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 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.

Renal impairment

Treatment with Pradaxa in patients with severe renal impairment (creatinine clearance (CrCL) < 30 ml/min) is contraindicated (see section 4.3).
In patients with moderate renal impairment (CrCL 30-50 ml/min), there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg (see sections 4.4 and 5.1).

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) (see sections 4.3, 4.4 and 5.2).

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

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

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

In patients with moderate renal impairment and concomitantly treated with dabigatran etexilate and verapamil, a dose reduction of Pradaxa to 75 mg daily should be considered (see sections 4.4 and 4.5).

Elderly

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

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

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

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

Gender

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

Switching

Pradaxa treatment to parenteral anticoagulant

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

Dabigatran etexilate should be given 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous Unfractionated Heparin (UFH)) (see section 4.5).

Paediatric population

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

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

Missed dose

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

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

Method of administration

Pradaxa should be swallowed as a whole with water, with or without food. Patients should be instructed not to open the capsule as this may increase the risk of bleeding (see sections 5.2 and 6.6).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Patients with severe renal impairment (CrCL < 30 ml/min)
- Active clinically significant bleeding
- Organic lesion at risk of bleeding
- Spontaneous or pharmacological impairment of haemostasis
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with systemic ketoconazole, 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. 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 (H2)-blocker treatment increase the risk of GI bleeding. The administration of a PPI can be considered to prevent GI bleeding.

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

Table 1 summarises factors which may increase the haemorrhagic risk.

<table>
<thead>
<tr>
<th>Pharmacodynamic and kinetic factors</th>
<th>Age ≥ 75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors increasing dabigatran plasma levels</td>
<td>Major:</td>
</tr>
<tr>
<td></td>
<td>• Moderate renal impairment (30-50 ml/min CrCL)</td>
</tr>
<tr>
<td></td>
<td>• P-gp inhibitor co-medication</td>
</tr>
<tr>
<td>Minor:</td>
<td>• Low body weight (&lt; 50 kg)</td>
</tr>
<tr>
<td>Pharmacodynamic interactions</td>
<td>• ASA</td>
</tr>
<tr>
<td></td>
<td>• NSAID</td>
</tr>
<tr>
<td></td>
<td>• Clopidogrel</td>
</tr>
<tr>
<td>Diseases / procedures with special haemorrhagic risks</td>
<td>• Congenital or acquired coagulation disorders</td>
</tr>
<tr>
<td></td>
<td>• Thrombocytopenia or functional platelet defects</td>
</tr>
<tr>
<td></td>
<td>• Active ulcerative GI disease</td>
</tr>
<tr>
<td></td>
<td>• Recent GI bleeding</td>
</tr>
<tr>
<td></td>
<td>• Recent biopsy or major trauma</td>
</tr>
<tr>
<td></td>
<td>• Recent ICH</td>
</tr>
<tr>
<td></td>
<td>• Brain, spinal or ophthalmic surgery</td>
</tr>
<tr>
<td></td>
<td>• Bacterial endocarditis</td>
</tr>
</tbody>
</table>

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

The activated partial thromboplastin time (aPTT) test is widely available and provides an approximate indication of the anticoagulation intensity achieved with dabigatran. In patients who are bleeding or at risk of bleeding, the aPTT test may be useful to assist in determining an excess of anticoagulant activity. However, the aPTT test has limited sensitivity and is not suitable for precise quantification of anticoagulant effect, especially at high plasma concentrations of dabigatran. High aPTT values should be interpreted with caution.

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

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

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

When severe bleedings occur treatment must be discontinued and the source of bleeding investigated (see section 4.9).
Agents that may enhance the risk of haemorrhage should not be administered concomitantly or should be administered with caution with Pradaxa (see section 4.5).

Interaction with P-gp inducers

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

Surgery and interventions

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

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

Preoperative phase

Table 2 summarizes discontinuation rules before invasive or surgical procedures.

<table>
<thead>
<tr>
<th>Renal function (CrCL in ml/min)</th>
<th>Estimated half-life (hours)</th>
<th>Stop dabigatran before elective surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>High risk of bleeding or major surgery</td>
</tr>
<tr>
<td>≥ 80</td>
<td>~ 13</td>
<td>2 days before</td>
</tr>
<tr>
<td>≥ 50-&lt; 80</td>
<td>~ 15</td>
<td>2-3 days before</td>
</tr>
<tr>
<td>≥ 30-&lt; 50</td>
<td>~ 18</td>
<td>4 days before</td>
</tr>
</tbody>
</table>

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, 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_{τ,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_{τ,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 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\textsubscript{0-\infty} and C\text(subscript max) values by 138 % and 135 %, respectively, after a single dose of 400 mg, and 153 % and 149 %, respectively, after multiple dosing of 400 mg ketoconazole once daily. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole (see section 4.4). Concomitant treatment with systemic ketoconazole is contraindicated (see section 4.3).

