommended. When clinically

relevant bleeding occurs, treatment should be interrupted.

For subjects with gastritis, esophagitis, or gastroesophageal reflux, the dose of 220 mg taken as one 110 mg capsule twice daily may be considered due to the elevated risk of major gastro-intestinal bleeding (see section 4.4).

Renal impairment

Treatment with Pradaxa in patients with severe renal impairment (creatinine clearance (CrCL) < 30 ml/min) is contraindicated (see section 4.3).

No dose adjustment is necessary in patients with mild renal impairment (CrCL 50- ≤ 80 ml/min). For patients with moderate renal impairment (CrCL 30-50 ml/min) the recommended dose of Pradaxa is also 300 mg taken as one 150 mg capsule twice daily. However, for patients with high risk of bleeding, a dose reduction of Pradaxa to 220 mg taken as one 110 mg capsule twice daily should be considered (see sections 4.4 and 5.2). Close clinical surveillance is recommended in patients with renal impairment.

Concomitant use of Pradaxa with strong P-glycoprotein (P-gp) inhibitors, i.e. amiodarone, quinidine or verapamil

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

Dosing should be reduced to 220 mg taken as one 110 mg capsule twice daily in patients who receive concomitantly dabigatran etexilate and verapamil (see sections 4.4 and 4.5). In this situation Pradaxa and verapamil should be taken at the same time.

Hepatic impairment

Patients with elevated liver enzymes > 2 X upper limit of normal (ULN) were excluded in the study investigating the prevention of stroke and SEE 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 sections 4.4 and 5.2).

Weight

Given the available clinical and kinetic data, no dose adjustment is necessary (see section 5.2), but close clinical surveillance is recommended in patients with a body weight < 50 kg (see section 4.4).

Gender

Given the available clinical and kinetic data, no dose adjustment is necessary (see section 5.2).

Switching

Pradaxa treatment to parenteral anticoagulant

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

Parenteral anticoagulants to 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)) (see section 4.5).

Pradaxa treatment to Vitamin K antagonists (VKA)

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

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

VKA to Pradaxa

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

Cardioversion

Patients can stay on dabigatran etexilate while being cardioverted.

Paediatric population

There is no relevant use of Pradaxa in the paediatric population in the indication: prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Pradaxa is not recommended for use in patients below 18 years due to lack of data on safety and efficacy.

Missed dose

A forgotten dabigatran etexilate dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose on, the missed dose should be omitted.

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

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 (see sections 5.2 and 6.6).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Patients with severe renal impairment (CrCL < 30 ml/min)
- Active clinically significant bleeding
- Organic lesion at risk of bleeding
- Spontaneous or pharmacological impairment of haemostasis
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with systemic ketoconazole, itraconazole, cyclosporine, and tacrolimus (see section 4.5)

4.4 Special warnings and precautions for use

Hepatic impairment

Patients with elevated liver enzymes $> 2 \times$ ULN were excluded in controlled clinical trials investigating the VTE prevention following elective hip or knee replacement surgery as well as in the study investigating the prevention of stroke and SEE 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.

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 haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site.

Factors, such as decreased renal function (30-50 ml/min CrCL), age \geq 75 years, low body weight < 50 kg, or strong P-gp inhibitor co-medication (e.g. amiodarone, quinidine or verapamil) are associated with increased dabigatran plasma levels (see sections 4.2, 4.5 and 5.2).

In the RE-LY study, dabigatran 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 (\geq 75 years). Use of acetylsalicylic acid (ASA), clopidogrel or non steroidal antiinflammatory drug (NSAID), as well as the presence of esophagitis, gastritis or gastroesophageal reflux requiring proton pump inhibitors (PPI) or histamine 2 (H2)-blocker treatment increase the risk of GI bleeding. In these patients a dosage of 220 mg dabigatran given as 110 mg capsule twice daily should be considered (see section 4.2). The administration of a PPI can be considered to prevent GI bleeding.

Close clinical surveillance (looking for signs of bleeding or anaemia) is recommended throughout the treatment period, especially if risk factors are combined (see section 5.1).

Table 1 summarises factors which may increase the haemorrhagic risk.

