ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

Pradaxa 75 mg hard capsules

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

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

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Hard capsule.

Capsules with white, opaque cap and white, 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**

*Primary Prevention of Venous Thromboembolism in Orthopaedic Surgery*

The recommended dose of Pradaxa and the duration of therapy for primary prevention of venous thromboembolism in orthopaedic surgery are shown in table 1.
Table 1: Dose recommendations and duration of therapy for primary prevention of venous thromboembolism in orthopaedic surgery

<table>
<thead>
<tr>
<th>Dose reduction recommended</th>
<th>Treatment initiation on the day of surgery 1-4 hours after completed surgery</th>
<th>Maintenance dose starting on the first day after surgery</th>
<th>Duration of maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients following elective knee replacement surgery</td>
<td>single capsule of 110 mg Pradaxa</td>
<td>220 mg Pradaxa once daily taken as 2 capsules of 110 mg</td>
<td>10 days</td>
</tr>
<tr>
<td>Patients following elective hip replacement surgery</td>
<td>single capsule of 75 mg Pradaxa</td>
<td>150 mg Pradaxa once daily taken as 2 capsules of 75 mg</td>
<td>10 days (knee replacement surgery) or 28-35 days (hip replacement surgery)</td>
</tr>
</tbody>
</table>

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

Assessment of renal function prior to and during Pradaxa treatment

In all patients and especially in the elderly (>75 years), as renal impairment may be frequent in this age group:
- Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with Pradaxa to exclude patients with severe renal impairment (i.e. CrCL < 30 mL/min) (see sections 4.3, 4.4 and 5.2).
- Renal function should also be assessed when a decline in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products).

The method to be used to estimate renal function (CrCL in mL/min) is the Cockcroft-Gault method.

Missed dose

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

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

Discontinuation of Pradaxa

Pradaxa treatment should not be discontinued without medical advice. Patients should be instructed to contact the treating physician if they develop gastrointestinal symptoms such as dyspepsia (see section 4.8).

Switching

Pradaxa treatment to parenteral anticoagulant:

*For patients with moderate renal impairment concomitantly treated with verapamil see Special populations
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:
The parenteral anticoagulant should be discontinued and Pradaxa should be started start 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).

**Special populations**

**Renal impairment**

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

In patients with moderate renal impairment (CrCL 30-50 mL/min), a dose reduction is recommended (see table 1 above and sections 4.4 and 5.1).

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

Dosing should be reduced as indicated in table 1 (see also 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 verapamil, a dose reduction of Pradaxa to 75 mg daily should be considered (see sections 4.4 and 4.5).

**Elderly**

For elderly patients > 75 years, a dose reduction is recommended (see table 1 above and sections 4.4 and 5.1).

**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**

No dose adjustment is necessary (see section 5.2).

**Paediatric population**

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

**Method of administration**

Pradaxa is for oral use. The capsules can be taken with or without food. Pradaxa should be swallowed as a whole with a glass of water, to facilitate delivery to the stomach. 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
- Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5)
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with the following strong P-gp inhibitors: systemic ketoconazole, cyclosporine, itraconazole and dronedarone (see section 4.5)
- Prosthetic heart valves requiring anticoagulant treatment (see section 5.1).

4.4 Special warnings and precautions for use

Haemorrhagic risk

Pradaxa should be used with caution in conditions with an increased risk of bleeding or with concomitant use of medicinal products affecting haemostasis by inhibition of platelet aggregation. Bleeding can occur at any site during therapy with Pradaxa. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site.

For situations of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effect of dabigatran is required, the specific reversal agent (Praxbind, idarucizumab) is available (see section 4.9).

Use of platelet aggregation inhibitors such as clopidogrel and acetylsalicylic acid (ASA) or non steroidal antiinflammatory drugs (NSAID), as well as the presence of esophagitis, gastritis or gastroesophageal reflux increase the risk of GI bleeding.

Risk factors

Table 2 summarises factors which may increase the haemorrhagic risk.

Table 2: 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>• Strong P-gp inhibitors (see section 4.3 and 4.5)</td>
</tr>
<tr>
<td></td>
<td>• Mild to moderate P-gp inhibitor co-medication (e.g. amiodarone, verapamil, quinidine and ticagrelor; see section 4.5)</td>
</tr>
<tr>
<td></td>
<td>Minor:</td>
</tr>
<tr>
<td></td>
<td>• Low body weight (&lt; 50 kg)</td>
</tr>
<tr>
<td>Pharmacodynamic interactions (see section 4.5)</td>
<td>• ASA and other platelet aggregation</td>
</tr>
</tbody>
</table>
inhibitors such as clopidogrel
• NSAID
• SSRIs or SNRIs
• Other medicinal products which may impair haemostasis

| Diseases / procedures with special haemorrhagic risks | Congenital or acquired coagulation disorders
| | Thrombocytopenia or functional platelet defects
| | Recent biopsy, major trauma
| | Bacterial endocarditis
| | Esophagitis, gastritis or gastroesophageal reflux

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

**Precautions and management of the haemorrhagic risk**

For the management of bleeding complications, see also section 4.9.

**Benefit-risk assessment**

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

**Close clinical surveillance**

Close observation for signs of bleeding or anaemia is recommended throughout the treatment period, especially if risk factors are combined (see table 2 above). Particular caution should be exercised when Pradaxa is co-administered with verapamil, amiodarone, quinidine or clarithromycin (P-gp inhibitors) and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment (see section 4.5).

Close observation for signs of bleeding is recommended in patients concomitantly treated with NSAIDs (see section 4.5).

**Discontinuation of Pradaxa**

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

When severe bleedings occur, treatment must be discontinued, the source of bleeding investigated and use of the specific reversal agent Praxbind (idarucizumab) may be considered (see section 4.9 Management of bleeding complications).

**Dose reduction**

A dose reduction is recommended as indicated in section 4.2.

**Use of proton-pump inhibitors**

The administration of a proton-pump inhibitor (PPI) can be considered to prevent GI bleeding.
Laboratory coagulation parameters

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

Table 3 shows coagulation test thresholds at trough that may be associated with an increased risk of bleeding (see section 5.1)

Table 3: Coagulation test thresholds at trough that may be associated with an increased risk of bleeding.

<table>
<thead>
<tr>
<th>Test (trough value)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>dTT [ng/mL]</td>
<td>&gt; 67</td>
</tr>
<tr>
<td>ECT [x-fold upper limit of normal]</td>
<td>No data</td>
</tr>
<tr>
<td>aPTT [x-fold upper limit of normal]</td>
<td>&gt; 1.3</td>
</tr>
<tr>
<td>INR</td>
<td>Should not be performed</td>
</tr>
</tbody>
</table>

Use of fibrinolytic medicinal products for the treatment of acute ischemic stroke

The use of fibrinolytic medicinal products for the treatment of acute ischemic stroke may be considered if the patient presents with a dTT, ECT or aPTT not exceeding the upper limit of normal (ULN) according to the local reference range.

Surgery and interventions

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

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.

Emergency surgery or urgent procedures

Pradaxa should be temporarily discontinued. When rapid reversal of the anticoagulation effect is required the specific reversal agent (Praxbind, idarucizumab) to Pradaxa is available.

Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Pradaxa treatment can be re-initiated 24 hours after administration of Praxbind (idarucizumab), if the patient is clinically stable and adequate haemostasis has been achieved.

Subacute surgery/interventions

Pradaxa should be temporarily discontinued. A surgery / intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed the risk of bleeding may be increased. This risk of bleeding should be weighed against the urgency of intervention.
**Elective surgery**

If possible, Pradaxa should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete haemostasis may be required consider stopping Pradaxa 2-4 days before surgery.

Table 4 summarises discontinuation rules before invasive or surgical procedures.

### Table 4: 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>Pradaxa should be stopped 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>

**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 Pradaxa. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

**Postoperative phase**

Pradaxa should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established.

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).

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

There are limited efficacy and safety data for Pradaxa 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.

**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. Hepatic impairment or liver disease expected to have any impact on survival is contraindicated (see section 4.3).

**Interaction with P-gp inducers**

Concomitant administration of P-gp inducers is expected to result in decreased dabigatran plasma concentrations, and should be avoided (see sections 4.5 and 5.2).
4.5 Interaction with other medicinal products and other forms of interaction

Transporter interactions

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors (see table 5) 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. Dose reductions may be required in combination with some P-gp inhibitors (see sections 4.2, 4.3, 4.4 and 5.1).

Table 5: Transporter interactions

<table>
<thead>
<tr>
<th>P-gp inhibitors</th>
<th>Concomitant use contraindicated (see section 4.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>Ketoconazole increased total dabigatran AUC_t___w and C_max_t___w values by 2.38-fold and 2.35-fold, respectively, after a single oral dose of 400 mg, and by 2.53-fold and 2.49-fold, respectively, after multiple oral dosing of 400 mg ketoconazole once daily.</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>When dabigatran etexilate and dronedarone were given at the same time total dabigatran AUC_t___w and C_max_t___w values increased by about 2.4-fold and 2.3-fold, respectively, after multiple dosing of 400 mg dronedarone bid, and about 2.1-fold and 1.9-fold, respectively, after a single dose of 400 mg.</td>
</tr>
<tr>
<td>Itraconazole, cyclosporine</td>
<td>Based on in vitro results a similar effect as with ketoconazole may be expected.</td>
</tr>
</tbody>
</table>

Concomitant use not recommended

| Tacrolimus                        | Tacrolimus has been found in vitro to have a similar level of inhibitory effect on P-gp as that seen with itraconazole and cyclosporine. Dabigatran etexilate has not been clinically studied together with tacrolimus. However, limited clinical data with another P-gp substrate (everolimus) suggest that the inhibition of P-gp with tacrolimus is weaker than that observed with strong P-gp inhibitors. |

Cautions to be exercised in case concomitant use (see sections 4.2 and 4.4)

<p>| Verapamil                          | When dabigatran etexilate (150 mg) was co-administered with oral verapamil, the C_max and AUC of dabigatran were increased but the magnitude of this change differs depending on timing of administration and formulation of verapamil (see sections 4.2 and 4.4). The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to the dabigatran etexilate intake (increase of C_max by about 2.8-fold and AUC by about 2.5-fold). The effect was progressively decreased with administration of an extended release formulation (increase of C_max by about 1.9-fold and AUC by about 1.7-fold) or administration of multiple doses of verapamil (increase of C_max by about 1.6-fold and AUC by about 1.5-fold). There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increase of C_max by about 1.1-fold and AUC by about 1.2-fold). This is explained by completed dabigatran absorption after 2 hours. |</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>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(_{\text{max}}) were increased by about 1.6-fold and 1.5-fold, respectively. In view of the long half-life of amiodarone the potential for an interaction may exist for weeks after discontinuation of amiodarone (see sections 4.2 and 4.4).</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Quinidine was given as 200 mg dose every 2nd hour up to a total dose of 1,000 mg. Dabigatran etexilate was given twice daily over 3 consecutive days, on the 3rd day either with or without quinidine. Dabigatran AUC(<em>{\text{t,ss}}) and C(</em>{\text{max,ss}}) were increased on average by 1.53-fold and 1.56-fold, respectively with concomitant quinidine (see sections 4.2 and 4.4).</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>When clarithromycin (500 mg twice daily) was administered together with dabigatran etexilate in healthy volunteers, increase of AUC by about 1.19-fold and C(_{\text{max}}) by about 1.15-fold was observed.</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>When a single dose of 75 mg dabigatran etexilate was coadministered simultaneously with a loading dose of 180 mg ticagrelor, the dabigatran AUC and C(<em>{\text{max}}) were increased by 1.73-fold and 1.95-fold, respectively. After multiple doses of ticagrelor 90 mg b.i.d. the increase of dabigatran exposure is 1.56-fold and 1.46-fold for C(</em>{\text{max}}) and AUC, respectively. Concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg dabigatran etexilate (in steady state) increased the dabigatran AUC(<em>{\text{t,ss}}) and C(</em>{\text{max,ss}}) by 1.49-fold and 1.65-fold, respectively, compared with dabigatran etexilate given alone. When a loading dose of 180 mg ticagrelor was given 2 hours after 110 mg dabigatran etexilate (in steady state), the increase of dabigatran AUC(<em>{\text{t,ss}}) and C(</em>{\text{max,ss}}) was reduced to 1.27-fold and 1.23-fold, respectively, compared with dabigatran etexilate given alone. This staggered intake is the recommended administration for start of ticagrelor with a loading dose. Concomitant administration of 90 mg ticagrelor b.i.d. (maintenance dose) with 110 mg dabigatran etexilate increased the adjusted dabigatran AUC(<em>{\text{t,ss}}) and C(</em>{\text{max,ss}}) 1.26-fold and 1.29-fold, respectively, compared with dabigatran etexilate given alone.</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Posaconazole also inhibits P-gp to some extent but has not been clinically studied. Caution should be exercised when Pradaxa is co-administered with posaconazole.</td>
</tr>
</tbody>
</table>

**P-gp inducers**

**Concomitant use should be avoided.**

- e.g. rifampicin, St. John’s wort (Hypericum perforatum), carbamazepine, or phenytoin
  - Concomitant administration is expected to result in decreased dabigatran concentrations. 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.

**Protease inhibitors such as ritonavir**

**Concomitant use not recommended**

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

<table>
<thead>
<tr>
<th>P-gp substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
</tr>
<tr>
<td>In a study performed with 24 healthy subjects, when Pradaxa was co-administered with digoxin, no changes on digoxin and no clinically relevant changes on dabigatran exposure have been observed.</td>
</tr>
</tbody>
</table>

Anticoagulants and antiplatelet aggregation medicinal products

There is no or only limited experience with the following treatments which may increase the risk of bleeding when used concomitantly with Pradaxa: anticoagulants such as unfractionated heparin (UFH), low molecular weight heparins (LMWH), and heparin derivatives (fondaparinux, desirudin), thrombolytic medicinal products, and vitamin K antagonists, rivaroxaban or other oral anticoagulants (see section 4.3), and antiplatelet aggregation medicinal products such as GPIIb/IIIa receptor antagonists, ticlopidine, prasugrel, ticagrelor, dextran, and sulfipyrazone (see section 4.4).

