Product Information as approved by the CHMP on 24 May 2012, pending endorsement by the European Commission

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 75 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 75 mg of dabigatran etexilate (as mesilate).
Excipients: Each hard capsule contains 2 micrograms sunset yellow (E110).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Imprinted capsules with 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".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

For both surgeries, if haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

Assessment of renal function (prevention of VTE):

In all patients:

- Renal function should be assessed by calculating the creatine clearance (CrCL) prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 ml/min) (see sections 4.3, 4.4 and 5.2). Pradaxa is contraindicated in patients with severe renal impairment
- Renal function should also be assessed when a decline in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, and with certain co-medications)

The method used to estimate renal function (CrCL in ml/min) during the clinical development of Pradaxa was the Cockgroft-Gault method. The formula is as follows:

- For creatinine in μmol/l:

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

- For creatinine in mg/dl:

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

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

Renal impairment (prevention of VTE)

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

In patients with moderate renal impairment (CrCL 30-50 ml/min), 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 (prevention of VTE)

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).

Elderly(prevention of VTE)

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

As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the CrCL prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 ml/min). While on treatment the renal function should also be assessed in

certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc) (see sections 4.3, 4.4 and 5.2).

Hepatic impairment (prevention of VTE)

Patients with elevated liver enzymes > 2 upper limit of normal (ULN) were excluded in clinical trials investigating the VTE prevention following elective hip or knee replacement surgery. No treatment experience is available for this subpopulation of patients, and therefore the use of Pradaxa is not recommended in this population (see sections 4.4 and 5.2).

Weight (prevention of VTE)

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

Gender (prevention of VTE)

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

Switching (prevention of VTE)

Pradaxa treatment to parenteral anticoagulant

It is recommended to wait 24 hours after the last dose before switching from Pradaxa to a parenteral anticoagulant (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 (prevention of VTE)

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 *(prevention of VTE)*

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

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

Method of administration *(prevention of VTE)*

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 listed in section 6.1
- Patients with severe renal impairment (CrCL < 30 ml/min) (see section 4.2)
- Active clinically significant bleeding
- Lesion or condition at significant risk of major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin, low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under the circumstances of switching therapy to or from Pradaxa (see section 4.2)
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and tacrolimus (see section 4.5)

4.4 Special warnings and precautions for use

Hepatic impairment

Patients with elevated liver enzymes > 2 ULN were excluded in controlled 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.

Haemorrhagic risk

As with all anticoagulants, dabigatran etexilate should be used with caution in conditions with an increased risk of bleeding and in situations with concomitant use of drugs affecting haemostasis. 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 ≥ 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).

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 (H_2)-blocker treatment increase the risk of GI bleeding. The administration of a PPI can be considered to prevent GI bleeding.

Bleeding risk may be increased in patients concomitantly treated with selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs) (see section 4.5).

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. Please also refer to contraindications in section 4.3.

Pharmacodynamic and kinetic factors	Age ≥ 75 years
Factors increasing dabigatran plasma levels	Major: • Moderate renal impairment (30-50 ml/min CrCL) • P-gp inhibitor co-medication (some P-gp inhibitors are contraindicated, see section

	4.3 and 4.5) <u>Minor:</u> • Low body weight (< 50 kg)
Pharmacodynamic interactions	• ASA • NSAID • Clopidogrel • SSRIs or SNRIs • Other drugs which may impair haemostasis
Diseases / procedures with special haemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Recent biopsy, major trauma • Bacterial endocarditis • Esophagitis, gastritis or gastroesophageal reflux

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

Pradaxa does not in general require routine anticoagulant monitoring. However, the measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. The INR test is unreliable in patients on Pradaxa and false positive INR elevations have been reported. Therefore INR tests should not be performed. Diluted thrombin time (dTT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information, but the tests are not standardized, and results should be interpreted with caution (see section 5.1).

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

Test (trough value)	
dTT [ng/ml]	> 67
ECT [x-fold upper limit of normal]	No data
aPTT [x-fold upper limit of normal]	> 1.3
INR	Should not 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).

<u>Interaction with P-gp inducers</u>

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 3 summarizes discontinuation rules before invasive or surgical procedures.

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

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, ticagrelor, dextran, sulfinpyrazone, 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).

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 NSAIDs increased the risk of bleeding by approximately 50 % on both dabigatran etexilate and warfarin. Therefore, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives > 12 hours, close observation for signs of bleeding is recommended (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 oral dose of 400 mg, and 153 % and 149 %, respectively, after multiple oral dosing of 400 mg ketoconazole once daily. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole (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 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 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 (increased of C_{max} by about 90 % and AUC by about 70 %) or administration of multiple doses of verapamil (increased of C_{max} by about 60 % and AUC by about 50 %).

Therefore, close clinical surveillance (looking for signs of bleeding or anaemia) is required when dabigatran is co-administered with verapamil. In patients with normal renal function after the 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). Close clinical surveillance is recommended when dabigatran etexilate is combined with verapamil and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.

There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increased of 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.

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

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

Gastric pH

Pantoprazole: When 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 data human 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 5419 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.

The most commonly reported adverse reactions are bleedings occurring in total in approximately 14 % of patients; the frequency of major bleeds (including wound site bleedings) is less than 2 %.

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.

Adverse reactions

Table 4 shows the adverse reactions ranked under headings of SOC and frequency using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare

(≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (can not be estimated from the available data).

SOC / Preferred Term.	Dabigatran etexilate 150 mg	Dabigatran etexilate 220 mg
Number of patients treated	2737	2682
Blood and lymphatic system disorders		
Anaemia	Common	Common
Thrombocytopenia	Uncommon	Uncommon
Haemoglobin decreased	Common	Common
Haematocrit decreased	Uncommon	Uncommon
Immune system disorder		
Drug hypersensitivity	Uncommon	Uncommon
Pruritus	Uncommon	Uncommon
Rash	Uncommon	Uncommon
Urticaria	Rare	Rare
Bronchospasm	Not known	Not known
Nervous system disorders		
Intracranial haemorrhage	Uncommon	Uncommon
Vascular disorders		
Haematoma	Uncommon	Uncommon
Haemorrhage	Uncommon	Uncommon
Wound haemorrhage	Uncommon	Uncommon
Respiratory, thoracic and mediastinal disorders		
Epistaxis	Common	Common
Haemoptysis	Uncommon	Uncommon
Gastrointestinal disorders		
Gastrointestinal haemorrhage	Common	Common
Rectal haemorrhage	Uncommon	Uncommon
Haemorrhoidal haemorrhage	Uncommon	Uncommon
Abdominal pain	Common	Common
Diarrhoea	Common	Common
Dyspepsia	Common	Common
Nausea	Common	Common
Gastrointestinal ulcer	Uncommon	Uncommon
Gastroesophagitis	Uncommon	Uncommon
Gastroesophageal reflux disease	Uncommon	Uncommon
Vomiting	Uncommon	Uncommon
Dysphagia	Uncommon	Uncommon
Hepatobiliary disorders		
Alanine aminotransferase increased	Uncommon	Uncommon
Aspartate aminotransferase increased	Uncommon	Uncommon
Hepatic function abnormal/ Liver function Test abnormal	Common	Common
Hepatic enzyme increased	Uncommon	Uncommon
Hyperbilirubinaemia	Uncommon	Uncommon
Skin and subcutaneous tissue disorder		
Skin haemorrhage	Uncommon	Uncommon
Musculoskeletal and connective tissue and bone disorders		
Haemarthrosis	Uncommon	Uncommon
Renal and urinary disorders		
Haematuria	Uncommon	Uncommon
General disorders and administration site conditions		
Injection site haemorrhage	Rare	Rare

Catheter site haemorrhage	Rare	Rare
Bloody discharge	Rare	Rare
Injury, poisoning and procedural complications		
Incision site haemorrhage	Uncommon	Uncommon
Traumatic haemorrhage	Uncommon	Uncommon
Post procedural haematoma	Uncommon	Uncommon
Post procedural haemorrhage	Uncommon	Uncommon
Anaemia postoperative	Uncommon	Uncommon
Post procedural discharge	Uncommon	Uncommon
Wound secretion	Uncommon	Uncommon
Surgical and medical procedures		
Wound drainage	Rare	Rare
Post procedural drainage	Rare	Rare

Bleeding

The table 5 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 N (%)	Dabigatran etexilate 220 mg N (%)	Enoxaparin N (%)
Treated	1866(100.0)	1825(100.0)	1848(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).

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 prescribers discretion.

Activated prothrombin complex concentrates (e.g., FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX and X, may be considered. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatran, but data on their usefulness in clinical settings and also on the possible risk of rebound thromboembolism is very limited. Coagulation tests may become unreliable following adminstration of suggested reversing agents. Caution should be exercised when interpreting these tests. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet drugs have been used. All symptomatic treatment should be given according to the physician's judgement.

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

As protein binding is low, dabigatran can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: direct thrombine 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. Dabigatran prolongs the thrombin time (TT), ECT, and aPTT.

The calibrated diluted TT (dTT) test provides an estimation of dabigatran plasma concentration that can be compared to the expected dabigatran plasma concentrations.

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

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

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

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

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

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

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

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 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 2076 patients (knee) and 3494 (hip) were treated respectively.

Composite of total VTE (including PE, proximal and distal DVT, whatever symptomatic or asymptomatic detected by routine venography) and all-cause mortality constituted the primary end-point for both studies. Composite of major VTE (including PE and proximal DVT, whatever symptomatic or asymptomatic detected by routine venography) and VTE-related mortality constituted a secondary end-point and is considered of better clinical relevance.
Results of both studies showed that the antithrombotic effect of 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 (5539 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-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 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	Dabigatran etexilate 150 mg	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 by treatment in the individual RE-MODEL and the RE-NOVATE studies

Trial	Dabigatran etexilate 220 mg	Dabigatran etexilate 150 mg	Enoxaparin 40 mg
RE-NOVATE (hip)			
Treated patients N	1146	1163	1154
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)

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 (see section 4.2 for information on paediatric use).

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 9.

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 9: 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)

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

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.

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) had 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 350
- Talc
- Hydroxypropylcellulose

Capsule shell
- Carrageenan
- Potassium Chloride
- Titanium Dioxide
- Indigo Carmine (E132)
- Sunset Yellow (E110)
- Hypromellose
- Water purified

Black printing ink

- Shellac
- N-Butyl alcohol
- Isopropyl alcohol

- Industrial methylated spirit
- Iron oxide black (E172)
- Purified water
- Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister and bottle: 3 years

Once the bottle is opened, the medicinal product must be used within 4 months

6.4 Special precautions for storage

Blister

Store in the original package in order to protect from moisture

Bottle

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

6.5 Nature and contents of container

Cartons containing 1, 3, or 6 blister strips (10 x 1, 30 x 1, 60 x 1) in perforated aluminium unit dose blisters. The blister consists of an aluminium lidding foil coated with polyvinylchloride-polyvinylacetate copolymer-acrylate (PVCAC acrylate) in contact with the product and an aluminium bottom foil with polyvinylchloride (PVC) in contact with the product.

Polypropylene bottle with a screw cap containing 60 hard capsules.

Not all pack sizes may be marketed.

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.

When taking a hard capsule out of the bottle, please observe the following instructions:

- The cap opens by pushing and turning.