Pharmacodynamic and kinetic factors	<ul style="list-style-type: none">• Age \geq 75 years
Factors increasing dabigatran plasma levels	<p><u>Major:</u></p> <ul style="list-style-type: none">• Moderate renal impairment (30-50 ml/min CrCL)• P-gp inhibitor co-medication <p><u>Minor:</u></p> <ul style="list-style-type: none">• Low body weight (< 50 kg)
Pharmacodynamic interactions	<ul style="list-style-type: none">• ASA• NSAID• Clopidogrel
Disease / procedures with special haemorrhagic risks	<ul style="list-style-type: none">• Congenital or acquired coagulation disorders• Thrombocytopenia or functional platelet defects• Active ulcerative GI disease• Recent GI bleeding• Recent biopsy or major trauma• Recent intracranial hemorrhage (ICH)• Brain, spinal or ophthalmic surgery• Bacterial endocarditis

The measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors.

The activated partial thromboplastin time (aPTT) test is widely available and provides an approximate indication of the anticoagulation intensity achieved with dabigatran. In patients who are bleeding or at risk of bleeding, the aPTT test may be useful to assist in determining an excess of anticoagulant activity. However, the aPTT test has limited sensitivity and is not

suitable for precise quantification of anticoagulant effect, especially at high plasma concentrations of dabigatran. An aPTT greater than 80 sec is associated with a higher risk of bleeding but high aPTT values should be interpreted with caution.

If required, more sensitive quantitative tests such as calibrated diluted Thrombin Time (dTT) should be performed (see section 5.1).

Patients who develop acute renal failure must discontinue Pradaxa (see section 4.3).

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

When severe bleedings occur treatment must be discontinued and the source of bleeding investigated (see section 4.9).

Agents that may enhance the risk of haemorrhage should not be administered concomitantly or should be administered with caution with Pradaxa (see section 4.5).

Interaction with P-gp inducers

Concomitant administration of P-gp inducers (such as rifampicin, St. John`s wort (*Hypericum perforatum*), carbamazepine, or phenytoin) is expected to result in decreased dabigatran plasma concentrations, and should be avoided (see sections 4.5 and 5.2).

Surgery and interventions

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

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

Preoperative phase

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)

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 the risk of bleeding may be increased. This risk of bleeding should be weighed against the urgency of intervention.

Spinal anaesthesia/epidural anaesthesia/lumbar puncture

Procedures such as spinal anaesthesia may require complete haemostatic function.

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

Post-surgical patients with an increased risk for bleeding

Patients at risk for bleeding or patients at risk of overexposure, notably patients with moderate renal impairment (CrCL 30-50 ml/min), should be treated with caution (see sections 4.4 and 5.1). Resume treatment after complete haemostasis is achieved.

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

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

Hip fracture surgery

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

Myocardial Infarction

In the phase III study RE-LY (see section 5.1.) the overall rate of myocardial infarction (MI) was 0.82, 0.81, and 0.64 % / year for dabigatran etexilate 110 mg twice daily, dabigatran etexilate 150 mg twice daily and warfarin, respectively, an increase in relative risk for dabigatran of 29 % and 27 % compared to warfarin (not statistically significant). Irrespective of therapy, the highest absolute risk of MI was seen in the following subgroups, with similar relative risk: patients with previous MI, patients ≥ 65 years with either diabetes or coronary artery disease, patients with left ventricular ejection fraction < 40 %, and patients with moderate renal dysfunction. Furthermore a higher risk of MI was seen in patients concomitantly taking ASA plus clopidogrel or clopidogrel alone.

Colorants

Pradaxa hard capsules contain the colorant sunset yellow (E110), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Anticoagulants and antiplatelet aggregation agents

The following treatments have not been studied and may increase the risk of bleeding when used concomitantly with Pradaxa: UFH, low molecular weight heparins (LMWH), and heparin derivatives (fondaparinux, desirudin), thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, prasugrel, dextran, sulfapyrazone, rivaroxaban, and vitamin K antagonists (see section 4.4).

UFH can be administered at doses necessary to maintain a patent central venous or arterial catheter (see sections 4.2 and 4.4).

Clopidogrel: In a phase I study in young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times compared to clopidogrel monotherapy. In addition, dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ and the coagulation measures for dabigatran effect or the inhibition of platelet aggregation as measure of clopidogrel effect remained essentially unchanged

comparing combined treatment and the respective mono-treatments. With a loading dose of 300 mg or 600 mg clopidogrel, dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ were increased by about 30-40 % (see section 4.4).

ASA: The effect of concomitant administration of dabigatran etexilate and ASA on the risk of bleeds was studied in patients with atrial fibrillation in a phase II study in which a randomized ASA co-administration was applied. Based on logistic regression analysis, co-administration of ASA and 150 mg dabigatran etexilate twice daily may increase the risk for any bleeding from 12 % to 18 % and 24 % with 81 mg and 325 mg ASA, respectively (see section 4.4).