UFH can be administered at doses necessary to maintain a patent central venous or arterial catheter (see section 4.3).

**Table 6: Interactions with anticoagulants and antiplatelet aggregation medicinal products**

<table>
<thead>
<tr>
<th>NSAIDs</th>
<th>NSAIDs given for short-term analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use, NSAIDs increased the risk of bleeding by approximately 50 % on both dabigatran etexilate and warfarin.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>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_{t,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_{t,ss} and C_{max,ss} were increased by about 30-40 % (see section 4.4).</td>
</tr>
<tr>
<td>ASA</td>
<td>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).</td>
</tr>
<tr>
<td>LMWH</td>
<td>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/IIa 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.</td>
</tr>
</tbody>
</table>

Other interactions

**Table 7: Other interactions**

Selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake
SSRIs, SNRIs | SSRIs and SNRIs increased the risk of bleeding in all treatment groups of a phase III clinical trial comparing dabigatran to warfarin for stroke prevention in atrial fibrillation patients (RE-LY).

**Substances influencing gastric pH**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pantoprazole</td>
<td>When Pradaxa was co-administered with pantoprazole, a decrease in the dabigatran AUC 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.</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Ranitidine administration together with Pradaxa had no clinically relevant effect on the extent of absorption of dabigatran.</td>
</tr>
</tbody>
</table>

**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.

**4.6 Fertility, pregnancy and lactation**

**Women of childbearing potential**

Women of childbearing potential should avoid pregnancy during treatment with Pradaxa.

**Pregnancy**

There is limited amount of 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.

Pradaxa should not be used during pregnancy unless clearly necessary.

**Breast-feeding**

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

**Fertility**

No human data available.

In animal studies an effect on female fertility was observed in the form of a decrease in implantations and an increase in pre-implantation loss at 70 mg/kg (representing a 5-fold higher plasma exposure level compared to patients). No other effects on female fertility were observed. There was no influence on male fertility. At doses that were toxic to the mothers (representing a 5- to 10-fold higher plasma exposure level to patients), a decrease in foetal body weight and 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**

Pradaxa has no or negligible influence on the ability to drive and use machines.
4.8 Undesirable effects

Summary of the safety profile

In actively controlled VTE prevention trials 6,684 patients were treated with 150 mg or 220 mg Pradaxa daily.

The most commonly reported events are bleedings occurring 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.

Tabulated list of adverse reactions

Table 8 shows the adverse reactions ranked under headings of System Organ Classes (SOC) and frequency using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 8: Adverse reactions

<table>
<thead>
<tr>
<th>SOC / Preferred term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin decreased</td>
<td>Common</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Haematocrit decreased</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Rare</td>
</tr>
<tr>
<td>Immune system disorder</td>
<td></td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>Rare</td>
</tr>
<tr>
<td>Angioedema</td>
<td>Rare</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Rare</td>
</tr>
<tr>
<td>Rash</td>
<td>Rare</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Rare</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Not known</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>Rare</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Haematoma</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Wound haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>Rare</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>Rare</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Rectal haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Haemorrhoidal haemorrhage</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Nausea</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrointestinal ulcer, including oesophageal ulcer</td>
<td>Rare</td>
</tr>
<tr>
<td>Gastroesophagitis</td>
<td>Rare</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>Rare</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Rare</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Rare</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Rare</td>
</tr>
</tbody>
</table>

### Hepatobiliary disorders

<table>
<thead>
<tr>
<th>Hepatic function abnormal/ Liver function Test abnormal</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine aminotransferase increased</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hepatic enzyme increased</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

### Skin and subcutaneous tissue disorder

| Skin haemorrhage                                      | Uncommon |

### Musculoskeletal and connective tissue disorders

| Haemarthrosis                                         | Uncommon |

### Renal and urinary disorders

| Genitourological haemorrhage, including haematuria     | Uncommon |

### General disorders and administration site conditions

| Injection site haemorrhage                            | Rare    |
| Catheter site haemorrhage                             | Rare    |
| Bloody discharge                                      | Rare    |

### Injury, poisoning and procedural complications

| Traumatic haemorrhage                                  | Uncommon |
| Post procedural haematoma                              | Uncommon |
| Post procedural haemorrhage                            | Uncommon |
| Post procedural discharge                              | Uncommon |
| Wound secretion                                        | Uncommon |
| Incision site haemorrhage                              | Rare    |
| Anaemia postoperative                                  | Rare    |

### Surgical and medical procedures

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

### Description of selected adverse reactions

#### Bleeding reactions

Due to the pharmacological mode of action, the use of Pradaxa may be associated with an increased risk of occult or overt bleeding from any tissue or organ. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia. In the clinical studies mucosal bleedings (e.g. gastrointestinal, genitourinary) were seen more frequently during long term Pradaxa treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit is of value to detect occult bleeding. The risk of bleedings may be increased in certain patient groups e.g. those patients with moderate renal impairment and/or on concomitant treatment affecting haemostasis or strong P-gp inhibitors (see section 4.4 Haemorrhagic risk). Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock.

Known bleeding complications such as compartment syndrome and acute renal failure due to hypoperfusion have been reported for Pradaxa. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient. A specific reversal agent for dabigatran, idarucizumab, is available in case of uncontrollable bleeding (see Section 4.9).

The table 9 shows the number (%) of patients experiencing the adverse reaction bleeding during the treatment period in the VTE prevention in the two pivotal clinical trials, according to dose.
Table 9: Number (%) of patients experiencing the adverse reaction bleeding

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 150 mg N (%)</th>
<th>Pradaxa 220 mg N (%)</th>
<th>Enoxaparin N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>1,866(100.0)</td>
<td>1,825(100.0)</td>
<td>1,848(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>

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Pradaxa doses 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. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. As protein binding is low, dabigatran can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies (see section 5.2).

Management of bleeding complications

In the event of haemorrhagic complications, Pradaxa treatment must be discontinued and the source of bleeding investigated. Depending on the clinical situation appropriate supportive treatment, such as surgical haemostasis and blood volume replacement, should be undertaken at the prescriber’s discretion.

For situations when rapid reversal of the anticoagulant effect of Pradaxa is required the specific reversal agent (Praxbind, idarucizumab) antagonizing the pharmacodynamic effect of Pradaxa is available (see section 4.4).

Coagulation factor concentrates (activated or non-activated) or recombinant Factor VIIa may be taken into account. There is some experimental evidence to support the role of these medicinal products in reversing the anticoagulant effect of dabigatran, but data on their usefulness in clinical settings and also on the possible risk of rebound thromboembolism is very limited. Coagulation tests may become unreliable following administration of suggested coagulation factor concentrates. Caution should be exercised when interpreting these tests. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet medicinal products have been used. All symptomatic treatment should be given according to the physician's judgement.

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

5.1 Pharmacodynamic properties

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

Mechanism of action

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 inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

Pharmacodynamic effects

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

There is a clear correlation between plasma dabigatran concentration and degree of anticoagulant effect based on phase II studies. Dabigatran prolongs the thrombin time (TT), ECT, and aPTT.