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

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/001
EU/1/08/442/002
EU/1/08/442/003
EU/1/08/442/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 March 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 110 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 110 mg of dabigatran etexilate (as mesilate).
Excipients: Each hard capsule contains 3 micrograms sunset yellow (E110).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Imprinted capsules with 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".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

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

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

For both surgeries, if haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

Assessment of renal function (prevention of VTE):

In all patients:

- Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 ml/min) (see sections 4.3, 4.4 and 5.2). Pradaxa is contraindicated in patients with severe renal impairment
- Renal function should also be assessed when a decline in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, and with certain co-medications)

The method used to estimate renal function (CrCL in ml/min) during the clinical development of Pradaxa was the Cockgroft-Gault method.The formula is as follows:

- For creatinine in μmol/l:

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

- For creatinine in mg/dl:

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

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

Renal impairment (prevention of VTE)

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

In patients with moderate renal impairment (CrCL 30-50 ml/min), 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 (prevention of VTE)

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).

Elderly (prevention of VTE)

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

As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the CrCL prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 ml/min). While on treatment the renal function should also be assessed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (such as hypovolemia, dehydration, and with certain comedications, etc) (see sections 4.3, 4.4 and 5.2).

Hepatic impairment (prevention of VTE)

Patients with elevated liver enzymes > 2 upper limit of normal (ULN) were excluded in clinical trials investigating the VTE prevention following elective hip or knee replacement surgery. No treatment experience is available for this subpopulation of patients, and therefore the use of Pradaxa is not recommended in this population (see sections 4.4 and 5.2).

Weight (prevention of VTE)

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

Gender (prevention of VTE)

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

Switching (prevention of VTE)

Pradaxa treatment to parenteral anticoagulant

It is recommended to wait 24 hours after the last dose before switching from Pradaxa to a parenteral anticoagulant (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 (prevention of VTE)

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 *(prevention of VTE)*

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

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

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

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

For the following two groups the recommended daily dose of Pradaxa is 220 mg taken as one 110 mg capsule twice daily:
- Patients aged 80 years or above
- Patients who receive concomitant verapamil

For the following groups, the daily dose of Pradaxa of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding:
- Patients between 75-80 years
- Patients with moderate renal impairment
- Patients with gastritis, esophagitis or gastroesophageal reflux
- Other patients at increased risk of bleeding

See further down and sections 4.4, 4.5, 5.1 and 5.2.

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 (SPAF)

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.

As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the CrCL prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 ml/min). 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 sections 4.3, 4.4 and 5.2).

Patients at risk of bleeding (SPAF)

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).

Assessment of renal function (SPAF):

In all patients:

- Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 ml/min) (see sections 4.3, 4.4 and 5.2). Pradaxa is contraindicated in patients with severe renal impairment
- Renal function should also be assessed when a decline in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, and with certain co-medications)

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

- Renal function should be assessed during treatment with Pradaxa at least once a year or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (e.g. hypovolaemia, dehydration, and with certain co-medications)

The method used to estimate renal function (CrCL in ml/min) during the clinical development of Pradaxa was the Cockgroft-Gault method. The formula is as follows:

- For creatinine in μmol/l:

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

- For creatinine in mg/dl:

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

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

Renal impairment (SPAF)

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

No dose adjustment is necessary in patients with mild renal impairment (CrCL 50- ≤ 80 ml/min). For patients with moderate renal impairment (CrCL 30-50 ml/min) the recommended dose of 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 (SPAF)

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.

Weight (SPAF)

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 (SPAF)

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

Hepatic impairment (SPAF)

Patients with elevated liver enzymes > 2 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).

Switching (SPAF)

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

Because Pradaxa can contribute to an elevated INR, INR testing should not be performed until Pradaxa has been stopped for at least 2 days.

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 (SPAF)

Patients can stay on dabigatran etexilate while being cardioverted.

Paediatric population (SPAF)

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 *(SPAF)*

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 *(prevention of VTE and SPAF)*

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 listed in section 6.1
- Patients with severe renal impairment (CrCL < 30 ml/min) (see section 4.2)
- Active clinically significant bleeding
- Lesion or condition at significant risk of major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin, low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under the circumstances of switching therapy to or from Pradaxa (see section 4.2)
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and tacrolimus (see section 4.5)

4.4 Special warnings and precautions for use

Hepatic impairment

Patients with elevated liver enzymes > 2 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 and in situations with concomitant use of drugs affecting haemostasis. 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 ≥ 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 a study of prevention of stroke and SEE in adult patients with nonvalvular atrial fibrillation, 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 (≥ 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 (H_2)-blocker treatment increase the risk of GI bleeding. In these atrial fibrillationpatients a dosage of 220 mg dabigatran given as 110 mg capsule twice daily should be considered and posology recommendations in section 4.2 be followed. The administration of a PPI can be considered to prevent GI bleeding.

Bleeding risk may be increased in patients concomitantly treated with selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs) (see section 4.5).

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. Please also refer to contraindications in section 4.3.

Pharmacodynamic and kinetic factors	Age ≥ 75 years
Factors increasing dabigatran plasma levels	Major: • Moderate renal impairment (30-50 ml/min CrCL) • P-gp inhibitor co-medication (some P-gp inhibitors are contraindicated, see section 4.3 and 4.5) Minor: • Low body weight (< 50 kg)
Pharmacodynamic interactions	• ASA • NSAID • Clopidogrel • SSRIs or SNRIs • Other drugs which may impair haemostasis
Diseases / procedures with special haemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Recent biopsy, major trauma • Bacterial endocarditis • Esophagitis, gastritis and gastroesophageal reflux

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

Pradaxa does not in general require routine anticoagulant monitoring. However, the measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. The INR test is unreliable in patients on Pradaxa and false positive INR elevations have been reported. Therefore INR tests should not be performed. Diluted thrombin time (dTT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information, but the tests are not standardized, and results should be interpreted with caution (see section 5.1).

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

Test (trough value)	Indication	
	Prevention of VTE	Prevention of stroke and SEE
dTT [ng/ml]	> 67	> 200
ECT [x-fold upper limit of normal]	No data	> 3
aPTT [x-fold upper limit of normal]	> 1.3	> 2
INR	Should not be performed	Should not be performed

(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).

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 dTT, ECT or aPTT not exceeding the ULN according to the local reference range.

Interaction with P-gp inducers

Concomitant administration of P-gp inducers (such as rifampicin, St. John`s wort (Hypericum perforatum), carbamazepine, or phenytoin) is expected to result in decreased dabigatran plasma concentrations, and should be avoided (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 3 summarizes discontinuation rules before invasive or surgical procedures.

Renal function (CrCL in ml/min)	Estimated half-life (hours)	Stop dabigatran before elective surgery	
		High risk of bleeding or major surgery	Standard risk
≥ 80	~ 13	2 days before	24 hours before
≥ 50-< 80	~ 15	2-3 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 (for cardioversion see section 4.2).

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. 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, ticagrelor, dextran, sulfinpyrazone, 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).

Only limited data on concomitant use of dabigatran etexilate and other anticoagulants are available, and no firm conclusions can be drawn. From the limited data collected in the phase III study RE-LY in patients with atrial fibrillation it was observed that the concomitant use of other oral or parenteral anticoagulants increases major bleeding rates with both dabigatran etexilate and warfarin by approximately 2.5-fold, mainly related to situations when switching from one anticoagulant to another (see section 4.3).

Clopidogrel and ASA: From the data collected in the phase III study RE-LY (see section 5.1) it was observed that the concomitant use of antiplatelets, ASA or clopidogrel approximately doubles major bleeding rates with both dabigatran etexilate and warfarin (see section 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) (see also subsection on ASA below).

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

NSAIDs: NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use in the RE-LY study, NSAIDs increased the risk of bleeding by approximately 50 % on both dabigatran etexilate and warfarin. Therefore, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives > 12 hours, close observation for signs of bleeding is recommended (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 oral dose of 400 mg, and 153 % and 149 %, respectively, after multiple oral dosing of 400 mg ketoconazole once daily. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole (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 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 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 (increased of C_{max} by about 90 % and AUC by about 70 %) or administration of multiple doses of verapamil (increased of C_{max} by about 60 % and AUC by about 50 %).

Therefore, close clinical surveillance (looking for signs of bleeding or anaemia) is required when dabigatran is co-administered with verapamil. In patients with normal renal function after hip or knee replacement surgery, receiving dabigatran etexilate and verapamil concomitantly, the dose of Pradaxa should be reduced to 150 mg taken once daily as 2 capsules of 75 mg. In patients with moderate renal impairment and concomitantly treated with dabigatran etexilate and verapamil, a dose reduction of Pradaxa to 75 mg daily should be considered (see sections 4.2 and 4.4).

For patients with atrial nonvalvular fibrillation treated for prevention of stroke and SEE, concomitantly receiving dabigatran etexilate and verapamil, the dose of Pradaxa should be reduced to 220 mg taken as one 110 mg capsule twice daily (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 (increased 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.

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

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

Gastric pH

Pantoprazole: When 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 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 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 patient 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 5 and 6 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 4 shows the adverse reactions identified from the primary VTE prevention studies after hip or knee replacement surgery and the prevention of thromboembolic stroke and SEE in patients with atrial fibrillation program ranked under headings of SOC and frequency using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (can not be estimated from the available data).

	Primary VTE prevention after hip or knee replacement surgery		Stroke and SEE prevention in patients with atrial fibrillation	
SOC / Preferred Term.	Dabigatran etexilate 150 mg once daily	Dabigatran etexilate 220 mg once daily	Dabigatran etexilate 110 mg twice daily	Dabigatran etexilate 150 mg twice daily
Number of patients treated	2,737	2,682	5,983	6,059
Blood and lymphatic system disorders				
Anaemia	Common	Common	Common	Common
Haemoglobin decreased	Common	Common	Uncommon	Uncommon
Thrombocytopenia	Uncommon	Uncommon	Uncommon	Uncommon
Haematocrit decreased	Uncommon	Uncommon	Rare	Rare
Immune system disorder				
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
Nervous system disorders				
Intracranial haemorrhage	Uncommon	Uncommon	Uncommon	Uncommon
Vascular disorders				
Haematoma	Uncommon	Uncommon	Uncommon	Uncommon
Wound haemorrhage	Uncommon	Uncommon	-	-
Haemorrhage	Uncommon	Uncommon	Uncommon	Uncommon
Respiratory, thoracic and mediastinal disorders				
Epistaxis	Common	Common	Common	Common
Haemoptysis	Uncommon	Uncommon	Uncommon	Uncommon
Gastrointestinal disorders				
Gastrointestinal haemorrhage	Common	Common	Common	Common
Abdominal pain	Common	Common	Common	Common
Diarrhoea	Common	Common	Common	Common
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
Hepatobiliary disorders				
Alanine aminotransferase increased	Uncommon	Uncommon	Uncommon	Uncommon
Aspartate aminotransferase increased	Uncommon	Uncommon	Uncommon	Uncommon
Hepatic function abnormal/ Liver function Test abnormal	Common	Common	Common	Common
Hepatic enzyme increased	Uncommon	Uncommon	Rare	Rare
Transaminases increased	Uncommon	Uncommon	-	-
Hyperbilirubinaemia	Uncommon	Uncommon	Rare	Rare
Skin and subcutaneous tissue disorder				
Skin haemorrhage	Uncommon	Uncommon	Uncommon	Uncommon
Musculoskeletal and connective tissue and bone disorders				
Haemarthrosis	Uncommon	Uncommon	Rare	Rare
Renal and urinary disorders				
Genitourological haemorrhage	-	-	Uncommon	Common
Haematuria	Uncommon	Uncommon	Uncommon	Uncommon
General disorders and administration site conditions				
Injection site haemorrhage	Rare	Rare	Rare	Rare
Catheter site haemorrhage	Rare	Rare	Rare	Rare
Bloody discharge	Rare	Rare	-	-
Injury, poisoning and procedural complications				
Traumatic Haemorrhage	Uncommon	Uncommon	-	-
Post procedural haematoma	Uncommon	Uncommon	-	-
Post procedural haemorrhage	Uncommon	Uncommon	-	-
Anaemia postoperative	Uncommon	Uncommon	-	-
Post procedural discharge	Uncommon	Uncommon	-	-
Wound secretion	Uncommon	Uncommon	-	-
Incision site haemorrhage	Uncommon	Uncommon	Uncommon	Uncommon
Surgical and medical procedures				
Wound drainage	Rare	Rare	-	-
Post procedural drainage	Rare	Rare	-	-

Prevention of VTE

Bleeding

The table 5 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	Dabigatran etexilate	Enoxaparin

	150 mg once daily N (%)	220 mg once daily N (%)	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

The table 6 shows bleeding events broken down to major and any bleeding in the pivotal study testing the prevention of thromboembolic stroke and SEE in patients with atrial fibrillation.