Amiodarone: When Pradaxa was co-administered with a single oral dose of 600 mg amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The dabigatran AUC and C\textsubscript{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\textsubscript{r,ss} and C\textsubscript{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\textsubscript{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\textsubscript{max} by about 180 % and AUC by about 150 %). The effect was progressively decreased with administration of an extended release formulation (increased of C\textsubscript{max} by about 90 % and AUC by about 70 %) or administration of multiple doses of verapamil (increased of C\textsubscript{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 $C_{\text{max}}$ by about 10 % and $\text{AUC}$ 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 $\text{AUC}$ by about 19 % and $C_{\text{max}}$ by about 15 % was observed without any clinical safety concern. However, in patients receiving dabigatran, a clinically relevant interaction cannot be excluded when combined with clarithromycin. Therefore, a close monitoring should be exercised when dabigatran etexilate is combined with clarithromycin and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.

The following potent P-gp inhibitors have not been clinically studied but from in vitro results a similar effect as with ketoconazole may be expected: Itraconazole, tacrolimus and cyclosporine, which are contra-indicated (see section 4.3).

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

**P-gp inducers**

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

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

**Other drugs affecting P-gp**

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

**P-gp substrate**

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

**Gastric pH**

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Pradaxa in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

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

Breast-feeding

There are no clinical data of the effect of dabigatran on infants during breast feeding. Breast-feeding should be discontinued during treatment with Pradaxa.

Fertility

No 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 embryofetal 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 3 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).
<table>
<thead>
<tr>
<th>SOC / Preferred Term.</th>
<th>Dabigatran etexilate 150 mg</th>
<th>Dabigatran etexilate 220 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients treated</td>
<td>2737</td>
<td>2682</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Haemoglobin decreased</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Haematocrit decreased</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Immune system disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Rash</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Not known</td>
<td>Not known</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematoma</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Wound haemorrhage</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Rectal haemorrhage</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Haemorrhoidal haemorrhage</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Nausea</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Gastrointestinal ulcer</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastroesophagitis</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hepatic function abnormal/Liver function Test abnormal</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Hepatic enzyme increased</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin haemorrhage</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue and bone disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemarthrosis</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematuria</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site haemorrhage</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Catheter site haemorrhage</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Bloody discharge</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incision site haemorrhage</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Traumatic haemorrhage</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Post procedural haematoma</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Post procedural haemorrhage</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Anaemia postoperative</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Post procedural discharge</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Wound secretion</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

**Surgical and medical procedures**

| Wound drainage                        | Rare     | Rare     |
| Post procedural drainage               | Rare     | Rare     |

**Bleeding**

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

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate</th>
<th>Dabigatran etexilate</th>
<th>Enoxaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>150 mg N (%)</td>
<td>220 mg N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Treated</td>
<td>1866(100.0)</td>
<td>1825(100.0)</td>
<td>1848(100.0)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>24 (1.3)</td>
<td>33 (1.8)</td>
<td>27 (1.5)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>258(13.8)</td>
<td>251(13.8)</td>
<td>247(13.4)</td>
</tr>
</tbody>
</table>

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 \( \geq 20 \text{ g/l} \)
  (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 \( \geq 2 \) 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.
As protein binding is low, dabigatran can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: direct 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.

Steady state (after day 3) geometric mean dabigatran peak plasma concentration, measured around 2 hours after 220 mg dabigatran etexilate administration, was 70.8 ng/ml, with a range of 35.2-162 ng/ml (25th-75th percentile range). The dabigatran geometric mean trough concentration, measured at the end of the dosing interval (i.e. 24 hours after a 220 mg dabigatran dose), was on average 22.0 ng/ml, with a range of 13.0-35.7 ng/ml (25th-75th percentile range) (see section 4.4).