The calibrated quantitative diluted TT (dTT) test provides an estimation of dabigatran plasma concentration that can be compared to the expected dabigatran plasma concentrations. When the calibrated dTT assay delivers a dabigatran plasma concentration result at or below the limit of quantification, an additional coagulation assay such as TT, ECT or aPTT should be considered.

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

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

In general, it can be assumed that these measures of anti-coagulant activity may reflect dabigatran levels and can provide guidance for the assessment of bleeding risk, i.e. exceeding the 90th percentile of dabigatran trough levels or a coagulation assay such as aPTT measured at trough (for aPTT thresholds see section 4.4, table 3) is considered to be associated with an increased risk of bleeding.

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

In a dedicated study exclusively in patients with moderate renal impairment (creatinine clearance, CrCL 30-50 mL/min) treated with dabigatran etexilate 150 mg QD, the dabigatran geometric mean trough concentration, measured at the end of the dosing interval, was on average 47.5 ng/mL, with a range of 29.6 - 72.2 ng/mL (25th-75th percentile range).

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

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

Clinical efficacy and safety

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 2,076 patients (knee) and 3,494 (hip) were treated respectively.

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

Results of both studies showed that the antithrombotic effect of Pradaxa 220 mg and 150 mg were statistically non-inferior to that of enoxaparin on total VTE and all-cause mortality. The point estimate for incidence of major VTE and VTE related mortality for the 150 mg dose was slightly worse than enoxaparin (table 10). Better results were seen with the 220 mg dose where the point estimate of Major VTE was slightly better than enoxaparin (table 10).

The clinical studies have been conducted in a patient population with a mean age > 65 years.

There were no differences in the phase 3 clinical studies for efficacy and safety data between men and women.

In the studied patient population of RE-MODEL and RE-NOVATE (5,539 patients treated), 51% suffered from concomitant hypertension, 9% from concomitant diabetes, 9% from concomitant coronary artery disease and 20% had a history of venous insufficiency. None of these diseases showed an impact on the effects of dabigatran on VTE-prevention or bleeding rates.

Data for the major VTE and VTE-related mortality endpoint were homogeneous with regards to the primary efficacy endpoint and are shown in table 10.

Data for the total VTE and all cause mortality endpoint are shown in table 11.

Data for adjudicated major bleeding endpoints are shown in table 12 below.
### Table 10: 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>Pradaxa 220 mg</th>
<th>Pradaxa 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</td>
<td>0.78</td>
<td>1.09</td>
<td></td>
</tr>
<tr>
<td>enoxaparin</td>
<td></td>
<td></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</td>
<td>0.73</td>
<td>1.08</td>
<td></td>
</tr>
<tr>
<td>enoxaparin</td>
<td></td>
<td></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 11: 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>Pradaxa 220 mg</th>
<th>Pradaxa 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</td>
<td>0.9</td>
<td>1.28</td>
<td></td>
</tr>
<tr>
<td>enoxaparin</td>
<td></td>
<td></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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95 % CI</td>
<td>(0.82, 1.13)</td>
<td>(0.92, 1.25)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 12: Major bleeding events by treatment in the individual RE-MODEL and the RE-NOVATE studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pradaxa 220 mg</th>
<th>Pradaxa 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>Treated patients N</td>
<td>1,146</td>
<td>1,163</td>
<td>1,154</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>N(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-MODEL (knee)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated patients N</td>
<td>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>
<tr>
<td>N(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

A phase II study examined dabigatran etexilate and warfarin in a total of 252 patients with recent mechanical valve replacement surgery (i.e. within the current hospital stay) and in patients who received a mechanical heart valve replacement more than three months ago. More thromboembolic events (mainly strokes and symptomatic/asymptomatic prosthetic valve thrombosis) and more
bleeding events were observed with dabigatran etexilate than with warfarin. In the early post-operative patients, major bleeding manifested predominantly as haemorrhagic pericardial effusions, specifically in patients who started dabigatran etexilate early (i.e. on Day 3) after heart valve replacement surgery (see section 4.3).

Paediatric population

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

\( C_{\text{max}} \) and AUC were dose proportional.

The oral bioavailability may be increased by 75% after a single dose and 37% at steady state 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 (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.

Biotransformation

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.

**Elimination**

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 13.

**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 13: 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>

Additionally, dabigatran exposure (at trough and peak) was assessed in a prospective open label randomized pharmacokinetic study in NVAF patients with severe renal impairment (defined as creatinine clearance [CrCl] 15-30 mL/min) receiving dabigatran etexilate 75 mg twice daily. This regimen resulted in a geometric mean trough concentration of 155 ng/ml (gCV of 76.9%), measured immediately before administration of the next dose and in a geometric mean peak concentration of 202 ng/ml (gCV of 70.6%) measured two hours after the administration of the last dose.

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

**Elderly patients**

Specific pharmacokinetic phase I studies with elderly subjects showed an increase of 40 to 60% in the AUC and of more than 25% in C_max compared to young subjects.
The effect by age on exposure to dabigatran was confirmed in the RE-LY study with an about 31% higher trough concentration for subjects ≥ 75 years and by about 22% lower trough level for subjects < 65 years compared to subjects between 65 and 75 years (see sections 4.2 and 4.4).

**Hepatic impairment**

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**

*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 repeated 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.

Dabigatran, the active moiety of dabigatran etexilate mesilate, is persistent in the environment.

### 6. PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

**Capsule content**

Tartaric acid
Acacia
Hypermellose
Dimeticone 350
Talc
Hydroxypropylcellulose

Capsule shell
Carrageenan
Potassium chloride
Titanium dioxide
Hypermellose

Black printing ink
Shellac
Iron oxide black (E172)
Potassium hydroxide

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 10 x 1, 30 x 1 or 60 x 1 hard capsules in perforated aluminium unit dose blisters.

Carton containing 6 blister strips (60 x 1) in perforated aluminium unit dose white blisters.

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:

- One individual blister should be teared off from the blister card along the perforated line.
- The backing foil should be peeled off and the capsule can be removed.
- 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, the following instructions should be observed:

- The cap opens by pushing and turning.
- After taking the capsule out, the cap should be returned on the bottle right away and the bottle should be tightly closed.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/001
EU/1/08/442/002
EU/1/08/442/003
EU/1/08/442/004
EU/1/08/442/017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATIOn

Date of first authorisation: 18 March 2008
Date of the latest renewal: 17 January 2013

10. DATE OF REVISION OF THE TEXT

1. **NAME OF THE MEDICINAL PRODUCT**

Pradaxa 110 mg hard capsules

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

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

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Hard capsule.