From the data collected in the phase III study RE-LY (see section 5.1) 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 (see section 4.4). The higher rate of bleeding events by ASA or clopidogrel co-medication was also observed for warfarin.

NSAIDs: NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use in the RE-LY study, NSAIDs increased the risk of bleeding by approximately 50 % on both dabigatran and warfarin. Therefore, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives > 12 hours, close observation for signs of bleeding is recommended (see section 4.4).

LMWH: The concomitant use of LMWHs, such as enoxaparin, and dabigatran etexilate has not been specifically investigated. After switching from 3-day treatment of once daily 40 mg enoxaparin s.c., 24 hours after the last dose of enoxaparin the exposure to dabigatran was slightly lower than that after administration of dabigatran etexilate (single dose of 220 mg) alone. A higher anti-FXa/FIIa activity was observed after dabigatran etexilate administration with enoxaparin pre-treatment compared to that after treatment with dabigatran etexilate alone. This is considered to be due to the carry-over effect of enoxaparin treatment, and regarded as not clinically relevant. Other dabigatran related anti-coagulation tests were not changed significantly by the pre-treatment of enoxaparin.

Interactions linked to dabigatran etexilate and dabigatran metabolic profile

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

Transporter interactions

P-gp inhibitors

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

If not otherwise specifically described, close clinical surveillance (looking for signs of bleeding or anaemia) is required when dabigatran is co-administered with strong P-gp inhibitors. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure (see sections 4.2, 4.4 and 5.1).

Systemic ketoconazole, cyclosporine, itraconazole and tacrolimus are contraindicated (see section 4.3). Caution should be exercised with other strong P-gp inhibitors (e.g. amiodarone, quinidine or verapamil) (see sections 4.2 and 4.4).

Ketoconazole: Ketoconazole increased total dabigatran $AUC_{0-\infty}$ and C_{max} values by 138 % and 135 %, respectively, after a single dose of 400 mg, and 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 (see section 4.4). Concomitant treatment with systemic ketoconazole is contraindicated (see section 4.3).

Amiodarone: When Pradaxa was co-administered with a single oral dose of 600 mg amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The dabigatran AUC and C_{max} were increased by about 60 % and 50 %, respectively. The mechanism of the interaction has not been completely clarified. In view of the long half-life of amiodarone the potential for drug interaction may exist for weeks after discontinuation of amiodarone (see sections 4.2 and 4.4).

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 (see section 4.2). Close clinical surveillance is recommended when dabigatran etexilate is combined with amiodarone and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.

Quinidine: Quinidine was given as a 200 mg dose every 2nd hour up to a total dose of 1000 mg. Dabigatran etexilate was given twice daily over 3 consecutive days, on the 3rd day either with or without quinidine. Dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ were increased on average by 53 % and 56 %, respectively with concomitant quinidine (see sections 4.2 and 4.4).

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 (see section 4.2). Close clinical surveillance is recommended when dabigatran etexilate is combined with quinidine and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.

Verapamil: When dabigatran etexilate (150 mg) was co-administered with oral verapamil, the C_{max} and AUC of dabigatran were increased but the magnitude of this change differs depending on timing of administration and formulation of verapamil (see sections 4.2 and 4.4).

The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to 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 (increase of C_{max} by about 90 % and AUC by about 70 %) or administration of multiple doses of verapamil (increase 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 sections 4.2 and 4.4).

For patients with nonvalvular atrial 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 (see section 4.2).

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 section 4.4).

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

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, tacrolimus and cyclosporine, which are contra-indicated (see section 4.3).

Neither clinical nor in vitro test results are available for posaconazole which is not recommended for concomitant treatment with Pradaxa. Inadequate clinical data are available regarding the co-administration of Pradaxa and dronedarone, and their co-administration is not recommended (see section 4.4).

P-gp inducers

Concomitant administration of a P-gp inducer (such as rifampicin, St. John's wort (*Hypericum perforatum*), carbamazepine, or phenytoin) is expected to result in decreased dabigatran concentrations and should be avoided (see sections 4.4 and 5.2).

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

Other drugs 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.

P-gp substrate

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.

Gastric pH

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Pradaxa in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Women of child-bearing potential should avoid pregnancy during treatment with dabigatran etexilate. Pradaxa should not be used during pregnancy unless clearly necessary.

Breast-feeding

There are no clinical data of the effect of dabigatran on infants during breast-feeding.

Breast-feeding should be discontinued during treatment with Pradaxa.

Fertility

No human data are available.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

A total of 10,084 patients were treated in 4 actively controlled VTE prevention trials with at least one dose of the medicinal product. Of these 5,419 were treated with 150 mg or 220 mg daily of Pradaxa, while 389 received doses less than 150 mg daily and 1168 received doses in excess of 220 mg daily.