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

Ethnic origin

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

Clinical trials in Venous Thromboembolism (VTE) prophylaxis following major joint replacement surgery

In 2 large randomized, parallel group, double-blind, dose-confirmatory trials, patients undergoing elective major orthopaedic surgery (one for knee replacement surgery and one for hip replacement surgery) received Pradaxa 75 mg or 110 mg within 1-4 hours of surgery followed by 150 mg or 220 mg 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 5). Better results were seen with the 220 mg dose where the point estimate of Major VTE was slightly better than enoxaparin (table 5).

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 5.

Data for the total VTE and all cause mortality endpoint are shown in table 6.

Data for adjudicated major bleeding endpoints are shown in table 7 below.

Table 5: Analysis of major VTE and VTE-related mortality during the treatment period in the RE-MODEL and the RE-NOVATE orthopaedic surgery studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dabigatran etexilate 220 mg</th>
<th>Dabigatran etexilate 150 mg</th>
<th>Enoxaparin 40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-NOVATE (hip)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>909</td>
<td>888</td>
<td>917</td>
</tr>
<tr>
<td>Incidences (%)</td>
<td>28 (3.1)</td>
<td>38 (4.3)</td>
<td>36 (3.9)</td>
</tr>
<tr>
<td>Risk ratio over enoxaparin</td>
<td>0.78</td>
<td>1.09</td>
<td></td>
</tr>
<tr>
<td>95 % CI</td>
<td>0.48, 1.27</td>
<td>0.70, 1.70</td>
<td></td>
</tr>
<tr>
<td>RE-MODEL (knee)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>506</td>
<td>527</td>
<td>511</td>
</tr>
<tr>
<td>Incidences (%)</td>
<td>13 (2.6)</td>
<td>20 (3.8)</td>
<td>18 (3.5)</td>
</tr>
<tr>
<td>Risk ratio over enoxaparin</td>
<td>0.73</td>
<td>1.08</td>
<td></td>
</tr>
<tr>
<td>95 % CI</td>
<td>0.36, 1.47</td>
<td>0.58, 2.01</td>
<td></td>
</tr>
</tbody>
</table>

Table 6: Analysis of total VTE and all cause mortality during the treatment period in the RE-NOVATE and the RE-MODEL orthopaedic surgery studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dabigatran etexilate 220 mg</th>
<th>Dabigatran etexilate 150 mg</th>
<th>Enoxaparin 40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-NOVATE (hip)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>880</td>
<td>874</td>
<td>897</td>
</tr>
<tr>
<td>Incidences (%)</td>
<td>53 (6.0)</td>
<td>75 (8.6)</td>
<td>60 (6.7)</td>
</tr>
<tr>
<td>Risk ratio over enoxaparin</td>
<td>0.9</td>
<td>1.28</td>
<td></td>
</tr>
<tr>
<td>95 % CI</td>
<td>(0.63, 1.29)</td>
<td>(0.93, 1.78)</td>
<td></td>
</tr>
<tr>
<td>RE-MODEL (knee)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>503</td>
<td>526</td>
<td>512</td>
</tr>
<tr>
<td>Incidences (%)</td>
<td>183 (36.4)</td>
<td>213 (40.5)</td>
<td>193 (37.7)</td>
</tr>
<tr>
<td>Risk ratio over</td>
<td>0.97</td>
<td>1.07</td>
<td></td>
</tr>
<tr>
<td>enoxaparin</td>
<td>95% CI</td>
<td>0.82, 1.13</td>
<td>0.92, 1.25</td>
</tr>
<tr>
<td>------------</td>
<td>--------</td>
<td>------------</td>
<td>------------</td>
</tr>
</tbody>
</table>

Table 7: Major bleeding events by treatment in the individual RE-MODEL and the RE-NOVATE studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dabigatran etexilate 220 mg</th>
<th>Dabigatran etexilate 150 mg</th>
<th>Enoxaparin 40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-NOVATE (hip)</td>
<td>Treated patients N 1146</td>
<td>1163</td>
<td>1154</td>
</tr>
<tr>
<td>Number of MBE N(%)</td>
<td>23 (2.0)</td>
<td>15 (1.3)</td>
<td>18 (1.6)</td>
</tr>
<tr>
<td>RE-MODEL (knee)</td>
<td>Treated patients N 679</td>
<td>703</td>
<td>694</td>
</tr>
<tr>
<td>Number of MBE N(%)</td>
<td>10 (1.5)</td>
<td>9 (1.3)</td>
<td>9 (1.3)</td>
</tr>
</tbody>
</table>

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 $C_{\text{max}}$ 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\text{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 8.

**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 8: Half-life of total dabigatran in healthy subjects and subjects with impaired renal function.