Capsules with light blue, opaque cap and light blue, opaque body of size 1 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with “R110”.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

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

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults

4.2 **Posology and method of administration**

**Posology**

*Primary prevention of Venous Thromboembolism in Orthopaedic Surgery*

The recommended doses of Pradaxa and the duration of therapy for primary prevention of venous thromboembolism in orthopaedic surgery are shown in table 1.
Table 1: Dose recommendations and duration of therapy for primary prevention of venous thromboembolism in orthopaedic surgery

<table>
<thead>
<tr>
<th>Patients following elective knee replacement surgery</th>
<th>Treatment initiation on the day of surgery 1-4 hours after completed surgery</th>
<th>Maintenance dose starting on the first day after surgery</th>
<th>Duration of maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>single capsule of 110 mg Pradaxa</td>
<td>220 mg Pradaxa once daily taken as 2 capsules of 110 mg</td>
<td>10 days</td>
<td></td>
</tr>
<tr>
<td>Patients following elective hip replacement surgery</td>
<td>single capsule of 75 mg Pradaxa</td>
<td>150 mg Pradaxa once daily taken as 2 capsules of 75 mg</td>
<td>10 days (knee replacement surgery) or 28-35 days (hip replacement surgery)</td>
</tr>
</tbody>
</table>

*Dose reduction recommended*

<table>
<thead>
<tr>
<th>Patients with moderate renal impairment (creatinine clearance (CrCL) 30-50 mL/min)</th>
<th>Maintenance dose starting on the first day after surgery</th>
<th>Duration of maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>single capsule of 75 mg Pradaxa</td>
<td>150 mg Pradaxa once daily taken as 2 capsules of 75 mg</td>
<td>10 days (knee replacement surgery) or 28-35 days (hip replacement surgery)</td>
</tr>
<tr>
<td>Patients who receive concomitant verapamil*, amiodarone, quinidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients aged 75 or above</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*For patients with moderate renal impairment concomitantly treated with verapamil see Special populations

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

**Assessment of renal function prior to and during Pradaxa treatment**

In all patients and especially in the elderly (>75 years), as renal impairment may be frequent in this age group:

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

The method to be used to estimate renal function (CrCL in mL/min) is the Cockcroft-Gault method.

**Missed dose**

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

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

**Discontinuation of Pradaxa**

Pradaxa treatment should not be discontinued without medical advice. Patients should be instructed to contact the treating physician if they develop gastrointestinal symptoms such as dyspepsia (see section 4.8).

**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:
The parenteral anticoagulant should be discontinued and Pradaxa should be started 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).

Special populations

Renal impairment

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

In patients with moderate renal impairment (CrCL 30-50 mL/min), a dose reduction is recommended (see table 1 above and sections 4.4 and 5.1).

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

Dosing should be reduced as indicated in table 1 (see also 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 verapamil, a dose reduction of Pradaxa to 75 mg daily should be considered (see sections 4.4 and 4.5).

Elderly

For elderly patients > 75 years, a dose reduction is recommended (see table 1 above and sections 4.4 and 5.1).

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

No dose adjustment is necessary (see section 5.2).

Paediatric population

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

Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors (SPAF)

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE)

The recommended doses of Pradaxa in the indications SPAF, DVT and PE are shown in table 2.
Table 2:  Dose recommendations for SPAF, DVT and PE

<table>
<thead>
<tr>
<th>Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors (SPAF)</th>
<th>300 mg Pradaxa taken as one 150 mg capsule twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE)</td>
<td>300 mg Pradaxa taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days</td>
</tr>
</tbody>
</table>

**Dose reduction recommended**

| Patients aged ≥80 years | daily dose of 220 mg Pradaxa taken as one 110 mg capsule twice daily |
| Patients who receive concomitant verapamil | daily dose of 220 mg Pradaxa taken as one 110 mg capsule twice daily |

**Dose reduction for consideration**

| Patients between 75-80 years | daily dose of Pradaxa of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding |
| Patients with moderate renal impairment (CrCL 30-50 mL/min) | daily dose of Pradaxa of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding |
| Patients with gastritis, esophagitis or gastroesophageal reflux | daily dose of Pradaxa of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding |
| Other patients at increased risk of bleeding | daily dose of Pradaxa of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding |

For DVT/PE the recommendation for the use of Pradaxa 220 mg taken as one 110 mg capsule twice daily is based on pharmacokinetic and pharmacodynamic analyses and has not been studied in this clinical setting. See further down and sections 4.4, 4.5, 5.1 and 5.2.

In case of intolerability to Pradaxa, patients should be instructed to immediately consult their treating physician in order to be switched to alternate acceptable treatment options for prevention of stroke and systemic embolism associated with atrial fibrillation or for DVT/PE.

**Assessment of renal function prior to and during Pradaxa treatment**

In all patients and especially in the elderly (>75 years), as renal impairment may be frequent in this age group:

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

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

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

The method to be used to estimate renal function (CrCL in mL/min) is the Cockcroft-Gault method.
Duration of use

The duration of use of Pradaxa in the indications SPAF, DVT and PE are shown in table 3.

Table 3: Duration of use for SPAF and DVT/PE

<table>
<thead>
<tr>
<th>Indication</th>
<th>Duration of use</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPAF</td>
<td>Therapy should be continued long term.</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4). Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.</td>
</tr>
</tbody>
</table>

Missed dose

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

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

Discontinuation of Pradaxa

Pradaxa treatment should not be discontinued without medical advice. Patients should be instructed to contact the treating physician if they develop gastrointestinal symptoms such as dyspepsia (see section 4.8).

Switching

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

Parenteral anticoagulants to Pradaxa:
The parenteral anticoagulant should be discontinued and Pradaxa should be started 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous Unfractionated Heparin (UFH)) (see section 4.5).

Pradaxa treatment to Vitamin K antagonists (VKA):
The starting time of the VKA should be adjusted based on CrCL as follows:
- CrCL ≥ 50 mL/min, VKA should be started 3 days before discontinuing Pradaxa
- CrCL ≥ 30-< 50 mL/min, VKA should be started 2 days before discontinuing Pradaxa

Because Pradaxa can impact the International Normalized Ratio (INR), the INR will better reflect VKA’s effect only after Pradaxa has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.

VKA to Pradaxa:
The VKA should be stopped. Pradaxa can be given as soon as the INR is < 2.0.

Cardioversion (SPAF)

Patients can stay on Pradaxa while being cardioverted.
Catheter ablation for atrial fbrillation (SPAF)

There are no data available for 110 mg twice daily Pradaxa treatment.

Special populations

Elderly

For dose modifications in this population see table 2 above.

Patients at risk of bleeding

Patients with an increased bleeding risk (see sections 4.4, 4.5, 5.1 and 5.2) should be closely monitored clinically (looking for signs of bleeding or anaemia). Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient (see table 2 above). A coagulation test (see section 4.4) may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. When excessive dabigatran exposure is identified in patients at high risk of bleeding, a reduced dose of 220 mg taken as one 110 mg capsule twice daily is recommended. When clinically relevant bleeding occurs, treatment should be interrupted.

For subjects with gastritis, esophagitis, or gastroesophageal reflux, a dose reduction may be considered due to the elevated risk of major gastro-intestinal bleeding (see table 2 above and section 4.4).

Renal impairment

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

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

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

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

Dose reductions are recommended for patients who receive concomitantly verapamil (see table 2 above and sections 4.4 and 4.5). In this situation Pradaxa and verapamil should be taken at the same time.

Weight

No dose adjustment is necessary (see section 5.2), but close clinical surveillance is recommended in patients with a body weight < 50 kg (see section 4.4).

Gender

No dose adjustment is necessary (see section 5.2).