In the pivotal RE-LY study investigating the prevention of stroke and SEE in patients with atrial fibrillation, a total of 12,091 patients were randomized to 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 patients with atrial fibrillation treated for the prevention of stroke and SEE (long-term treatment for up to 3 years) experienced adverse reactions.

The most commonly reported adverse reactions are bleedings occurring in total in approximately 14 % of patients treated short-term for elective hip or knee replacement surgery, and 16.5 % in patients with atrial fibrillation treated for the prevention of stroke and SEE.

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 4 and 5 below.

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

Adverse reactions

Table 3 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 ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

Table 3	Primary VTE prevention after hip or knee replacement surgery		Stroke and SEE prevention in patients with atrial fibrillation	
	Dabigatran etexilate 150mg once daily	Dabigatran etexilate 220mg once daily	Dabigatran etexilate 110mg twice daily	Dabigatran etexilate 150mg twice daily
Number of patients treated	2,737	2,682	5,983	6,059
<i>Blood and lymphatic system disorders</i>				
Anemia	Common	Common	Common	Common
Haemoglobin decreased	Common	Common	Uncommon	Uncommon
Thrombocytopenia	Uncommon	Uncommon	Uncommon	Uncommon
Haematocrit decreased	Uncommon	Uncommon	Rare	Rare
<i>Immune system disorders</i>				
Drug hypersensitivity	Uncommon	Uncommon	Uncommon	Uncommon
Rash	Uncommon	Uncommon	Uncommon	Uncommon
Pruritus	Uncommon	Uncommon	Uncommon	Uncommon
Urticaria	Rare	Rare	Rare	Rare
Bronchospasm	Not known	Not known	Not known	Very rare
<i>Nervous system disorders</i>				
Intracranial haemorrhage	Uncommon	Uncommon	Uncommon	Uncommon
<i>Vascular disorders</i>				
Haematoma	Uncommon	Uncommon	Uncommon	Uncommon
Wound haemorrhage	Uncommon	Uncommon	-	-
Haemorrhage	Uncommon	Uncommon	Uncommon	Uncommon
<i>Respiratory, thoracic and mediastinal disorders</i>				
Epistaxis	Common	Common	Common	Common
Haemoptysis	-	-	Uncommon	Uncommon
<i>Gastrointestinal disorders</i>				
Gastrointestinal haemorrhage	Common	Common	Common	Common
Abdominal pain	Common	Common	Common	Common
Diarrhoea	Common	Common	Common	Common

Table 3	Primary VTE prevention after hip or knee replacement surgery		Stroke and SEE prevention in patients with atrial fibrillation	
	SOC / Preferred Term	Dabigatran etexilate 150mg once daily	Dabigatran etexilate 220mg once daily	Dabigatran etexilate 110mg twice daily
Dyspepsia	Common	Common	Common	Common
Nausea	Common	Common	Common	Common
Rectal haemorrhage	Uncommon	Uncommon	Uncommon	Uncommon
Haemorrhoidal haemorrhage	Uncommon	Uncommon	Uncommon	Uncommon
Gastrointestinal ulcer	Uncommon	Uncommon	Uncommon	Uncommon
Gastroesophagitis	Uncommon	Uncommon	Uncommon	Uncommon
Gastroesophageal reflux disease	Uncommon	Uncommon	Uncommon	Uncommon
Vomiting	Uncommon	Uncommon	Uncommon	Uncommon
Dysphagia	Uncommon	Uncommon	Uncommon	Uncommon
<i>Hepatobiliary disorders</i>				
Alanine aminotransferase increased	Uncommon	Uncommon	Uncommon	Uncommon
Aspartate aminotransferase increased	Uncommon	Uncommon	Uncommon	Uncommon
Hepatic function abnormal / Liver function test abnormal	Uncommon	Uncommon	Uncommon	Uncommon
Hepatic enzyme increased	Uncommon	Uncommon	Rare	Rare
Transaminases increased	Uncommon	Uncommon	-	-
Hyperbilirubinaemia	Uncommon	Uncommon	Rare	Rare
<i>Skin and subcutaneous tissue disorders</i>				
Skin hemorrhage	Uncommon	Uncommon	Uncommon	Uncommon
<i>Musculoskeletal and connective tissue and bone disorders</i>				
Haemarthrosis	Uncommon	Uncommon	Rare	Rare
<i>Renal and urinary disorders</i>				
Genitourological haemorrhage	-	-	Uncommon	Common
Haematuria	Uncommon	Uncommon	Uncommon	Uncommon
<i>General disorders and administration site conditions</i>				
Injection site haemorrhage	Rare	Rare	Rare	Rare
Catheter site haemorrhage	Rare	Rare	Rare	Rare
Bloody discharge	Uncommon	Uncommon	-	-
<i>Injury, poisoning and procedural complications</i>				
Traumatic haemorrhage	Uncommon	Uncommon	-	-
Post procedural haematoma	Uncommon	Uncommon	-	-