	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) (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 prescribers discretion.

Activated prothrombin complex concentrates (e.g., FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX and X, may be considered. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatran, but data on their usefulness in clinical settings and also on the possible risk of rebound thromboembolism is very limited. Coagulation tests may become unreliable following adminstration of suggested reversing agents. Caution should be exercised when interpreting these tests. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet drugs have been used. All symptomatic treatment should be given according to the physician's judgement.

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

As protein binding is low, dabigatran can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: direct thrombine 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. Dabigatran prolongs the thrombin time (TT), ECT, and aPTT.

The calibrated diluted TT (dTT) test provides an estimation of dabigatran plasma concentration that can be compared to the expected dabigatran plasma concentrations.

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

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

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

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

In patients treated for prevention of VTEs after hip or knee replacement surgery with 220 mg dabigatran etexilate once daily,
- the 90th percentile of dabigatran plasma concentrations was 67 ng/ml, measured at trough (20-28 hours after the previous dose) (see section 4.4 and 4.9),
- the 90th percentile of aPTT at trough (20-28 hours after the previous dose) was 51 seconds, which would be 1.3-fold upper limit of normal.

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

<u>Prevention of stroke and SEE in adult patients with nonvalvular atrial fibrillation with one or more risk factors</u>
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).For patients with atrial nonvalvular fibrillation treated for prevention of stroke and SEE with 150 mg dabigatran etexilate twice daily,
- the 90th percentile of dabigatran plasma concentrations measured at trough (10-16 hours after the previous dose) was about 200 ng/ml,

- an ECT at trough (10-16 hours after the previous dose), elevated approximately 3-fold upper limit of normal refers to the observed 90th percentile of ECT prolongation of 103 seconds,
- an aPTT ratio greater than 2-fold upper limit of normal (aPTT prolongation of about 80 seconds), at trough (10-16 hours after the previous dose) reflects the 90th percentile of observations.

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 PE, proximal and distal DVT, whatever symptomatic or asymptomatic detected by routine venography) and all-cause mortality constituted the primary end-point for both studies. Composite of major VTE (including PE and proximal DVT, whatever symptomatic or asymptomatic detected by routine venography) and VTE-related mortality constituted a secondary end-point and is considered of better clinical relevance.
Results of both studies showed that the antithrombotic effect of 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 7). Better results were seen with the 220 mg dose where the point estimate of Major VTE was slightly better than enoxaparin (table 7).

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 7.

Data for the total VTE and all cause mortality endpoint are shown in table 8.

Data for adjudicated major bleeding endpoints are shown in table 9 below.

Table 7: Analysis of major VTE and VTE-related mortality during the treatment period in the RE-MODEL and the RE-NOVATE orthopaedic surgery studies.

Trial	Dabigatran etexilate 220 mg once daily	Dabigatran etexilate 150 mg once daily	Enoxaparin 40 mg
RE-NOVATE (hip)			

N	909	888	917
Incidences (%)	28 (3.1)	38 (4.3)	36 (3.9)
Risk ratio over enoxaparin	0.78	1.09	
95 % CI	0.48, 1.27	0.70, 1.70	
RE-MODEL (knee)			
N	506	527	511
Incidences (%)	13 (2.6)	20 (3.8)	18 (3.5)
Risk ratio over enoxaparin	0.73	1.08	
95 % CI	0.36, 1.47	0.58, 2.01	

Table 8: 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 9: Major bleeding events by treatment in the individual RE-MODEL and the RE-NOVATE studies.

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

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

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

In the RE-LY study, a total of 18,113 patients were randomized, with a mean age of 71.5 years and a mean $CHADS_2$ score of 2.1. The patient population was 64 % male, 70 % Caucasian and 16 % Asian. For patients randomized to warfarin, the mean percentage of time in therapeutic range (TTR) (INR 2-3) was 64.4 % (median TTR 67 %).

The RE-LY study demonstrated that dabigatran etexilate, at a dose of 110 mg twice daily, is non-inferior to warfarin in the prevention of stroke and 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 10-12 display details of key results in the overall population:

Table 10: Analysis of first occurrence of stroke or SEE (primary endpoint) during the study period in RE-LY.

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

% refers to yearly event rate

Table 11: Analysis of first occurrence of ischemic or haemorrhagic strokes during the study period in RE-LY.

	Dabigatran etexilate 110 mg twice daily	Dabigatran etexilate 150 mg twice daily	Warfarin
Subjects randomized	6,015	6,076	6,022
Stroke			
Incidences (%)	171 (1.44)	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	
SEE			
Incidences (%)	15 (0.13)	13 (0.11)	21 (0.18)
Hazard ratio vs. warfarin (95 % CI)	0.71 (0.37, 1.38)	0.61 (0.30, 1.21)	
p-value	0.3099	0.1582	
Ischemic stroke			
Incidences (%)	152 (1.28)	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	
Haemorrhagic stroke			
Incidences (%)	14 (0.12)	12 (0.10)	45 (0.38)
Hazard ratio vs. warfarin (95 % CI)	0.31 (0.17, 0.56)	0.26 (0.14, 0.49)	
p-value	< 0.001	< 0.001	

% refers to yearly event rate

Table 12: Analysis of all cause and cardiovascular survival during the study period in RE-LY.

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

% refers to yearly event rate

Tables 13-14 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 13: 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. The concomitant use of antiplatelets ASA or clopidogrel approximately doubles MBE rates with both dabigatran etexilate and warfarin. There was no significant interaction of treatment effects with the subgroups of renal function and $CHADS_2$ score.

Table 14: 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)
ASA use	0.85 (0.68, 1.05)	0.92 (0.75, 1.14)

Clopidogrel use	0.88 (0.56, 1.37)	0.95 (0.62, 1.46)

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 (see section 4.2 for information on paediatric use).

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 15.

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 15: 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)

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

The median CrCL in RE-LY was 68.4 ml/min. Almost half (45.8 %) of the RE-LY patients had a CrCL > 50-< 80 ml/min. Patients with moderate renal impairment (CrCL between 30-50 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) had 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 350
- Talc
- Hydroxypropylcellulose

Capsule shell
- Carrageenan
- Potassium Chloride
- Titanium Dioxide

- Indigo Carmine (E132)
- Sunset Yellow (E110)
- Hypromellose
- Water purified

Black printing ink

- Shellac
- N-Butyl alcohol
- Isopropyl alcohol
- Industrial methylated spirit
- Iron oxide black (E172)
- Purified water
- Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister and bottle: 3 years

Once the bottle is opened, the medicinal product must be used within 4 months.

6.4 Special precautions for storage

Blister

Store in the original package in order to protect from moisture.

Bottle

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

6.5 Nature and contents of container

Cartons containing 1, 3, or 6 blister strips (10 x 1, 30 x 1, 60 x 1) and a multipack containing 3 packs of 60 x 1 hard capsules (180 hard capsules) in perforated aluminium unit dose blisters. The blister consists of an aluminium lidding foil coated with polyvinylchloride-polyvinylacetate copolymer-acrylate (PVCAC acrylate) in contact with the product and an aluminium bottom foil with polyvinylchloride (PVC) in contact with the product.

Polypropylene bottle with a screw cap containing 60 hard capsules.

Not all pack sizes may be marketed.

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.

When taking a hard capsule out of the bottle, please observe the following instructions:

- The cap opens by pushing and turning.

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

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/005
EU/1/08/442/006
EU/1/08/442/007
EU/1/08/442/008
EU/1/08/442/014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 March 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 150 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 150 mg of dabigatran etexilate (as mesilate).
Excipients: Each hard capsule contains 4 micrograms sunset yellow (E110).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Imprinted capsules with 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

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

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

4.2 Posology and method of administration

Posology

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

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

- Patients aged 80 years or above
- Patients who receive concomitant verapamil

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

- Patients between 75-80 years
- Patients with moderate renal impairment
- Patients with gastritis, esophagitis or gastroesophageal reflux
- Other patients at increased risk of bleeding

See further down and sections 4.4, 4.5, 5.1 and 5.2.

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 (SPAF)

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.

As renal impairment may be frequent in the elderly (>75 years), renal function should be assessed by calculating the CrCL prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 ml/min). 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 sections 4.3, 4.4 and 5.2).

Patients at risk of bleeding (SPAF)

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).

Assessment of renal function (SPAF):

In all patients:

- Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 ml/min) (see sections 4.3, 4.4 and 5.2). Pradaxa is contraindicated in patients with severe renal impairment
- Renal function should also be assessed when a decline in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, and with certain co-medications)

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

- Renal function should be assessed during treatment with Pradaxa at least once a year or more frequently as needed in certain clinical situations when it is suspected that the renal function could decline or deteriorate (e.g. hypovolaemia, dehydration, and with certain co-medications)

The method used to estimate renal function (CrCL in ml/min) during the clinical development of Pradaxa was the Cockgroft-Gault method. The formula is as follows:

- For creatinine in μmol/l:

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

- For creatinine in mg/dl:

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

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

Renal impairment (SPAF)

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

No dose adjustment is necessary in patients with mild renal impairment (CrCL 50- ≤ 80 ml/min). For patients with moderate renal impairment (CrCL 30-50 ml/min) the recommended dose of 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(SPAF)

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.

Weight (SPAF)

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 (SPAF)

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

Hepatic impairment (SPAF)

Patients with elevated liver enzymes > 2 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).

Switching (SPAF)

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

Because Pradaxa can contribute to an elevated INR, INR testing should not be performed until Pradaxa has been stopped for at least 2 days.

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 (SPAF)

Patients can stay on dabigatran etexilate while being cardioverted.