Paediatric population
There is no relevant use of Pradaxa in the paediatric population for the indication of prevention of stroke and systemic embolism in patients with NVAF.

For the indication DVT/PE, the safety and efficacy of Pradaxa in children from birth to less than 18 years of age have not yet been established. Currently available data are described in section 4.8 and 5.1, but no recommendation on a posology can be made.

Method of administration

Pradaxa is for oral use. The capsules can be taken with or without food. Pradaxa should be swallowed as a whole with a glass of water, to facilitate delivery to the stomach. 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
- Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fonaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5)
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with the following strong P-gp inhibitors: systemic ketoconazole, cyclosporine, itraconazole and dronedarone (see section 4.5)
- Prosthetic heart valves requiring anticoagulant treatment (see section 5.1).

4.4 Special warnings and precautions for use

Haemorrhagic risk

Pradaxa should be used with caution in conditions with an increased risk of bleeding or with concomitant use of medicinal products affecting haemostasis by inhibition of platelet aggregation. Bleeding can occur at any site during therapy with Pradaxa. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site.

For situations of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effect of dabigatran is required, the specific reversal agent (Praxbind, idarucizumab) is available (see section 4.9).

In clinical trials, Pradaxa was associated with higher rates of major gastrointestinal (GI) bleeding. An increased risk was seen in the elderly (≥ 75 years) for the 150 mg twice daily dose regimen. Further risk factors (see also table 4) comprise co-medication with platelet aggregation inhibitors such as clopidogrel and acetylsalicylic acid (ASA) or non steroidal antiinflammatory drugs (NSAID), as well as the presence of esophagitis, gastritis or gastroesophageal reflux.
### Risk factors

Table 4 summarises factors which may increase the haemorrhagic risk.

#### Table 4: Risk 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>• Strong P-gp inhibitors (see section 4.3 and 4.5)</td>
</tr>
<tr>
<td></td>
<td>• Mild to moderate P-gp inhibitor co-medication (e.g. amiodarone, verapamil, quinidine and ticagrelor; see section 4.5)</td>
</tr>
<tr>
<td></td>
<td>Minor:</td>
</tr>
<tr>
<td></td>
<td>• Low body weight (&lt; 50 kg)</td>
</tr>
<tr>
<td>Pharmacodynamic interactions (see section 4.5)</td>
<td>• ASA and other platelet aggregation inhibitors such as clopidogrel</td>
</tr>
<tr>
<td></td>
<td>• NSAID</td>
</tr>
<tr>
<td></td>
<td>• SSRIs or SNRIs</td>
</tr>
<tr>
<td></td>
<td>• Other medicinal products which may impair haemostasis</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>• Recent biopsy, major trauma</td>
</tr>
<tr>
<td></td>
<td>• Bacterial endocarditis</td>
</tr>
<tr>
<td></td>
<td>• Esophagitis, gastritis and gastroesophageal reflux</td>
</tr>
</tbody>
</table>

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

### Precautions and management of the haemorrhagic risk

For the management of bleeding complications, see also section 4.9.

### Benefit-risk assessment

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

### Close clinical surveillance

Close observation for signs of bleeding or anaemia is recommended throughout the treatment period, especially if risk factors are combined (see table 4 above). Particular caution should be exercised when Pradaxa is co-administered with verapamil, amiodarone, quinidine or clarithromycin (P-gp inhibitors) and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment (see section 4.5).

Close observation for signs of bleeding is recommended in patients concomitantly treated with NSAIDs (see section 4.5).
Discontinuation of Pradaxa

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

When severe bleedings occur, treatment must be discontinued, the source of bleeding investigated and use of the specific reversal agent Praxbind (idarucizumab) may be considered (see section 4.9 Management of bleeding complications).

Dose reduction

A dose reduction should be either considered or is recommended as indicated in section 4.2.

Use of proton-pump inhibitors

The administration of a proton-pump inhibitor (PPI) can be considered to prevent GI bleeding.

Laboratory coagulation parameters

Although Pradaxa does not in general require routine anticoagulant monitoring, the measurement of dabigatran related anticoagulation may be helpful to detect excessive high exposure to dabigatran in the presence of additional risk factors.

Diluted thrombin time (dTT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information, but results should be interpreted with caution due to inter-test variability (see section 5.1). The International Normalised Ratio (INR) test is unreliable in patients on Pradaxa and false positive INR elevations have been reported. Therefore, INR tests should not be performed.

Table 5 shows coagulation test thresholds at trough that may be associated with an increased risk of bleeding (see section 5.1)

<table>
<thead>
<tr>
<th>Test (trough value)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary prevention of venous thromboembolism in orthopaedic surgery</td>
</tr>
<tr>
<td>dTT [ng/mL]</td>
<td>&gt; 67</td>
</tr>
<tr>
<td>ECT [x-fold upper limit of normal]</td>
<td>No data</td>
</tr>
<tr>
<td>aPTT [x-fold upper limit of normal]</td>
<td>&gt; 1.3</td>
</tr>
<tr>
<td>INR</td>
<td>Should not be performed</td>
</tr>
</tbody>
</table>

Use of fibrinolytic medicinal products for the treatment of acute ischemic stroke

The use of fibrinolytic medicinal products for the treatment of acute ischemic stroke may be considered if the patient presents with a dTT, ECT or aPTT not exceeding the upper limit of normal (ULN) according to the local reference range.

Surgery and interventions

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

Patients can stay on Pradaxa while being cardioverted. There are no data available for 110 mg twice daily Pradaxa treatment in patients undergoing catheter ablation for atrial fibrillation (see section 4.2).
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.

**Emergency surgery or urgent procedures**

Pradaxa should be temporarily discontinued. When rapid reversal of the anticoagulation effect is required the specific reversal agent (Praxbind, idarucizumab) to Pradaxa is available.

Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Pradaxa treatment can be re-initiated 24 hours after administration of Praxbind (idarucizumab), if the patient is clinically stable and adequate haemostasis has been achieved.

**Subacute surgery/interventions**

Pradaxa should be temporarily discontinued. A surgery / intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed the risk of bleeding may be increased. This risk of bleeding should be weighed against the urgency of intervention.

**Elective surgery**

If possible, Pradaxa should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete haemostasis may be required consider stopping Pradaxa 2-4 days before surgery.

Table 6 summarises discontinuation rules before invasive or surgical procedures.

**Table 6: 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>Pradaxa should be stopped 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>

**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 Pradaxa. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

**Postoperative phase**

Pradaxa should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established.

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

There are limited efficacy and safety data for Pradaxa 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.

Hepatic impairment

Patients with elevated liver enzymes > 2 ULN were excluded in the main trials. No treatment experience is available for this subpopulation of patients, and therefore the use of Pradaxa is not recommended in this population. Hepatic impairment or liver disease expected to have any impact on survival is contraindicated (see section 4.3).

Interaction with P-gp inducers

Concomitant administration of P-gp inducers is expected to result in decreased dabigatran plasma concentrations, and should be avoided (see sections 4.5 and 5.2).