Table 3	Primary VTE prevention after hip or knee replacement surgery		Stroke and SEE prevention in patients with atrial fibrillation	
	SOC / Preferred Term	Dabigatran etexilate 150mg once daily	Dabigatran etexilate 220mg once daily	Dabigatran etexilate 110mg twice daily
Post procedural haemorrhage	Uncommon	Uncommon	-	-
Anaemia postoperative	Uncommon	Uncommon	-	-
Post procedural discharge	Uncommon	Uncommon	-	-
Wound secretion	Uncommon	Uncommon	-	-
Incision site haemorrhage	Rare	Rare	Rare	Rare
<i>Surgical and medical procedures</i>				
Wound drainage	Uncommon	Uncommon	-	-
Post procedural drainage	Rare	Rare	-	-

Prevention of VTE

Bleeding

Table 4 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.

Table 4	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 major bleeding events 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 ≥ 20 g/l (corresponds to 1.24 mmol/l) 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

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

Table 5	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 %)
- GI 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 %)

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

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

Major bleeds were classified as life-threatening if they fulfilled one or more of the following criteria: Fatal bleed; symptomatic intracranial bleed; reduction in haemoglobin of at least 50 g/l; transfusion of at least 4 units of blood or packed cells; a bleed associated with hypotension requiring the use of intravenous inotropic agents; a bleed that necessitated surgical intervention.

Subjects randomized to dabigatran etexilate 110 mg twice daily or 150 mg twice daily had a significantly lower risk for life-threatening bleeds and intracranial bleeding compared to warfarin [$p < 0.05$]. Both dose strengths of dabigatran etexilate had also a statistically significant lower total bleed rate. Subjects randomized to dabigatran etexilate 110 mg twice daily had a significantly lower risk for major bleeds compared with warfarin (hazard ratio 0.80 [$p=0.0026$]). Subjects randomized to dabigatran etexilate 150 mg twice daily had a significantly higher risk for major GI bleeds compared with warfarin (hazard ratio 1.47 [$p=0.0008$]). This effect was seen primarily in patients ≥ 75 years.

The clinical benefit of dabigatran with regard to stroke and SEE prevention and decreased risk of ICH compared to warfarin is preserved across individual subgroups, e.g. renal impairment, age, concomitant medication use such as anti-platelet agents or P-gp inhibitors. While certain patient subgroups are at an increased risk of major bleeding when treated with an anticoagulant, the excess bleeding risk for dabigatran is due to GI bleeding, typically seen within the first 3-6 months following initiation of dabigatran etexilate therapy.

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) (not statistically significant) (see section 5.1).

4.9 Overdose

Doses of dabigatran etexilate beyond those recommended expose the patient to increased risk of bleeding.

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

Excessive anticoagulation may require interruption of Pradaxa treatment. There is no specific antidote to dabigatran. 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 supportive treatment, such as surgical haemostasis and blood volume replacement, should be undertaken at the prescriber's discretion.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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 clear correlation between plasma dabigatran concentration and degree of anticoagulant effect based on phase II studies.

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) (see section 4.4).

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

Steady state geometric mean dabigatran peak plasma concentration, measured around 2 hours after 150 mg dabigatran etexilate administration twice daily, was 175 ng/ml, with a

range of 117-275 ng/ml (25th–75th percentile range). The dabigatran geometric mean trough concentration, measured at trough in the morning, at the end of the dosing interval (i.e. 12 hours after the 150 mg dabigatran evening dose), was on average 91.0 ng/ml, with a range of 61.0-143 ng/ml (25th–75th percentile range).

If the dTT is used, dabigatran concentrations above 200 ng/ml, measured at trough after 150 mg twice daily dosing (10-16 hours after the previous dose), are associated with an increased risk of bleeding (see sections 4.4 and 4.9).

Ethnic origin

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

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 or 220 mg once daily thereafter, haemostasis having been secured, or enoxaparin 40 mg on the day prior to surgery and daily thereafter.