Paediatric population (SPAF)

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 *(SPAF)*

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

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

Method of administration *(SPAF)*

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 listed in section 6.1
- Patients with severe renal impairment (CrCL < 30 ml/min) (see section 4.2)
- Active clinically significant bleeding
- Lesion or condition at significant risk of major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin, low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc),

oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under the circumstances of switching therapy to or from Pradaxa (see section 4.2)
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and tacrolimus (see section 4.5)

4.4 Special warnings and precautions for use

Hepatic impairment

Patients with elevated liver enzymes > 2 ULN were excluded from 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 and in situations with concomitant use of drugs affecting haemostasis. 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 ≥ 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 a study of prevention of stroke and SEE in adult patients with nonvalvular atrial fibrillation, 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 (≥ 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 (H_2)-blocker treatment increase the risk of GI bleeding. In these atrial fibrillationpatients a dosage of 220 mg dabigatran given as 110 mg capsule twice daily should be considered and posology recommendations in section 4.2 be followed. The administration of a PPI can be considered to prevent GI bleeding.

Bleeding risk may be increased in patients concomitantly treated with selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs) (see section 4.5).

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. Please also refer to contraindications in section 4.3.

Pharmacodynamic and kinetic factors	Age ≥ 75 years
Factors increasing dabigatran plasma levels	Major: • Moderate renal impairment (30-50 ml/min CrCL) • P-gp inhibitor co-medication (some P-gp inhibitors are contraindicated, see section 4.3 and 4.5) Minor: • Low body weight (< 50 kg)
Pharmacodynamic interactions	• ASA

	• NSAID • Clopidogrel • SSRIs or SNRIs • Other drugs which may impair haemostasis
Diseases / procedures with special haemorrhagic risks	• Congenital or acquired coagulation disorders • Thrombocytopenia or functional platelet defects • Recent biopsy, major trauma • Bacterial endocarditis • Esophagitis, gastritis or gastroesophageal reflux

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

Pradaxa does not in general require routine anticoagulant monitoring. However, the measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. The INR test is unreliable in patients on Pradaxa and false positive INR elevations have been reported. Therefore INR tests should not be performed. Diluted thrombin time (dTT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information, but the tests are not standardized, and results should be interpreted with caution (see section 5.1).

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

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

(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).

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 dTT, ECT or aPTT not exceeding the ULN according to the local reference range.

Interaction with P-gp inducers

Concomitant administration of P-gp inducers (such as rifampicin, St. John`s wort (Hypericum perforatum), carbamazepine, or phenytoin) is expected to result in decreased dabigatran plasma concentrations, and should be avoided (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 3 summarizes discontinuation rules before invasive or surgical procedures.

Renal function (CrCL in ml/min)	Estimated half-life (hours)	Stop dabigatran before elective surgery	
		High risk of bleeding or major surgery	Standard risk
≥ 80	~ 13	2 days before	24 hours before
≥ 50-< 80	~ 15	2-3 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 (for cardioversion see section 4.2).

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.

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. 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, ticagrelor, dextran, sulfinpyrazone, 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).

Only limited data on concomitant use of dabigatran etexilate and other anticoagulants are available, and no firm conclusions can be drawn. From the limited data collected in the phase III study RE-LY in patients with atrial fibrillation it was observed that the concomitant use of other oral or parenteral anticoagulants increases major bleeding rates with both dabigatran etexilate and warfarin by approximately 2.5-fold, mainly related to situations when switching from one anticoagulant to another (see section 4.3).

From the data collected in the phase III study RE-LY in patients with atrial fibrillation (see section 5.1), it was observed that the concomitant use of antiplatelets ASA or clopidogrel approximately doubles major bleeding rates with both dabigatran etexilate and warfarin (see section 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) (see also subsection on ASA below).

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

NSAIDs: NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use in the RE-LY study, NSAIDs increased the risk of bleeding by approximately 50% on both dabigatran etexilate and warfarin. Therefore, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives > 12 hours, close observation for signs of bleeding is recommended (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 oral dose of 400 mg, and 153 % and 149 %, respectively, after multiple oral dosing of 400 mg ketoconazole once daily. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole (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 Close clinical surveillance is recommended when dabigatran etexilate is combined with amiodarone and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.

Quinidine: Quinidine was given as 200 mg dose every 2nd hour up to a total dose of 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). 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 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 (increased of C_{max} by about 90 % and AUC by about 70 %) or administration of multiple doses of verapamil (increased of C_{max} by about 60 % and AUC by about 50 %).

Patients 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 (increased 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.

<u>Co-medication with selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs)</u>

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

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 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

In the pivotal study investigating the prevention of stroke and SEE in patients with atrial fibrillation, a total of 12,091 patients were randomized. 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, 22 % of patient with atrial fibrillation treated for the prevention of stroke and SEE (long-term treatment for up to 3 years) experienced adverse reactions.

The most commonly reported adverse reactions are bleedings occurring in total in approximately 16,5 % in patients with atrial fibrillation treated for the prevention of stroke and SEE.

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 4 shows the adverse reactions identified from the prevention of thromboembolic stroke and SEE in patients with atrial fibrillation program ranked under headings of System Organ Class (SOC) and frequency using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (can not be estimated from the available data).

	Stroke and SEE prevention in patients with atrial fibrillation	
SOC / Preferred Term.	Dabigatran etexilate 110 mg twice daily	Dabigatran etexilate 150 mg twice daily
Number of patients treated	5,983	6,059
Blood and lymphatic system disorders		
Anaemia	Common	Common
Haemoglobin decreased	Uncommon	Uncommon
Thrombocytopenia	Uncommon	Uncommon
Haematocrit decreased	Rare	Rare
Immune system disorder		
Drug hypersensitivity	Uncommon	Uncommon
Rash	Uncommon	Uncommon
Pruritus	Uncommon	Uncommon
Urticaria	Rare	Rare
Bronchospasm	Not known	Very Rare
Nervous system disorders		
Intracranial haemorrhage	Uncommon	Uncommon
Vascular disorders		
Haematoma	Uncommon	Uncommon
Haemorrhage	Uncommon	Uncommon
Respiratory, thoracic and mediastinal disorders		
Epistaxis	Common	Common
Haemoptysis	Uncommon	Uncommon
Gastrointestinal disorders		
Gastrointestinal haemorrhage	Common	Common
Abdominal pain	Common	Common
Diarrhoea	Common	Common
Dyspepsia	Common	Common
Nausea	Common	Common
Rectal haemorrhage	Uncommon	Uncommon
Haemorrhoidal haemorrhage	Uncommon	Uncommon
Gastrointestinal ulcer	Uncommon	Uncommon
Gastroesophagitis	Uncommon	Uncommon
Gastroesophageal reflux disease	Uncommon	Uncommon
Vomiting	Uncommon	Uncommon
Dysphagia	Uncommon	Uncommon
Hepatobiliary disorders		
Alanine aminotransferase increased	Uncommon	Uncommon

Aspartate aminotransferase increased	Uncommon	Uncommon
Hepatic function abnormal/ Liver function Test abnormal	Common	Common
Hepatic enzyme increased	Rare	Rare
Hyperbilirubinaemia	Rare	Rare
Skin and subcutaneous tissue disorder		
Skin haemorrhage	Uncommon	Uncommon
Musculoskeletal and connective tissue and bone disorders		
Haemarthrosis	Rare	Rare
Renal and urinary disorders		
Genitourological haemorrhage	Uncommon	Common
Haematuria	Uncommon	Uncommon
General disorders and administration site conditions		
Injection site haemorrhage	Rare	Rare
Catheter site haemorrhage	Rare	Rare
Injury, poisoning and procedural complications		
Incision site haemorrhage	Uncommon	Uncommon

Bleeding

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

	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) (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 prescribers discretion.

Activated prothrombin complex concentrates (e.g., FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX and X, may be considered. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatran, but data on their usefulness in clinical settings and also on the possible risk of rebound thromboembolism is very limited. Coagulation tests may become unreliable following adminstration of suggested reversing agents. Caution should be exercised when interpreting these tests. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet drugs have been used. All symptomatic treatment should be given according to the physician's judgement.

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

As protein binding is low, dabigatran can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: direct thrombine 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. Dabigatran prolongs the thrombin time (TT), ECT, and aPTT.

The calibrated diluted TT (dTT) test provides an estimation of dabigatran plasma concentration that can be compared to the expected dabigatran plasma concentrations.

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

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

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

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

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

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

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

In the RE-LY study, a total of 18,113 patients were randomized, with a mean age of 71.5 years and a mean $CHADS_2$ score of 2.1. The patient population was 64 % male, 70 % Caucasian and 16 % Asian.

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

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

Tables 6-8 display details of key results in the overall population:

Table 6: Analysis of first occurrence of stroke or SEE (primary endpoint) during the study period in RE-LY.

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

% refers to yearly event rate

Table 7: Analysis of first occurrence of ischemic or haemorrhagic strokes during the study period in RE-LY.

	Dabigatran etexilate 110 mg twice daily	Dabigatran etexilate 150 mg twice daily	Warfarin
Subjects randomized	6,015	6,076	6,022
Stroke			
Incidences (%)	171 (1.44)	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	
SEE			
Incidences (%)	15 (0.13)	13 (0.11)	21 (0.18)
Hazard ratio vs. warfarin (95 % CI)	0.71 (0.37, 1.38)	0.61 (0.30, 1.21)	
p-value	0.3099	0.1582	
Ischemic stroke			
Incidences (%)	152 (1.28)	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	
Haemorrhagic stroke			
Incidences (%)	14 (0.12)	12 (0.10)	45 (0.38)
Hazard ratio vs. warfarin (95 % CI)	0.31 (0.17, 0.56)	0.26 (0.14, 0.49)	
p-value	< 0.001	< 0.001	

% refers to yearly event rate

Table 8: Analysis of all cause and cardiovascular survival during the study period in RE-LY.

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

% refers to yearly event rate

Tables 9-10 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 9: 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. The concomitant use of antiplatelets ASA or clopidogrel approximately doubles MBE rates with both dabigatran and warfarin. There was no significant interaction of treatment effects with the subgroups of renal function and $CHADS_2$ score.

Table 10: 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)
ASA use	0.85 (0.68, 1.05)	0.92 (0.75, 1.14)

Clopidogrel use	0.88 (0.56, 1.37)	0.95 (0.62, 1.46)

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 (see section 4.2 for information on paediatric use).

Ethnic origin

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

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, GI paresis, and surgical effects independent of the oral medicinal product formulation. It was demonstrated in a further study that slow and delayed absorption is usually only present on the day of surgery. On subsequent days absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after medicinal product administration.

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

The oral bioavailability may be increased by 75 % 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 11.

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 11: 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)

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

The median CrCL in RE-LY was 68.4 ml/min. Almost half (45.8 %) of the RE-LY patients had a CrCL > 50-< 80 ml/min. Patients with moderate renal impairment (CrCL between 30 and 50 ml/min) had on average 2.29-fold and 1.81-fold higher pre- and post-dose dabigatran plasma concentrations, respectively, when compared with patients without renal impairment (CrCL ≥ 80 ml/min).

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
In atrial fibrillation patients females had on average 30 % higher trough and post-dose concentrations. No dose adjustment is recommended (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) had 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 350
- Talc
- Hydroxypropylcellulose

Capsule shell

- Carrageenan
- Potassium Chloride
- Titanium Dioxide
- Indigo Carmine (E132)
- Sunset Yellow (E110)
- Hypromellose
- Water purified

Black printing ink

- Shellac
- N-Butyl alcohol
- Isopropyl alcohol
- Industrial methylated spirit
- Iron oxide black (E172)
- Purified water
- Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister and bottle: 3 years

Once the bottle is opened, the medicinal product must be used within 4 months.