Myocardial Infarction (MI)

In the phase III study RE-LY (SPAF, see section 5.1) the overall rate of MI was 0.82, 0.81, and 0.64 %/year for dabigatran etexilate 110 mg twice daily, dabigatran etexilate 150 mg twice daily and warfarin, respectively, an increase in relative risk for dabigatran of 29 % and 27 % compared to warfarin. Irrespective of therapy, the highest absolute risk of MI was seen in the following subgroups, with similar relative risk: patients with previous MI, patients ≥ 65 years with either diabetes or coronary artery disease, patients with left ventricular ejection fraction < 40 %, and patients with moderate renal dysfunction. Furthermore a higher risk of MI was seen in patients concomitantly taking ASA plus clopidogrel or clopidogrel alone.

In the three active controlled DVT/PE phase III studies, a higher rate of MI was reported in patients who received dabigatran etexilate than in those who received warfarin: 0.4% vs. 0.2% in the short-term RE-COVER and RE-COVER II studies; and 0.8% vs. 0.1% in the long-term RE-MEDY trial. The increase was statistically significant in this study (p=0.022).

In the RE-SONATE study, which compared dabigatran etexilate to placebo, the rate of MI was 0.1% for patients who received dabigatran etexilate and 0.2% for patients who received placebo

Active Cancer Patients (DVT/PE)

The efficacy and safety have not been established for DVT/PE patients with active cancer.

4.5 Interaction with other medicinal products and other forms of interaction

Transporter interactions

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors (see table 7) 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. Dose reductions may be required in combination with some P-gp inhibitors (see sections 4.2, 4.3, 4.4 and 5.1).
### Table 7: Transporter interactions

<table>
<thead>
<tr>
<th>P-gp inhibitors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Concomitant use contraindicated (see section 4.3)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Ketoconazole</strong></td>
<td>Ketoconazole increased total dabigatran AUC&lt;sub&gt;0-∞&lt;/sub&gt; and C&lt;sub&gt;max&lt;/sub&gt; values by 2.38-fold and 2.35-fold, respectively, after a single oral dose of 400 mg, and by 2.53-fold and 2.49-fold, respectively, after multiple oral dosing of 400 mg ketoconazole once daily.</td>
</tr>
<tr>
<td><strong>Dronedarone</strong></td>
<td>When dabigatran etexilate and dronedarone were given at the same time total dabigatran AUC&lt;sub&gt;0-∞&lt;/sub&gt; and C&lt;sub&gt;max&lt;/sub&gt; values increased by about 2.4-fold and 2.3-fold, respectively, after multiple dosing of 400 mg dronedarone bid, and about 2.1-fold and 1.9-fold, respectively, after a single dose of 400 mg.</td>
</tr>
<tr>
<td><strong>Itraconazole, cyclosporine</strong></td>
<td>Based on <em>in vitro</em> results a similar effect as with ketoconazole may be expected.</td>
</tr>
<tr>
<td><strong>Concomitant use not recommended</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Tacrolimus</strong></td>
<td>Tacrolimus has been found <em>in vitro</em> to have a similar level of inhibitory effect on P-gp as that seen with itraconazole and cyclosporine. Dabigatran etexilate has not been clinically studied together with tacrolimus. However, limited clinical data with another P-gp substrate (everolimus) suggest that the inhibition of P-gp with tacrolimus is weaker than that observed with strong P-gp inhibitors.</td>
</tr>
<tr>
<td><strong>Cautions to be exercised in case concomitant use (see sections 4.2 and 4.4)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Verapamil</strong></td>
<td>When dabigatran etexilate (150 mg) was co-administered with oral verapamil, the C&lt;sub&gt;max&lt;/sub&gt; and AUC of dabigatran were increased but the magnitude of this change differs depending on timing of administration and formulation of verapamil (see sections 4.2 and 4.4). The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to the dabigatran etexilate intake (increase of C&lt;sub&gt;max&lt;/sub&gt; by about 2.8-fold and AUC by about 2.5-fold). The effect was progressively decreased with administration of an extended release formulation (increase of C&lt;sub&gt;max&lt;/sub&gt; by about 1.9-fold and AUC by about 1.7-fold) or administration of multiple doses of verapamil (increase of C&lt;sub&gt;max&lt;/sub&gt; by about 1.6-fold and AUC by about 1.5-fold). There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increase of C&lt;sub&gt;max&lt;/sub&gt; by about 1.1-fold and AUC by about 1.2-fold). This is explained by completed dabigatran absorption after 2 hours.</td>
</tr>
<tr>
<td><strong>Amiodarone</strong></td>
<td>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&lt;sub&gt;max&lt;/sub&gt; were increased by about 1.6-fold and 1.5-fold, respectively. In view of the long half-life of amiodarone the potential for an interaction may exist for weeks after discontinuation of amiodarone (see sections 4.2 and 4.4).</td>
</tr>
<tr>
<td><strong>Quinidine</strong></td>
<td>Quinidine was given as 200 mg dose every 2nd hour up to a total dose of 1,000 mg. Dabigatran etexilate was given twice daily over 3 consecutive days, on the 3&lt;sup&gt;rd&lt;/sup&gt; day either with or without quinidine. Dabigatran AUC&lt;sub&gt;ss&lt;/sub&gt; and C&lt;sub&gt;max,ss&lt;/sub&gt; were increased on average by 1.53-fold and 1.56-fold, respectively with concomitant quinidine (see sections 4.2 and 4.4).</td>
</tr>
<tr>
<td><strong>Clarithromycin</strong></td>
<td>When clarithromycin (500 mg twice daily) was administered together with</td>
</tr>
<tr>
<td><strong>dabigatran etexilate</strong> in healthy volunteers, increase of AUC by about 1.19-fold and <strong>C_{max}</strong> by about 1.15-fold was observed.</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td></td>
</tr>
<tr>
<td><strong>Ticagrelor</strong> When a single dose of 75 mg dabigatran etexilate was coadministered simultaneously with a loading dose of 180 mg ticagrelor, the dabigatran AUC and <strong>C_{max}</strong> were increased by 1.73-fold and 1.95-fold, respectively. After multiple doses of ticagrelor 90 mg b.i.d. the increase of dabigatran exposure is 1.56-fold and 1.46-fold for <strong>C_{max}</strong> and AUC, respectively. Concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg dabigatran etexilate (in steady state) increased the dabigatran AUC_{\tau,ss} and C_{max,ss} by 1.49-fold and 1.65-fold, respectively, compared with dabigatran etexilate given alone. When a loading dose of 180 mg ticagrelor was given 2 hours after 110 mg dabigatran etexilate (in steady state), the increase of dabigatran AUC_{\tau,ss} and C_{max,ss} was reduced to 1.27-fold and 1.23-fold, respectively, compared with dabigatran etexilate given alone. This staggered intake is the recommended administration for start of ticagrelor with a loading dose. Concomitant administration of 90 mg ticagrelor b.i.d. (maintenance dose) with 110 mg dabigatran etexilate increased the adjusted dabigatran AUC_{\tau,ss} and C_{max,ss} 1.26-fold and 1.29-fold, respectively, compared with dabigatran etexilate given alone.</td>
<td></td>
</tr>
<tr>
<td><strong>Posaconazole</strong> Posaconazole also inhibits P-gp to some extent but has not been clinically studied. Caution should be exercised when Pradaxa is co-administered with posaconazole.</td>
<td></td>
</tr>
<tr>
<td><strong>P-gp inducers</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Concomitant use should be avoided.</strong></td>
<td></td>
</tr>
<tr>
<td>e.g. rifampicin, St. John’s wort (Hypericum perforatum), carbamazepine, or phenytoin Concomitant administration is expected to result in decreased dabigatran concentrations. 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.</td>
<td></td>
</tr>
<tr>
<td><strong>Protease inhibitors such as ritonavir</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Concomitant use not recommended</strong></td>
<td></td>
</tr>
<tr>
<td>e.g. ritonavir and its combinations with other protease inhibitors These affect P-gp (either as inhibitor or as inducer). They have not been studied and are therefore not recommended for concomitant treatment with Pradaxa.</td>
<td></td>
</tr>
<tr>
<td><strong>P-gp substrate</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Digoxin</strong> In a study performed with 24 healthy subjects, when Pradaxa was co-administered with digoxin, no changes on digoxin and no clinically relevant changes on dabigatran exposure have been observed.</td>
<td></td>
</tr>
</tbody>
</table>
Anticoagulants and antiplatelet aggregation medicinal products