In the RE-MODEL trial (knee replacement) treatment was for 6-10 days and in the RE-NOVATE trial (hip replacement) for 28-35 days. Totals of 2,076 patients (knee) and 3,494 (hip) were treated respectively.

Composite of total VTE (including pulmonary embolism, proximal and distal deep vein thrombosis, whether symptomatic or asymptomatic detected by routine venography) and all-cause mortality constituted the primary end-point for both studies. Composite of major VTE (including pulmonary embolism and proximal deep vein thrombosis, whether symptomatic or asymptomatic detected by routine venography) and VTE-related mortality constituted a secondary end-point and is considered of better clinical relevance.

Results of both studies showed that the antithrombotic effect of 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 6). Better results were seen with the 220 mg dose, where the point estimate of major VTE was slightly better than enoxaparin (Table 6).

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 6.

Data for the total VTE and all-cause mortality endpoint are shown in Table 7.

Data for adjudicated major bleeding endpoints are shown in Table 8 below.

Table 6: Analysis of major VTE and VTE-related 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	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 7: 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 8: Major bleeding events (MBE) by treatment in the individual RE-NOVATE and RE-MODEL studies.

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

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

The clinical evidence for the efficacy of dabigatran etexilate is derived from the RE-LY study (**R**andomized **E**valuation of **L**ong-term anticoagulant therap**Y**) a multi-centre, multi-national, randomized parallel group study of two blinded doses of dabigatran etexilate (110 mg and 150 mg twice daily) compared to open-label warfarin in patients with atrial fibrillation at moderate to high risk of stroke and SEE. The primary objective in this study was to determine if dabigatran etexilate was non-inferior to warfarin in reducing the occurrence of the composite endpoint stroke and SEE. Statistical superiority was also analyzed.

In the RE-LY study, a total of 18,113 patients were randomized, with a mean age of 71.5 years and a mean CHADS2 score of 2.1. The patient population was 64 % male, 70 % Caucasian and 16 % Asian.

In addition to documented non-valvular atrial fibrillation (AF) e.g., persistent, paroxysmal, or permanent, 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

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

The RE-LY study demonstrated that dabigatran etexilate, at a dose of 110 mg twice daily, is non-inferior to warfarin in the prevention of stroke and SEE in subjects with atrial fibrillation, with a reduced risk of ICH, total bleeding and major bleeding. The dose of 150 mg twice daily reduces significantly the risk of ischemic and haemorrhagic stroke, vascular death, ICH and total bleeding compared to warfarin. Major bleeding rates with this dose were comparable to warfarin. Myocardial infarction rates were slightly increased with dabigatran etexilate 110 mg twice daily and 150 mg twice daily compared to warfarin (hazard ratio 1.29; $p=0.0929$ and hazard ratio 1.27; $p=0.1240$, respectively). With improving monitoring of INR the observed benefits of dabigatran etexilate compared to warfarin diminish.

Tables 9-11 display details of key results in the overall population.

Table 9: Analysis of first occurrence of stroke or SEE (primary endpoint) during the study period in RE-LY.

Table 9	Dabigatran etexilate 110 mg twice daily	Dabigatran etexilate 150 mg twice daily	Warfarin
Subjects randomized	6,015	6,076	6,022
<i>Stroke and/or SEE</i>			
Incidences (%)	183 (1.54)	134 (1.11)	202 (1.71)
Hazard ratio vs. warfarin (95 % CI)	0.90 (0.74, 1.10)	0.65 (0.52, 0.81)	
p-value superiority	$p=0.2943$	$p=0.0001$	

% refers to yearly event rate

Table 10: Analysis of first occurrence of ischemic or haemorrhagic strokes during the study period in RE-LY.

Table 10	Dabigatran etexilate 110 mg twice daily	Dabigatran etexilate 150 mg twice daily	Warfarin
Subjects randomized	6,015	6,076	6,022
<i>Stroke</i>			
Incidences (%)	171 (1.44)	122 (1.01)	186 (1.58)
Hazard ratio vs. warfarin (95 % CI)	0.91 (0.74, 1.12)	0.64 (0.51, 0.81)	
p-value	0.3828	0.0001	
<i>SEE</i>			
Incidences (%)	15 (0.13)	13 (0.11)	21 (0.18)
Hazard ratio vs. warfarin (95 % CI)	0.71 (0.37, 1.38)	0.61 (0.30, 1.21)	
p-value	0.3099	0.1582	
<i>Ischemic stroke</i>			
Incidences (%)	152 (1.28)	103 (0.86)	134 (1.14)
Hazard ratio vs. warfarin (95 % CI)	1.13 (0.89, 1.42)	0.75 (0.58, 0.97)	
p-value	0.3139	0.0296	
<i>Haemorrhagic stroke</i>			
Incidences (%)	14 (0.12)	12 (0.10)	45 (0.38)
Hazard ratio vs. warfarin (95 % CI)	0.31 (0.17, 0.56)	0.26 (0.14, 0.49)	
p-value	< 0.001	< 0.001	

% refers to yearly event rate

Table 11: Analysis of all-cause and vascular mortality during the study period in RE-LY.