6.4 Special precautions for storage

Blister

Store in the original package in order to protect from moisture .

Bottle

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

6.5 Nature and contents of container

Cartons containing 1, 3, or 6 blister strips (10 x 1, 30 x 1, 60 x 1) and a multipack containing 3 packs of 60 x 1 hard capsules (180 hard capsules) in perforated aluminium unit dose blisters. The blister consists of an aluminium lidding foil coated with polyvinylchloride-polyvinylacetate copolymer-acrylate (PVCAC acrylate) in contact with the product and an aluminium bottom foil with polyvinylchloride (PVC) in contact with the product.

Polypropylene bottle with a screw cap containing 60 hard capsules.

Not all pack sizes may be marketed.

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.

When taking a hard capsule out of the bottle, please observe the following instructions:

- The cap opens by pushing and turning.

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

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/009
EU/1/08/442/010
EU/1/08/442/011
EU/1/08/442/012
EU/1/08/442/013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 August 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Not applicable

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan (RMP)
The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Medicinal product subject to medical prescription.

The MAH shall provide an educational pack for each therapeutic indication, targeting all physicians who are expected to prescribe/use Pradaxa. This educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Pradaxa and providing guidance on how to manage that risk.

The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority prior to distribution of the educational pack. The educational pack must be available for distribution for both therapeutic indications prior to the launch of the new indication (prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more risk factors) in the Member State.

The physician educational pack should contain:

- The Summary of Product Characteristics
- Prescriber Guide

- Patient Alert Cards

The Prescriber Guide should contain the following key safety messages:

- Details of populations potentially at higher risk of bleeding
- Recommendation for kidney function measurement
- Recommendations for dose reduction in at risk populations
- Management of overdose situations
- The use of coagulation tests and their interpretation
- That all patients should be provided with a Patient alert card and be counselled about:
  - Signs or symptoms of bleeding and when to seek attention from a health care provider.
  - Importance of treatment compliance
  - Necessity to carry the Patient alert card with them at all times
  - The need to inform Health Care Professionals that they are taking Pradaxa if they need to have any surgery or invasive procedure.
- An instruction how to take Pradaxa

The Patient alert card should contain the following key safety messages:

- Signs or symptoms of bleeding and when to seek attention from a health care provider.
- Importance of treatment compliance
- Necessity to carry the Patient alert card with them at all times
- The need to inform Health Care Professionals that they are taking Pradaxa if they need to have any surgery or invasive procedure.
- An instruction how to take Pradaxa

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR BLISTER for 75 mg

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 75 mg hard capsules
Dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains sunset yellow (E 110) (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

10 x 1 hard capsule
30 x 1 hard capsule
60 x 1 hard capsule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Should be swollowed whole, do not chew or break the capsule.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/001
EU/1/08/442/002
EU/1/08/442/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 75 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR BLISTER for 110 mg

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 110 mg hard capsules
Dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains sunset yellow (E 110) (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

10 x 1 hard capsule
30 x 1 hard capsule
60 x 1 hard capsule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Should be swollowed whole, do not chew or break the capsule.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/005
EU/1/08/442/006
EU/1/08/442/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 110 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACK OF 180 (3 PACKS OF 60 HARD-CAPSULES) – WITHOUT BLUE BOX – 110 mg HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 110 mg hard capsules
Dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains sunset yellow (E 110) (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

60 x 1 hard capsule. Component of a multipack, can not be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Should be swollowed whole, do not chew or break the capsule.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH

Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/014

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 110 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACK OF 180 (3 PACKS OF 60 HARD CAPSULES) WRAPPED IN TRANSPARENT FOIL – INCLUDING THE BLUE BOX – 110 mg HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 110 mg hard capsules
Dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains sunset yellow (E 110) (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack comprising 3 packs, each containing 60 x 1 hard capsule.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Should be swollowed whole, do not chew or break the capsule.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/014

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 110 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX FOR BLISTER for 150 mg

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 150 mg hard capsules
Dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains sunset yellow (E 110) (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

10 x 1 hard capsule
30 x 1 hard capsule
60 x 1 hard capsule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Should be swollowed whole, do not chew or break the capsule.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/009
EU/1/08/442/010
EU/1/08/442/011

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 150 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACK OF 180 (3 PACKS OF 60 HARD-CAPSULES) – WITHOUT BLUE BOX – 150 mg HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 150 mg hard capsules
Dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains sunset yellow (E 110) (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

60 x 1 hard capsule. Component of a multipack, can not be sold seperately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Should be swollowed whole, do not chew or break the capsule.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH

Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 150 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACK OF 180 (3 PACKS OF 60 HARD CAPSULES) WRAPPED IN TRANSPARENT FOIL – INCLUDING THE BLUE BOX – 150 mg HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 150 mg hard capsules
Dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains sunset yellow (E 110) (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack comprising 3 packs, each containing 60 x 1 hard capsule.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Should be swollowed whole, do not chew or break the capsule.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 150 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR 75 mg

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 75 mg hard capsules
Dabigatran etexilate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Peel back

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR 110 mg

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 110 mg hard capsules
Dabigatran etexilate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Peel back

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR 150 mg

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 150 mg hard capsules
Dabigatran etexilate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Peel back

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

FOLDING BOX AND LABEL FOR BOTTLE for 75 mg

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 75 mg hard capsules
Dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains sunset yellow (E110) (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Should be swollowed whole, do not chew or break the capsule.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Once opened, the product must be used within 4 months.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 75 mg (only applicable for folding box, not applicable for bottle label)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING.

FOLDING BOX AND LABEL FOR BOTTLE for 110 mg

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 110 mg hard capsules
Dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains sunset yellow (E110) (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Should be swollowed whole, do not chew or break the capsule.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Once opened, the product must be used within 4 months.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 110 mg (only applicable for folding box, not applicable for bottle label)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING.

FOLDING BOX AND LABEL FOR BOTTLE for 150 mg

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 150 mg hard capsules
Dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains sunset yellow (E110) (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Should be swollowed whole, do not chew or break the capsule.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Once opened, the product must be used within 4 months.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 150 mg (only applicable for folding box, not applicable for bottle label)

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Pradaxa 75 mg hard capsules
dabigatran etexilate

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

In this leaflet:

1. What Pradaxa is and what it is used for

What is Pradaxa

Pradaxa is a medicine which contains the active substance dabigatran etexilate. It works by blocking a substance in the body which is involved in blood clot formation.

What Pradaxa is used for

Pradaxa is used to prevent the formation of blood clots in the veins after knee or hip replacement surgery.

2. What you need to know before you take Pradaxa

Do not take Pradaxa

- if you are allergic to dabigatran etexilate, dabigatran or any of the other ingredients of this medicine (listed in section 6).
- if you have severely reduced kidney function.
- if you are currently bleeding.
- if you have a disease in an organ of the body that increases the risk of serious bleeding.
- if you have an increased tendency to bleed. This may be inborn, of unknown cause or due to other medicines.
- if you have a severely reduced liver function or liver disease which could possibly cause death.
- if you are taking oral ketoconazole or itraconazole, medicines to treat fungal infections.
- if you are taking cyclosporine or tacrolimus, medicines to prevent organ rejection after transplantation.
- if you are taking medicines to prevent blood clotting (e.g. warfarin, rivaroxaban, apixaban or heparin), except when changing anticoagulant treatment.

Warnings and precautions

Talk to your doctor before taking Pradaxa. You may also need to talk to your doctor during treatment with Pradaxa if you experience symptoms or if you have to undergo surgery. Tell your doctor if you have or have had any medical conditions or illnesses, in particular any of those included in the following list:

- if you have a liver disease that is associated with changes in the blood tests, the use of Pradaxa is not recommended.

- if you have an increased bleeding risk, as could be the case in the following situations:
  - if you have been recently bleeding.
  - if you have had a surgical tissue removal (biopsy) in the past month.
  - if you have had a serious injury (e.g. a bone fracture, head injury or any injury requiring surgical treatment).
  - if you are suffering from an inflammation of the gullet or stomach.
  - if you have problems with reflux of gastric juice into the gullet.
  - if you are receiving medicines which could increase the risk of bleeding.
  - if you are taking anti-inflammatory medicines.
  - if you are suffering from an infection of the heart (bacterial endocarditis).
  - if you know you have impaired kidney function, or you are suffering from dehydration (symptoms include feeling thirsty and passing reduced amounts of dark-coloured (concentrated) urine).
  - if you are older than 75 years.
  - if you weigh 50 kg or less.

- if you have had or if you are at risk to develop a heart attack.

- if you undergo a planned surgery. Pradaxa will need to be stopped temporarily due to an increased bleeding risk during and shortly after an operation. If possible, Pradaxa should be stopped at least 24 hours before an operation. In patients with a higher risk for bleeding your doctor may decide to stop treatment earlier.

- if you need to undergo an unplanned surgery. If possible, a surgery should be delayed until at least 12 hours after the last dose. If surgery cannot be delayed, there may be an increased risk of bleeding. Your doctor will consider this risk of bleeding together with the urgency of the surgery.

- if you have a tube (catheters) inserted into the back:
  A tube can be inserted into your back e.g. for anaesthesia or pain relief during or after surgery. If you are administered Pradaxa after removal of a catheter, your doctor will examine you regularly.

- if you fall or injure yourself during treatment, especially if you hit your head, please seek urgent medical attention. You may need to be checked by a doctor, as you may be at increased risk of bleeding.

Children and adolescents

Pradaxa should not be used in children and adolescents.

Other medicines and Pradaxa

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription. For instance:

- Medicines to reduce blood clotting (e.g. warfarin, phenprocoumon, heparin, clopidogrel, prasugrel, ticagrelor, rivaroxaban)
- Anti-inflammatory and pain reliever medicines (e.g. aspirine)

- St. John´s wort, a herbal medicine for depression
- Antidepressant medicines called selective serotonin re-uptake inhibitors or serotonin-norepinephrine re-uptake inhibitors
- Rifampicin or clarithromycin, two antibiotics
- Medicines to treat abnormal heart beats (e.g. Amiodarone, dronedarone, quinidine, verapamil)
  If you are taking amiodarone-, quinidine- or verapamil-containing medicines, you should be treated with a reduced dose of 150 mg Pradaxa taken once a day as 2 capsules of 75 mg, because your bleeding risk may be increased. Pradaxa and these medicines should be taken at the same time.
  If you are taking verapamil containing medicines and your kidney function is decreased by more than half, you should be treated with a reduced dose of 75 mg Pradaxa because your bleeding risk may be increased.
- Medicines to treat fungal infections (e.g. ketoconazole, itraconazole, fluconazole), unless they are only applied to the skin
- Medicines to prevent organ rejection after transplantation (e.g. tacrolimus, cyclosporine)
- Anti-viral medicines for AIDS (e.g. ritonavir)
- Medicines for treatment of epilepsy (e.g. carbamazepine, phenytoin)

Pregnancy, breast-feeding and fertility

The effects of Pradaxa on pregnancy and the unborn child are not known. You should not take Pradaxa if you are pregnant unless your doctor advises you that it is safe to do so. If you are a woman of child-bearing age, you should avoid becoming pregnant while you are taking Pradaxa.