<table>
<thead>
<tr>
<th>glomerular filtration rate (CrCL), [ml/min]</th>
<th>gMean (gCV%; range) half-life [h]</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 80</td>
<td>13.4 (25.7%; 11.0-21.6)</td>
</tr>
<tr>
<td>≥ 50-&lt; 80</td>
<td>15.3 (42.7%;11.7-34.1)</td>
</tr>
<tr>
<td>≥ 30-&lt; 50</td>
<td>18.4 (18.5%;13.3-23.0)</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>27.2(15.3%; 21.6-35.0)</td>
</tr>
</tbody>
</table>

**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\text{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 polyvinylchlide (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
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/.
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 swallowed 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
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 swallowed 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
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 swallowed 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
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>12.</td>
<td><strong>MARKETING AUTHORISATION NUMBER(S)</strong></td>
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<td>EU/1/08/442/014</td>
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<tr>
<td>13.</td>
<td><strong>BATCH NUMBER</strong></td>
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<td></td>
<td>Lot</td>
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<tr>
<td>14.</td>
<td><strong>GENERAL CLASSIFICATION FOR SUPPLY</strong></td>
</tr>
<tr>
<td></td>
<td>Medicinal product subject to medical prescription.</td>
</tr>
<tr>
<td>15.</td>
<td><strong>INSTRUCTIONS ON USE</strong></td>
</tr>
<tr>
<td>16.</td>
<td><strong>INFORMATION IN BRAILLE</strong></td>
</tr>
<tr>
<td></td>
<td>Pradaxa 110 mg</td>
</tr>
</tbody>
</table>
### 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 swallowed 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 swallowed 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
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
### 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 separately.

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.  
Should be swallowed 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
<table>
<thead>
<tr>
<th>Section</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>12. MARKETING AUTHORISATION NUMBER(S)</td>
<td>EU/1/08/442/012</td>
</tr>
<tr>
<td>13. BATCH NUMBER</td>
<td>Lot</td>
</tr>
<tr>
<td>14. GENERAL CLASSIFICATION FOR SUPPLY</td>
<td>Medicinal product subject to medical prescription.</td>
</tr>
<tr>
<td>15. INSTRUCTIONS ON USE</td>
<td></td>
</tr>
<tr>
<td>16. INFORMATION IN BRAILLE</td>
<td>Pradaxa 150 mg</td>
</tr>
</tbody>
</table>
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 swallowed 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
<table>
<thead>
<tr>
<th>Section</th>
<th>Content</th>
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</thead>
<tbody>
<tr>
<td>12. MARKETING AUTHORISATION NUMBER(S)</td>
<td>EU/1/08/442/012</td>
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<tr>
<td>13. BATCH NUMBER</td>
<td>Lot</td>
</tr>
<tr>
<td>14. GENERAL CLASSIFICATION FOR SUPPLY</td>
<td>Medicinal product subject to medical prescription.</td>
</tr>
<tr>
<td>15. INSTRUCTIONS ON USE</td>
<td></td>
</tr>
<tr>
<td>16. INFORMATION IN BRAILLE</td>
<td>Pradaxa 150 mg</td>
</tr>
<tr>
<td><strong>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</strong></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>BLISTER FOR 75 mg</strong></td>
<td></td>
</tr>
</tbody>
</table>

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**

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<table>
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<tr>
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<tbody>
<tr>
<td>1.</td>
<td><strong>NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td></td>
<td>Pradaxa 110 mg hard capsules</td>
</tr>
<tr>
<td></td>
<td>Dabigatran etexilate</td>
</tr>
<tr>
<td>2.</td>
<td><strong>NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
</tr>
<tr>
<td></td>
<td>Boehringer Ingelheim (logo)</td>
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<tr>
<td>3.</td>
<td><strong>EXPIRY DATE</strong></td>
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<td></td>
<td>EXP</td>
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<tr>
<td>4.</td>
<td><strong>BATCH NUMBER</strong></td>
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<td>Lot</td>
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<tr>
<td>5.</td>
<td><strong>OTHER</strong></td>
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<tr>
<td></td>
<td>Peel back</td>
</tr>
<tr>
<td>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</td>
<td></td>
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<tr>
<td>---------------------------------------------------</td>
<td></td>
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<tr>
<td>BLISTER FOR 150 mg</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradaxa 150 mg hard capsules</td>
</tr>
<tr>
<td>Dabigatran etexilale</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boehringer Ingelheim (logo)</td>
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</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
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</thead>
<tbody>
<tr>
<td>EXP</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot</td>
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</table>