Table 11	Dabigatran etexilate 110 mg twice daily	Dabigatran etexilate 150 mg twice daily	Warfarin
Subjects randomized	6,015	6,076	6,022
<i>All-cause mortality</i>			
Incidences (%)	446 (3.75)	438 (3.64)	487 (4.13)
Hazard ratio vs. warfarin (95 % CI)	0.91 (0.80, 1.03)	0.88 (0.77, 1.00)	
p-value	0.1308	0.0517	
<i>Vascular mortality</i>			
Incidences (%)	289 (2.43)	274 (2.28)	317 (2.69)
Hazard ratio vs. warfarin (95 % CI)	0.90 (0.77, 1.06)	0.85 (0.72, 0.99)	
p-value	0.2081	0.0430	

% refers to yearly event rate

Tables 12-13 display results of the primary efficacy and safety endpoint in relevant sub-populations.

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

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

Endpoint	Dabigatran etexilate 110 mg twice daily vs. warfarin	Dabigatran etexilate 150 mg twice daily vs. warfarin
Age (years)		
< 65	1.10 (0.64, 1.87)	0.51 (0.26, 0.98)
≥ 65 and < 75	0.87 (0.62, 1.20)	0.68 (0.47, 0.96)
≥ 75	0.88 (0.66, 1.17)	0.67 (0.49, 0.90)
≥ 80	0.68 (0.44, 1.05)	0.65 (0.43, 1.00)
CrCL (ml/min)		
≥ 30 and < 50	0.89 (0.61, 1.31)	0.47 (0.30, 0.74)
≥ 50 and < 80	0.91 (0.68, 1.20)	0.65 (0.47, 0.88)
≥ 80	0.83 (0.52, 1.32)	0.71 (0.44, 1.15)

For the primary safety endpoint of major bleeding there was an interaction of treatment effect and age. The relative risk of bleeding with dabigatran compared to warfarin increased with age. Relative risk was highest in patients ≥ 75 years. There was no significant interaction of treatment effects with the subgroups of renal function and CHADS2 score.

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

Endpoint	Dabigatran etexilate 110 mg twice daily vs. warfarin	Dabigatran etexilate 150 mg twice daily vs. warfarin
Age (years)		
< 65	0.33 (0.19, 0.59)	0.36 (0.21, 0.62)
≥ 65 and < 75	0.70 (0.56, 0.89)	0.80 (0.64, 1.00)
≥ 75	1.01 (0.83, 1.23)	1.18 (0.98, 1.43)
≥ 80	1.12 (0.84, 1.49)	1.35 (1.03, 1.77)
CrCL (ml/min)		
≥ 30 and < 50	1.00 (0.77, 1.29)	0.94 (0.72, 1.21)
≥ 50 and < 80	0.76 (0.61, 0.93)	0.89 (0.73, 1.08)
≥ 80	0.59 (0.43, 0.82)	0.84 (0.62, 1.13)

Paediatric population

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

5.2 Pharmacokinetic properties

After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran, which is the active form in plasma. The cleavage of the prodrug dabigatran etexilate by esterase-catalysed hydrolysis to the active principle dabigatran is the

predominant metabolic reaction. The absolute bioavailability of dabigatran following oral administration of Pradaxa was approximately 6.5 %.

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

Absorption

A study evaluating post-operative absorption of dabigatran etexilate, 1-3 hours following surgery, demonstrated relatively slow absorption compared with that in healthy volunteers, showing a smooth plasma concentration-time profile without high peak plasma concentrations. Peak plasma concentrations are reached at 6 hours following administration in a postoperative period due to contributing factors such as anaesthesia, gastrointestinal paresis, and surgical effects independent of the oral medicinal product formulation. It was demonstrated in a further study that slow and delayed absorption is usually only present on the day of surgery. On subsequent days absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after medicinal product administration.

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

The oral bioavailability may be increased by 75 % compared to the reference capsule formulation when the pellets are taken without the Hydroxypropylmethylcellulose (HPMC) capsule shell. Hence, the integrity of the HPMC capsules should always be preserved in clinical use to avoid unintentionally increased bioavailability of dabigatran etexilate. Therefore, patients should be advised not to open the capsules and taking the pellets alone (e.g. sprinkled over food or into beverages) (see section 4.2).