You should not breast-feed while you are taking Pradaxa.

Driving and using machines

The effect of Pradaxa on the ability to drive and use machines is not known. Your doctor will tell you when you can start to drive.

Pradaxa contains sunset yellow

Pradaxa hard capsules contain a colorant with the name sunset yellow, which may cause allergic reactions.

3. How to take Pradaxa

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Pradaxa can be taken with or without food. The capsule should be swallowed whole with some water. Do not break, chew, or empty the pellets from the capsule since this may increase the risk of bleeding.

The generally recommended dose of Pradaxa is 220 mg once a day (taken as 2 capsules of 110 mg).

If your kidney function is decreased by more than half or if you are 75 years of age or older, the recommended dose is 150 mg once a day (taken as 2 capsules of 75 mg).

If you are taking amiodarone-, quinidine- or verapamil-containing medicines the recommended dose is 150 mg once a day (taken as 2 capsules of 75 mg).

If you are taking verapamil containing medicines and your kidney function is decreased by more than half, you should be treated with a reduced dose of 75 mg Pradaxa because your bleeding risk may be increased.

After knee replacement surgery

You should start treatment with Pradaxa within 1-4 hours after surgery finishes, taking a single capsule. Thereafter two capsules once a day should be taken for a total of 10 days.

After hip replacement
You should start treatment with Pradaxa within 1-4 hours after surgery finishes, taking a single capsule. Thereafter two capsules once a day should be taken for a total of 28-35 days.

For both surgery types, treatment should not be started if there is bleeding from the site of operation. If the treatment cannot be started until the day after surgery, dosing should be started with 2 capsules once a day.

When taking Pradaxa capsules out of the blister pack, please observe the following instructions

- take the capsules by peeling off the backing foil of the blister card.
- do not push the capsules through the blister foil.
- do not peel off the blister foil until a capsule is required.

When taking Pradaxa capsules out of the bottle, please observe the following instructions

- push and turn for opening.

Change of anticoagulant treatment

- *Changing from treatment with Pradaxa to anticoagulant treatment given by injection:*
  Do not start treatment with injectable anticoagulant medicines (for example, heparin) until 24 hours after the final dose of Pradaxa.

- *Changing from anticoagulant treatment given by injection to treatment with Pradaxa:*
  Start taking Pradaxa 0-2 hours before the time you would have had the next injection.

If you take more Pradaxa than you should
If you take more Pradaxa than recommended, you may have an increased risk of bleeding. Your doctor can perform a blood test to assess the risk of bleeding.
Inform your doctor as soon as possible, if you take more than the prescribed dose of Pradaxa. If bleeding occurs, surgical treatment or treatment with blood transfusions may be required.

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

If you stop taking Pradaxa
Take Pradaxa exactly as prescribed. Do not stop taking Pradaxa without first consulting your doctor. Stopping Pradaxa may increase the risk of developing a blood clot in patients treated after hip- or knee-replacement surgery.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

As this medicine affects blood clotting, most side effects are related to signs such as bruising or bleeding. Although rarely reported in clinical trials, major or severe bleeding may occur and,

regardless of location, may become disabling, life-threatening or even lead to death. In some cases these bleedings may not be obvious.

Tell your doctor immediately, if you experience any of the following side effects: long or excessive bleeding, exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling. Your doctor may decide to keep you under closer observation or change your medicine.

The side effects are listed below, grouped by how likely they are to happen:

With Pradaxa the following side effects are known:

Common side effects (affects 1 to 10 users in 100):
- A fall in the number of red cells in the blood
- A fall in the amount of haemoglobin in the blood (the substance in the red blood cells)
- Nosebleed
- Bleeding into the stomach or bowel
- Belly ache or stomach ache
- Frequent loose or liquid bowel movements
- Indigestion
- Feeling sick
- Unusual laboratory test results on liver function

Uncommon side effects (affects 1 to 10 users in 1,000):
- Bleeding
  Bleeding may happen from piles, into the rectum, under the skin, in the brain, into a joint, from or after an injury or after an operation.
- Coughing of blood or blood stained sputum
- Bruising occurring after an operation
- Bleeding from a surgical incision
- Exudation of a small amount of liquid from the incision made for a surgical procedure
- Wound secretion (liquid exuding from the surgical wound)
- Haematoma formation
- Blood in the urine that stains the urine pink or red
- Blood found in the urine on laboratory testing
- Blood detected in the stools by a laboratory test
- A fall in the number of platelets in the blood
- A fall in the number of red cells in the blood after an operation
- A decrease in the proportion of red cells in the blood
- Allergic reaction
- Sudden change of the skin which affects its colour and appearance
- Itching
- Blain in the alimentary tract
- Inflammation of the gullet and stomach
- Reflux of gastric juice into the gullet
- Vomiting
- Difficulty in swallowing

Rare side effects (affects 1 to 10 in 10,000):
- Bleeding from the site of entry of an injection
- Bleeding from the site of entry of a catheter into a vein
- Blood-stained discharge from the site of entry of a catheter into a vein
- Fluid exiting a wound
- Fluid exiting a wound after an operation
- Skin rash notable for dark red, raised, itchy bumps caused by an allergic reaction

Not known (cannot be estimated from the available data):
- Difficulty in breathing or wheezing

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. Your doctor may decide to change the medicine.

5. How to store Pradaxa

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, blister or bottle. The expiry date refers to the last day of that month.

Blister: Store in the original package in order to protect from moisture.
Bottle: Once opened, the medicine must be used within 4 months. Keep the bottle tightly closed. Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Pradaxa contains

- The active substance is dabigatran, which is administered in the form of 75 mg dabigatran etexilate given as mesilate.

- The other ingredients are tartaric acid, acacia, hypromellose, dimeticone 350, talc, and hydroxypropylcellulose.

- The capsule shell contains carrageenan, potassium chloride, titanium dioxide, indigo carmine, sunset yellow, hypromellose and purified water.

- The black printing ink contains shellac, N-butyl alcohol, isopropyl alcohol, industrial methylated spirit, iron oxide black, purified water and propylene glycol.

What Pradaxa looks like and contents of the pack

Pradaxa is a hard capsule.

Pradaxa 75 mg hard capsules have an opaque, light blue-coloured cap and an opaque, cream-coloured body. The Boehringer Ingelheim logo is printed on the cap and “R75” on the body of the capsule.

Pradaxa 75 mg hard capsules are available in packs containing 10 x 1, 30 x 1, 60 x 1capsules in aluminium perforated unit dose blisters.

Pradaxa 75 mg hard capsules are also available in polypropylene (plastic) bottles with 60 hard capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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D-55216 Ingelheim am Rhein
Germany

Manufacturer

Boehringer Ingelheim Pharma GmbH & Co. KG
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This leaflet was last approved in XX/YYYY

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

PACKAGE LEAFLET: INFORMATION FOR THE USER

Pradaxa 110 mg hard capsules
dabigatran etexilate

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

In this leaflet:

1. What Pradaxa is and what it is used for

What is Pradaxa

Pradaxa is a medicine which contains the active substance dabigatran etexilate. It works by blocking a substance in the body which is involved in blood clot formation.

What Pradaxa is used for

Pradaxa is used to prevent the formation of blood clots in the veins after knee or hip replacement surgery.

Pradaxa is a medicine which is used to reduce the risk of brain or body vessel obstruction by blood clot formation in patients with an abnormal heart beat (atrial fibrillation) and additional risk factors. Pradaxa is a blood thinner medicine that lowers the risk of blood clot formation.

2. What you need to know before you take Pradaxa

Do not take Pradaxa

- if you are allergic to dabigatran etexilate, dabigatran or any of the other ingredients of this medicine (listed in section 6).
- if you have severely reduced kidney function.
- if you are currently bleeding.
- if you have a disease in an organ of the body that increases the risk of serious bleeding.
- if you have an increased tendency to bleed. This may be inborn, of unknown cause or due to other medicines.
- if you have a severely reduced liver function or liver disease which could possibly cause death.
- if you are taking oral ketoconazole or itraconazole, medicines to treat fungal infections.
- if you are taking cyclosporine or tacrolimus, medicines to prevent organ rejection after transplantation.
- if you are taking medicines to prevent blood clotting (e.g.warfarin, rivaroxaban, apixaban or heparin), except when changing anticoagulant treatment.

Warnings and precautions

Talk to your doctor before taking Pradaxa. You may also need to talk to your doctor during treatment with Pradaxa if you experience symptoms or if you have to undergo surgery. Tell your doctor if you have or have had any medical conditions or illnesses, in particular any of those included in the following list:

- if you have a liver disease that is associated with changes in the blood tests, the use of Pradaxa is not recommended.

- if you have an increased bleeding risk, as could be the case in the following situations:
  - if you have been recently bleeding.
  - if you have had a surgical tissue removal (biopsy) in the past month.
  - if you have had a serious injury (e.g. a bone fracture, head injury or any injury requiring surgical treatment).
  - if you are suffering from an inflammation of the gullet or stomach.
  - if you have problems with reflux of gastric juice into the gullet.
  - if you are receiving medicines which could increase the risk of bleeding.
  - if you are taking anti-inflammatory medicines.
  - if you are suffering from an infection of the heart (bacterial endocarditis).
  - if you know you have impaired kidney function, or you are suffering from dehydration (symptoms include feeling thirsty and passing reduced amounts of dark-coloured (concentrated) urine).
  - if you are older than 75 years.
  - if you weigh 50 kg or less.

- if you have had or if you are at risk to develop a heart attack.

- if you undergo a planned surgery. Pradaxa will need to be stopped temporarily due to an increased bleeding risk during and shortly after an operation. If possible, Pradaxa should be stopped at least 24 hours before an operation. In patients with a higher risk for bleeding your doctor may decide to stop treatment earlier.

- if you need to undergo an unplanned surgery. If possible, a surgery should be delayed until at least 12 hours after the last dose. If surgery cannot be delayed, there may be an increased risk of bleeding. Your doctor will consider this risk of bleeding together with the urgency of the surgery.

- if you have a tube (catheters) inserted into the back:
  A tube can be inserted into your back e.g. for anaesthesia or pain relief during or after surgery. If you are administered Pradaxa after removal of a catheter, your doctor will examine you regularly.

- if you fall or injure yourself during treatment, especially if you hit your head, please seek urgent medical attention. You may need to be checked by a doctor, as you may be at increased risk of bleeding.

Children and adolescents

Pradaxa should not be used in children and adolescents.