<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peel back</td>
</tr>
</tbody>
</table>
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**FOLDING BOX AND LABEL FOR BOTTLE for 75 mg**

<table>
<thead>
<tr>
<th>1. <strong>NAME OF THE MEDICINAL PRODUCT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradaxa 75 mg hard capsules</td>
</tr>
<tr>
<td>Dabigatran etexilate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. <strong>STATEMENT OF ACTIVE SUBSTANCE(S)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Each hard capsule contains 75 mg dabigatran etexilate (as mesilate).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. <strong>LIST OF EXCIPIENTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Contains sunset yellow (E110) (see leaflet for further information).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. <strong>PHARMACEUTICAL FORM AND CONTENTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>60 hard capsules</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. <strong>METHOD AND ROUTE(S) OF ADMINISTRATION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral use.</td>
</tr>
<tr>
<td>Should be swallowed whole, do not chew or break the capsule.</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. <strong>SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. <strong>OTHER SPECIAL WARNING(S), IF NECESSARY</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>8. <strong>EXPIRY DATE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
<tr>
<td>Once opened, the product must be used within 4 months.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. <strong>SPECIAL STORAGE CONDITIONS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep the bottle tightly closed. Store in the original package in order to protect from moisture.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>10. <strong>SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any unused product or waste material should be disposed of in accordance with local requirements.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>11. <strong>NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</strong></th>
</tr>
</thead>
</table>
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**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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</thead>
<tbody>
<tr>
<td>Pradaxa 110 mg hard capsules</td>
</tr>
<tr>
<td>Dabigatran etexilate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each hard capsule contains 110 mg dabigatran etexilate (as mesilate).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contains sunset yellow (E110) (see leaflet for further information).</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 hard capsules</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral use.</td>
</tr>
<tr>
<td>Should be swollowed whole, do not chew or break the capsule.</td>
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<tr>
<td>Read the package leaflet before use.</td>
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<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
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<tbody>
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<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
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<tr>
<th>8. EXPIRY DATE</th>
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<tbody>
<tr>
<td>EXP</td>
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<tr>
<td>Once opened, the product must be used within 4 months.</td>
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<table>
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<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
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<tbody>
<tr>
<td>Keep the bottle tightly closed. Store in the original package in order to protect from moisture.</td>
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<table>
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<tr>
<th>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any unused product or waste material should be disposed of in accordance with local requirements.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
</table>
Boehringer Ingelheim International GmbH  
Binger Str. 173  
D-55216 Ingelheim am Rhein  
Germany

<table>
<thead>
<tr>
<th>12. MARKETING AUTHORISATION NUMBER(S)</th>
<th>EU/1/08/442/008</th>
</tr>
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<tr>
<th>13. BATCH NUMBER</th>
<th>Lot</th>
</tr>
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<tr>
<th>14. GENERAL CLASSIFICATION FOR SUPPLY</th>
<th>Medicinal product subject to medical prescription.</th>
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<tr>
<th>15. INSTRUCTIONS ON USE</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>16. INFORMATION IN BRAILLE</th>
<th>Pradaxa 110 mg (only applicable for folding box, not applicable for bottle label)</th>
</tr>
</thead>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING.

FOLDING BOX AND LABEL FOR BOTTLE for 150 mg

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradaxa 150 mg hard capsules</td>
</tr>
<tr>
<td>Dabigatran etexilate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each hard capsule contains 150 mg dabigatran etexilate (as mesilate).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contains sunset yellow (E110) (see leaflet for further information).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 hard capsules</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral use.</td>
</tr>
<tr>
<td>Should be swallowed whole, do not chew or break the capsule.</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
<tr>
<td>Once opened, the product must be used within 4 months.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep the bottle tightly closed. Store in the original package in order to protect from moisture.</td>
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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
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
2. What you need to know before you take Pradaxa
3. How to take Pradaxa
4. Possible side effects
5. How to store Pradaxa
6. Contents of the pack and other information

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.

Warnings and precautions

Talk to your doctor before taking Pradaxa. 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 have a moderately impaired kidney function.
  ▪ 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.

**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, rivaroxaban)
- Anti-inflammatory and pain reliever medicines (e.g. aspirine)
- St. John’s wort, a herbal medicine for depression
- 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 1 capsules 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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Manufacturer

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This leaflet was last approved in XXYYYY

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