Distribution

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

C_{max} and the area under the plasma concentration-time curve were dose proportional. Plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of 11 hours in healthy elderly subjects. After multiple doses a terminal half-life of about 12-14 hours was observed. The half-life was independent of dose. Half-life is prolonged if renal function is impaired as shown in Table 14.

Metabolism and elimination

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

Dabigatran is subject to conjugation forming pharmacologically active acylglucuronides. Four positional isomers, 1-O, 2-O, 3-O, 4-O-acylglucuronide exist, each accounts for less than 10 % of total dabigatran in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods. Dabigatran is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 ml/min corresponding to the glomerular filtration rate.

Special populations

Renal insufficiency

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

In a small number of volunteers with severe renal insufficiency (CrCL 10-30 ml/min),

the exposure (AUC) to dabigatran was approximately 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal insufficiency (see sections 4.2, 4.3 and 4.4).

Table 14: 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 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 phase I studies with elderly subjects showed an increase of 40 % to 60 % in the AUC and of more than 25 % in C_{max} compared to young subjects.

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

Hepatic insufficiency

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

Body weight

The dabigatran trough concentrations were about 20 % lower in patients with a body weight > 100 kg compared with 50-100 kg. The majority (80.8 %) of the subjects were in the ≥ 50 kg and < 100 kg category with no clear difference detected (see sections 4.2 and 4.4). Limited clinical data in patients < 50 kg are available.

Gender

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

Ethnic origin

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

Pharmacokinetic interactions

The pro-drug dabigatran etexilate but not dabigatran is a substrate of the efflux transporter P-gp. Therefore co-medications with P-gp transporter inhibitors (amiodarone, verapamil, clarithromycin, quinidine and ketoconazole) and inducers (rifampicin) have been investigated (see sections 4.2, 4.4 and 4.5).

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

5.3 Preclinical safety data

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Capsule fill: tartaric acid, acacia, hypromellose, dimeticone, talc, hydroxypropylcellulose
Capsule shell: carrageenan, potassium chloride, titanium dioxide, indigo carmine (E132), sunset yellow (E110), hypromellose, purified water, and black printing ink.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister and bottle: 3 years

Once the bottle is opened, the product must be used within 30 days.

6.4 Special precautions for storage

Store below 25°C in the original package in order to protect from moisture.

6.5 Presentation

Cartons containing aluminum blisters. Polypropylene bottles.

10, 30 or 60 hard capsules.

6.6 Special precautions for disposal and other handling

When taking Pradaxa capsules out of the blister pack, the following instructions should be followed:

- The hard capsules should be taken out of the blister card by peeling off the backing foil.
- The hard capsules should not be pushed through the blister foil.
- The blister foil should only be peeled off when a hard capsule is required.

7. MARKETING AUTHORISATION

Pradaxa 75 mg hard capsules

Reg. no. 142 95 32973

Pradaxa 110 mg hard capsules

Reg. no. 142 96 32974

Pradaxa 150 mg hard capsules

Reg. no. 145 63 33359

MANUFACTURER: Boehringer Ingelheim Pharma GmbH & Co. KG, Germany

REGISTRATION OWNER: Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 91003

The format of this leaflet was determined by the Ministry of Health, and its content was checked and approved by it in July 2011.

Pradaxa[®]

dabigatran etexilate

- **For the prevention of stroke and systemic embolism in patients with atrial fibrillation**
- **For VTE prevention after hip or knee replacement surgery**

- Pradaxa is available in three dosage strengths – 75 mg, 110 mg and 150 mg.
- Pradaxa 150 mg and 110 mg are indicated for the Prevention of stroke and systemic embolism in adult patients with atrial fibrillation. The recommended doses are either 150 mg bid or 110 mg bid, for a daily dose of 300 mg or 220 mg (depending on the patient, see leaflet for details).
- Pradaxa 110 mg and 75 mg are indicated for the Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery. The recommended doses are either 2 capsules of 110 mg once daily or 2 capsules of 75 mg once daily, for a daily dose of 220 mg or 150 mg (depending on the patient, see leaflet for details).

Marketed by:



Rafa Laboratories Ltd.

Under license from:



Boehringer
Ingelheim

For further information contact the Medical Information Department, P.O.B 405 Jerusalem 91003, Tel: 02-5893939, Fax: 02-5870282, e-mail: med.info@rafa.co.il, website: www.rafa.co.il ; www.pradaxa.co.il