Other medicines and Pradaxa

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription. For instance:

- Medicines to reduce blood clotting (e.g. warfarin, phenprocoumon**,** heparin, clopidogrel, prasugrel, ticagrelor, rivaroxaban)
- Anti-inflammatory and pain reliever medicines (e.g. aspirine)
- St. John´s wort, a herbal medicine for depression
- Antidepressant medicines called selective serotonin re-uptake inhibitors or serotonin-norepinephrine re-uptake inhibitors
- Rifampicin or clarithromycin, two antibiotics
- Medicines to treat abnormal heart beats (e.g. Amiodarone, dronedarone, quinidine, verapamil)
  Prevention of blood clot formation after knee or hip replacement surgery
  If you are taking amiodarone-, quinidine- or verapamil-containing medicines, you should be treated with a reduced dose of 150 mg Pradaxa taken once a day as 2 capsules of 75 mg, because your bleeding risk may be increased. Pradaxa and these medicines should be taken at the same time.
  If you are taking verapamil containing medicines and your kidney function is decreased by more than half, you should be treated with a reduced dose of 75 mg Pradaxa because your bleeding risk may be increased.
  Prevention of brain or body vessel obstruction by blood clot formation developing after abnormal heart beats
  If you are taking verapamil-containing medicines, you should be treated with a reduced Pradaxa dose of 220 mg taken as one 110 mg capsule twice a day, because your bleeding risk may be increased. Pradaxa and verapamil-containing medicines should be taken at the same time.
- Medicines to treat fungal infections (e.g. ketoconazole, itraconazole, fluconazole), unless they are only applied to the skin
- Medicines to prevent organ rejection after transplantation (e.g. tacrolimus, cyclosporine)
- Anti-viral medicines for AIDS (e.g. ritonavir)
- Medicines for treatment of epilepsy (e.g. carbamazepine, phenytoin)

Pregnancy, breast-feeding and fertility

The effects of Pradaxa on pregnancy and the unborn child are not known. You should not take Pradaxa if you are pregnant unless your doctor advises you that it is safe to do so. If you are a woman of child-bearing age, you should avoid becoming pregnant while you are taking Pradaxa.

You should not breast-feed while you are taking Pradaxa.

Driving and using machines

The effect of Pradaxa on the ability to drive and use machines is not known. Your doctor will tell you when you can start to drive.

Pradaxa contains sunset yellow

Pradaxa hard capsules contain a colorant with the name sunset yellow, which may cause allergic reactions.

3. How to take Pradaxa

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Pradaxa can be taken with or without food. The capsule should be swallowed whole with some water. Do not break, chew, or empty the pellets from the capsule since this may increase the risk of bleeding.

Take Pradaxa as recommended for the following conditions:

Prevention of blood clot formation after knee or hip replacement surgery

The generally recommended dose of Pradaxa is 220 mg once a day (taken as 2 capsules of 110 mg).

If your kidney function is decreased by more than half or if you are 75 years of age or older, the recommended dose is 150 mg once a day (taken as 2 capsules of 75 mg).

If you are taking amiodarone-, quinidine- or verapamil-containing medicines the recommended dose is 150 mg once a day (taken as 2 capsules of 75 mg).

If you are taking verapamil containing medicines and your kidney function is decreased by more than half, you should be treated with a reduced dose of 75 mg Pradaxa because your bleeding risk may be increased.

After knee replacement surgery

You should start treatment with Pradaxa within 1-4 hours after surgery finishes, taking a single capsule. Thereafter two capsules once a day should be taken for a total of 10 days.

After hip replacement
You should start treatment with Pradaxa within 1-4 hours after surgery finishes, taking a single capsule. Thereafter two capsules once a day should be taken for a total of 28-35 days.

For both surgery types, treatment should not be started if there is bleeding from the site of operation. If the treatment cannot be started until the day after surgery, dosing should be started with 2 capsules once daily.

Prevention of brain or body vessel obstruction by blood clot formation developing after abnormal heart beats

The recommended dose of Pradaxa is 300 mg taken as one 150 mg capsule twice a day.

If you are 80 years or older, the recommended dose of Pradaxa is 220 mg taken as one 110 mg capsule twice a day.

If you are taking verapamil-containing medicines, you should be treated with a reduced Pradaxa dose of 220 mg taken as one 110 mg capsule twice a day, because your bleeding risk may be increased.

If you have a potentially higher risk for bleeding, your doctor may decide to prescribe a dose of Pradaxa 220 mg taken as one 110 mg capsule twice a day.

When taking Pradaxa capsules out of the blister pack, please observe the following instructions

- take the capsules by peeling off the backing foil of the blister card.
- do not push the capsules through the blister foil.
- do not peel off the blister foil until a capsule is required.

When taking Pradaxa capsules out of the bottle, please observe the following instructions

- push and turn for opening

Change of anticoagulant treatment

- *Changing from treatment with Pradaxa to anticoagulant treatment given by injection:*

  Prevention of blood clot formation after knee or hip replacement surgery
  Do not start treatment with injectable anticoagulant medicines (for example, heparin) until 24 hours after the final dose of Pradaxa.

Prevention of brain or body vessel obstruction by blood clot formation developing after abnormal heart beats
Do not start treatment with injectable anticoagulant medicines (for example, heparin) until 12 hours after the final dose of Pradaxa.

- *Changing from anticoagulant treatment given by injection to treatment with Pradaxa:*
  Start taking Pradaxa 0-2 hours before the time you would have had the next injection.

Prevention of brain or body vessel obstruction by blood clot formation developing after abnormal heart beats

- *Changing from Pradaxa to blood thinners containing vitamin-K antagonists (e.g. phenprocoumon):*
  Your doctor needs to do blood-measurements and instruct you when to start vitamin-K antagonist treatment.

- *Changing from blood thinners containing vitamin-K antagonists (e.g. phenprocoumon) to Pradaxa:*
  Stop taking the medicine containing a vitamin-K antagonist. Your doctor needs to do blood-measurements and instruct you when to start Pradaxa treatment.

If you take more Pradaxa than you should
If you take more Pradaxa than recommended, you may have an increased risk of bleeding. Your doctor can perform a blood test to assess the risk of bleeding.
Inform your doctor as soon as possible, if you take more than the prescribed dose of Pradaxa. If bleeding occurs, surgical treatment or treatment with blood transfusions may be required.

If you forget to take Pradaxa

Prevention of blood clot formation after knee or hip replacement surgery
Continue with your remaining daily doses of Pradaxa at the same time of the next day.
Do not take a double dose to make up for missed individual doses.

Prevention of brain or body vessel obstruction by blood clot formation developing after abnormal heart beats
A forgotten dose can still be taken up to 6 hours prior to the next due dose.
A missed dose should be omitted if the remaining time is below 6 hours prior to the next due dose.
Do not take a double dose to make up for missed individual doses.

If you stop taking Pradaxa
Take Pradaxa exactly as prescribed. Do not stop taking Pradaxa without first consulting your doctor. Stopping Pradaxa may increase the risk of developing a blood clot in patients treated after hip- or knee-replacement surgery or increase the risk of a brain or body vessel obstruction in patients with abnormal heart beats.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

As this medicine affects blood clotting, most side effects are related to signs such as bruising or bleeding. Although rarely reported in clinical trials, major or severe bleeding may occur and, regardless of location, may become disabling, life-threatening or even lead to death. In some cases these bleedings may not be obvious.

Tell your doctor immediately, if you experience any of the following side effects: long or excessive bleeding, exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling. Your doctor may decide to keep you under closer observation or change your medicine.

The side effects are listed below, grouped by how likely they are to happen:

With Pradaxa the following side effects are known:

Common side effects (affects 1 to 10 users in 100):
- Nosebleed
- Bleeding into the stomach or bowel
- Belly ache or stomach ache
- Frequent loose or liquid bowel movements
- Indigestion
- Feeling sick
- Unusual laboratory test results on liver function

Uncommon side effects (affects 1 to 10 users in 1,000):
- Bleeding
- Bleeding may happen from piles, into the rectum, under the skin or in the brain.
- Coughing of blood or blood stained sputum
- Bleeding from a surgical incision
- Haematoma formation
- Blood in the urine that stains the urine pink or red
- A fall in the number of platelets in the blood
- Allergic reaction
- Sudden change of the skin which affects its colour and appearance
- Itching
- Blain in the alimentary tract
- Inflammation of the gullet and stomach
- Reflux of gastric juice into the gullet
- Vomiting
- Difficulty in swallowing

Rare side effects (affects 1 to 10 in 10,000):
- Bleeding from the site of entry of an injection
- Bleeding from the site of entry of a catheter into a vein
- Skin rash notable for dark red, raised, itchy bumps caused by an allergic reaction

Not known (cannot be estimated from the available data):
- Difficulty in breathing or wheezing

The following additional side effects may be experienced:

<u>Prevention of blood clot formation after knee or hip replacement surgery</u>	<u>Prevention of brain or body vessel obstruction by blood clot formation developing after abnormal heart beats</u>
Common side effects (affects 1 to 10 users in 100):	
- A fall in the number of red cells in the blood - A fall in the amount of haemoglobin in the blood (the substance in the red blood cells)	
Uncommon side effects (affects 1 to 10 users in 1,000):	

− Bleeding Bleeding may happen into a joint, from or after an injury, or after an operation − Bruising occurring after an operation − Exudation of a small amount of liquid from the incision made for a surgical procedure − Wound secretion (liquid exuding from the surgical wound) − Blood found in the urine on laboratory testing − Blood detected in the stools by a laboratory test − A fall in the number of red cells in the blood after an operation − A decrease in the proportion of red cells in the blood	− Bleeding from penis/vagina or urinary tract − A fall in the amount of haemoglobin in the blood (the substance in the red blood cells)
Rare side effects (affects 1 to 10 in 10,000):	
− Blood-stained discharge from the site of entry of a catheter into a vein − Fluid exiting a wound − Fluid exiting a wound after an operation	− Bleeding into a joint − A decrease in the proportion of red cells in the blood − Liver enzymes increased − Yellowing of the skin or whites of the eyes, caused by liver or blood problems

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. Your doctor may decide to change the medicine.

Prevention of brain or body vessel obstruction by blood clot formation developing after abnormal heart beats:
In a clinical trial the rate of heart attacks with Pradaxa was numerically higher than with warfarin. The overall occurence was low.

5. How to store Pradaxa

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, blister or bottle. The expiry date refers to the last day of that month.

Blister: Store in the original package in order to protect from moisture.
Bottle: Once opened, the medicine must be used within 4 months. Keep the bottle tightly closed. Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Pradaxa contains

- The active substance is dabigatran, which is administered in the form of 110 mg dabigatran etexilate given as mesilate.

- The other ingredients are tartaric acid, acacia, hypromellose, dimeticone 350, talc, and hydroxypropylcellulose.

- The capsule shell contains carrageenan, potassium chloride, titanium dioxide, indigo carmine, sunset yellow, hypromellose and purified water.

- The black printing ink contains shellac, N-butyl alcohol, isopropyl alcohol, industrial methylated spirit, iron oxide black, purified water and propylene glycol.

What Pradaxa looks like and contents of the pack

Pradaxa is a hard capsule.

Pradaxa 110 mg hard capsules have an opaque, light blue-coloured cap and an opaque, cream-coloured body. The Boehringer Ingelheim logo is printed on the cap and “R110” on the body of the capsule.

Pradaxa 110 mg hard capsules are available in packs containing 10 x 1, 30 x 1, 60 x 1 or a multipack containing 3 packs of 60 x 1 hard capsules (180 hard capsules) in aluminium perforated unit dose blisters.

Pradaxa 110 mg hard capsules are also available in polypropylene (plastic) bottles with 60 hard capsules.

Not all pack sizes may be marketed.

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This leaflet was last approved in XX/YYYY

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

PACKAGE LEAFLET: INFORMATION FOR THE USER

Pradaxa 150 mg hard capsules
dabigatran etexilate

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

In this leaflet:

1. What Pradaxa is and what it is used for

What is Pradaxa

Pradaxa is a medicine which contains the active substance dabigatran etexilate. It works by blocking a substance in the body which is involved in blood clot formation.

What Pradaxa is used for

Pradaxa is a medicine which is used to reduce the risk of brain or body vessel obstruction by blood clot formation in patients with an abnormal heart beat (atrial fibrillation) and additional risk factors. Pradaxa is a blood thinner medicine that lowers the risk of blood clot formation.

2. What you need to know before you take Pradaxa

Do not take Pradaxa

- if you are allergic to dabigatran etexilate, dabigatran or any of the other ingredients of this medicine (listed in section 6).
- if you have severely reduced kidney function.
- if you are currently bleeding.
- if you have a disease in an organ of the body that increases the risk of serious bleeding.
- if you have an increased tendency to bleed. This may be inborn, of unknown cause or due to other medicines.
- if you have a severely reduced liver function or liver disease which could possibly cause death.
- if you are taking oral ketoconazole or itraconazole, medicines to treat fungal infections.
- if you are taking cyclosporine or tacrolimus, medicines to prevent organ rejection after transplantation.
- if you are taking medicines to prevent blood clotting (e.g.warfarin, rivaroxaban, apixaban or heparin), except when changing anticoagulant treatment.

Warnings and precautions

Talk to your doctor before taking Pradaxa. You may also need to talk to your doctor during treatment with Pradaxa if you experience symptoms or if you have to undergo surgery.Tell your doctor if you have or have had any medical conditions or illnesses, in particular any of those included in the following list:

- if you have a liver disease that is associated with changes in the blood tests, the use of Pradaxa is not recommended.

- if you have an increased bleeding risk, as could be the case in the following situations:
  - if you have been recently bleeding.
  - if you have had a surgical tissue removal (biopsy) in the past month.
  - if you have had a serious injury (e.g. a bone fracture, head injury or any injury requiring surgical treatment).
  - if you are suffering from an inflammation of the gullet or stomach.
  - if you have problems with reflux of gastric juice into the gullet.
  - if you are receiving medicines which could increase the risk of bleeding.
  - if you are taking anti-inflammatory medicines.
  - if you are suffering from an infection of the heart (bacterial endocarditis).
  - if you know you have impaired kidney function, or you are suffering from dehydration (symptoms include feeling thirsty and passing reduced amounts of dark-coloured (concentrated) urine).
  - if you are older than 75 years.
  - if you weigh 50 kg or less.

- if you have had or if you are at risk to develop a heart attack.

- if you undergo a planned surgery. Pradaxa will need to be stopped temporarily due to an increased bleeding risk during and shortly after an operation. If possible, Pradaxa should be stopped at least 24 hours before an operation. In patients with a higher risk for bleeding your doctor may decide to stop treatment earlier.

- if you need to undergo an unplanned surgery. If possible, a surgery should be delayed until at least 12 hours after the last dose. If surgery cannot be delayed, there may be an increased risk of bleeding. Your doctor will consider this risk of bleeding together with the urgency of the surgery.

- if you have a tube (catheters) inserted into the back:
  A tube can be inserted into your back e.g. for anaesthesia or pain relief during or after surgery. If you are administered Pradaxa after removal of a catheter, your doctor will examine you regularly.

- if you fall or injure yourself during treatment, especially if you hit your head, please seek urgent medical attention. You may need to be checked by a doctor, as you may be at increased risk of bleeding.

Children and adolescents

Pradaxa should not be used in children and adolescents.

Other medicines and Pradaxa

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription. For instance:

- Medicines to reduce blood clotting (e.g. warfarin, phenprocoumon**,** heparin, clopidogrel, prasugrel, ticagrelor, rivaroxaban)

- Anti-inflammatory and pain reliever medicines (e.g. aspirine)
- St. John´s wort, a herbal medicine for depression
- Antidepressant medicines called selective serotonin re-uptake inhibitors or serotonin-norepinephrine re-uptake inhibitors
- Rifampicin or clarithromycin, two antibiotics
- Medicines to treat abnormal heart beats (e.g. Amiodarone, dronedarone, quinidine, verapamil)
  If you are taking verapamil-containing medicines, you should be treated with a reduced Pradaxa dose of 220 mg taken as one 110 mg capsule twice a day, because your bleeding risk may be increased. Pradaxa and verapamil-containing medicines should be taken at the same time.
  Medicines to treat fungal infections (e.g. ketoconazole, itraconazole, fluconazole), unless they are only applied to the skin
- Medicines to prevent organ rejection after transplantation (e.g. tacrolimus, cyclosporine)
- Anti-viral medicines for AIDS (e.g. ritonavir)
- Medicines for treatment of epilepsy (e.g. carbamazepine, phenytoin)

Pregnancy, breast-feeding and fertility

The effects of Pradaxa on pregnancy and the unborn child are not known. You should not take Pradaxa if you are pregnant unless your doctor advises you that it is safe to do so. If you are a woman of child-bearing age, you should avoid becoming pregnant while you are taking Pradaxa.

You should not breast-feed while you are taking Pradaxa.

Driving and using machines

The effect of Pradaxa on the ability to drive and use machines is not known. Your doctor will tell you when you can start to drive.

Pradaxa contains sunset yellow

Pradaxa hard capsules contain a colorant with the name sunset yellow, which may cause allergic reactions.

3. How to take Pradaxa

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The recommended dose of Pradaxa is 300 mg taken as one 150 mg capsule twice a day.

If you are 80 years or older, the recommended dose of Pradaxa is 220 mg taken as one 110 mg capsule twice daily.

If you are taking verapamil-containing medicines, you should be treated with a reduced Pradaxa dose of 220 mg taken as one 110 mg capsule twice a day, because your bleeding risk may be increased.

If you have a potentially higher risk for bleeding, your doctor may decide to prescribe a dose of Pradaxa 220 mg taken as one 110 mg capsule twice a day.

Pradaxa can be taken with or without food. The capsule should be swallowed whole with some water. Do not break, chew, or empty the pellets from the capsule since this may increase the risk of bleeding.

When taking Pradaxa capsules out of the blister pack, please observe the following instructions

- take the capsules by peeling off the backing foil of the blister card.

- do not push the capsules through the blister foil.
- do not peel off the blister foil until a capsule is required.

When taking Pradaxa capsules out of the bottle, please observe the following instructions

- push and turn for opening

Change of anticoagulant treatment

- *Changing from treatment with Pradaxa to anticoagulant treatment given by injection:*
  Do not start treatment with injectable anticoagulant medicines (for example, heparin) until 12 hours after the final dose of Pradaxa.

- *Changing from anticoagulant treatment given by injection to treatment with Pradaxa:*
  Start taking Pradaxa 0-2 hours before the time you would have had the next injection.

- *Changing from Pradaxa to blood thinners containing vitamin-K antagonists (e.g. phenprocoumon):*
  Your doctor needs to do blood-measurements and instruct you when to start vitamin-K antagonist treatment.

- *Changing from blood thinners containing vitamin-K antagonists (e.g. phenprocoumon) to Pradaxa:*
  Stop taking the medicine containing a vitamin-K antagonist. Your doctor needs to do blood-measurements and instruct you when to start Pradaxa treatment.

If you take more Pradaxa than you should
If you take more Pradaxa than recommended, you may have an increased risk of bleeding. Your doctor can perform a blood test to assess the risk of bleeding.
Inform your doctor as soon as possible, if you take more than the prescribed dose of Pradaxa. If bleeding occurs, surgical treatment or treatment with blood transfusions may be required.

If you forget to take Pradaxa

A forgotten dose can still be taken up to 6 hours prior to the next due dose.
A missed dose should be omitted if the remaining time is below 6 hours prior to the next due dose.
Do not take a double dose to make up for missed individual doses.

If you stop taking Pradaxa
Take Pradaxa exactly as prescribed. Do not stop taking Pradaxa without first consulting your doctor. Stopping Pradaxa may increase the risk of a brain or body vessel obstruction in patients with abnormal heart beats.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

As this medicine affects blood clotting, most side effects are related to signs such as bruising or bleeding. Although rarely reported in clinical trials, major or severe bleeding may occur and, regardless of location, may become disabling, life-threatening or even lead to death. In some cases these bleedings may not be obvious.

Tell your doctor immediately, if you experience any of the following side effects: long or excessive bleeding, exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling.

Your doctor may decide to keep you under closer observation or change your medicine.

The side effects are listed below, grouped by how likely they are to happen:

With Pradaxa the following side effects are known:

Common side effects (affects 1 to 10 users in 100):
- Nosebleed
- Bleeding into the stomach or bowel
- Belly ache or stomach ache
- Bleeding from penis/vagina or urinary tract
- Frequent loose or liquid bowel movements
- Indigestion
- Feeling sick
- Unusual laboratory test results on liver function

Uncommon side effects (affects 1 to 10 users in 1,000):
- Bleeding
- Bleeding may happen from piles, into the rectum, under the skin or in the brain.
- Bleeding from a surgical incision
- Haematoma formation
- Coughing of blood or blood stained sputum
- Blood in the urine that stains the urine pink or red
- A fall in the number of platelets in the blood
- A fall in the amount of haemoglobin in the blood (the substance in the red blood cells)
- Allergic reaction
- Sudden change of the skin which affects its colour or appearance
- Itching
- Blain in the alimentary tract
- Inflammation of the gullet and stomach
- Reflux of gastric juice into the gullet
- Vomiting
- Difficulty in swallowing

Rare side effects (affects 1 to 10 users in 10,000):
- Bleeding into a joint
- Bleeding from the site of entry of an injection
- Bleeding from the site of entry of a catheter into a vein
- A decrease in the proportion of red cells in the blood
- Liver enzymes increased
- Yellowing of the skin or whites of the eyes, caused by liver or blood problems
- Skin rash notable for dark red, raised, itchy bumps caused by an allergic reaction

Very rare side effects (affects less than 1 user in 10,000):
- Difficulty in breathing or wheezing

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. Your doctor may decide to change the medicine.

In a clinical trial the rate of heart attacks with Pradaxa was numerically higher than with warfarin. The overall occurence was low.

5. How to store Pradaxa

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, blister or bottle. The expiry date refers to the last day of that month.

Blister: Store in the original package in order to protect from moisture.
Bottle: Once opened, the medicine must be used within 4 months. Keep the bottle tightly closed. Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Pradaxa contains

- The active substance is dabigatran, which is administered in the form of 150 mg dabigatran etexilate given as mesilate.

- The other ingredients are tartaric acid, acacia, hypromellose, dimeticone 350, talc, and hydroxypropylcellulose.

- The capsule shell contains carrageenan, potassium chloride, titanium dioxide, indigo carmine, sunset yellow, hypromellose and purified water.

- The black printing ink contains shellac, N-butyl alcohol, isopropyl alcohol, industrial methylated spirit, iron oxide black, purified water and propylene glycol.

What Pradaxa looks like and contents of the pack

Pradaxa is a hard capsule.

Pradaxa 150 mg hard capsules have an opaque, light blue-coloured cap and an opaque, cream-coloured body. The Boehringer Ingelheim logo is printed on the cap and “R150” on the body of the capsule.

Pradaxa 150 mg hard capsules are available in packs containing 10 x 1, 30 x 1, 60 x 1 or a multipack containing 3 packs of 60 x 1 hard capsules (180 hard capsules) in aluminium perforated unit dose blisters.

Pradaxa 150 mg hard capsules are also available in polypropylene (plastic) bottles with 60 hard capsules.

Not all pack sizes may be marketed.

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