There is no or only limited experience with the following treatments which may increase the risk of bleeding when used concomitantly with Pradaxa: anticoagulants such as unfractionated heparin (UFH), low molecular weight heparins (LMWH), and heparin derivatives (fondaparinux, desirudin), thrombolytic medicinal products, and vitamin K antagonists, rivaroxaban or other oral anticoagulants (see section 4.3), and antiplatelet aggregation medicinal products such as GPIIb/IIIa receptor antagonists, ticlopidine, prasugrel, ticagrelor, dextran, and sulfipyrazone (see section 4.4).

From the data collected in the phase III study RE-LY (see section 5.1) it was observed that the concomitant use of other oral or parenteral anticoagulants increases major bleeding rates with both dabigatran etexilate and warfarin by approximately 2.5-fold, mainly related to situations when switching from one anticoagulant to another (see section 4.3). Furthermore, concomitant use of antiplatelets, ASA or clopidogrel approximately doubled major bleeding rates with both dabigatran etexilate and warfarin (see section 4.4).

UFH can be administered at doses necessary to maintain a patent central venous or arterial catheter (see section 4.3).

Table 8: Interactions with anticoagulants and antiplatelet aggregation medicinal products

| NSAIDs | NSAIDs given for short-term analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use in the RE-LY study, NSAIDs increased the risk of bleeding by approximately 50% on both dabigatran etexilate and warfarin. |
| Clopidogrel | 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\textsubscript{\text{fss}}, C\textsubscript{\text{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\textsubscript{\text{fss}}, C\textsubscript{\text{max,ss}} were increased by about 30-40% (see section 4.4). |
| ASA | 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). |
| 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. |

Other interactions

Table 9: Other interactions

| Selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs) | SSRIs, SNRIs increased the risk of bleeding in RE-LY in all treatment groups, |

37
Substances influencing gastric pH

<table>
<thead>
<tr>
<th>Substance</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pantoprazole</td>
<td>When Pradaxa was co-administered with pantoprazole, a decrease in the dabigatran AUC 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.</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Ranitidine administration together with Pradaxa had no clinically relevant effect on the extent of absorption of dabigatran.</td>
</tr>
</tbody>
</table>

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.

### 4.6 Fertility, pregnancy and lactation

#### Women of childbearing potential

Women of childbearing potential should avoid pregnancy during treatment with Pradaxa.

#### Pregnancy

There is limited amount of 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.

Pradaxa should not be used during pregnancy unless clearly necessary.

#### Breast-feeding

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

#### Fertility

No human data available.

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

### 4.7 Effects on ability to drive and use machines

Pradaxa has no or negligible influence on the ability to drive and use machines.
4.8 Undesirable effects

Summary of the safety profile

The safety of Pradaxa has been evaluated in ten phase III studies including 23,393 patients exposed to Pradaxa (see Table 10).

Table 10: Number of patients studied, maximum daily dose in phase III studies

<table>
<thead>
<tr>
<th>Indication</th>
<th>Number of patients treated with Pradaxa</th>
<th>Maximum daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>pVTEp orthopaedic surgery</td>
<td>6,684</td>
<td>220 mg</td>
</tr>
<tr>
<td>Stroke and systemic embolism prevention in patients with atrial fibrillation</td>
<td>6,059</td>
<td>300 mg</td>
</tr>
<tr>
<td></td>
<td>5,983</td>
<td>220 mg</td>
</tr>
<tr>
<td>DVT/PE treatment (RE-COVER, RE-COVER II)</td>
<td>2,553</td>
<td>300 mg</td>
</tr>
<tr>
<td>DVT/PE prevention (RE-MEDY, RE-SONATE)</td>
<td>2,114</td>
<td>300 mg</td>
</tr>
</tbody>
</table>

In total, about 9 % of patients treated for elective hip or knee surgery (short-term treatment for up to 42 days), 22 % of patient with atrial fibrillation treated for the prevention of stroke and systemic embolism (long-term treatment for up to 3 years), 14 % of patient treated for DVT/PE and 15 % of patients treated for DVT/PE prevention experienced adverse reactions.

The most commonly reported events are bleedings occurring in approximately 14 % of patients treated short-term for elective hip or knee replacement surgery, 16.6 % in patients with atrial fibrillation treated long-term for the prevention of stroke and systemic embolism, and in 14.4 % of patients treated for DVT/PE. Furthermore, bleeding occurred in 19.4 % of patients in the DVT/PE prevention trial RE-MEDY and in 10.5 % of patient in the DVT/PE prevention trial RE-SONATE.

Since the patient populations treated in the three indications are not comparable and bleeding events are distributed over several System Organ Classes (SOC), a summary description of major and any bleeding are broken down by indication and given in tables 12-16 below.

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

Tabulated list of adverse reactions

Table 11 shows the adverse reactions identified from the primary VTE prevention studies after hip or knee replacement surgery, the study in the prevention of thromboembolic stroke, and systemic embolism in patients with atrial fibrillation and the studies in DVT/PE treatment and in-DVT/PE prevention. They are ranked under headings of SOC and frequency using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 11: Adverse reactions
<table>
<thead>
<tr>
<th>SOC / Preferred term.</th>
<th>Primary VTE prevention after hip or knee replacement surgery</th>
<th>Stroke and systemic embolism prevention in patients with atrial fibrillation</th>
<th>DVT/PE treatment and DVT/PE prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>Uncommon</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Haemoglobin decreased</td>
<td>Common</td>
<td>Uncommon</td>
<td>Not known</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Rare</td>
<td>Uncommon</td>
<td>Rare</td>
</tr>
<tr>
<td>Haematocrit decreased</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Not known</td>
</tr>
<tr>
<td>Immune system disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Rash</td>
<td>Rare</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Rare</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Angioedema</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Not known</td>
<td>Not known</td>
<td>Not known</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>Rare</td>
<td>Uncommon</td>
<td>Rare</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematoma</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>Rare</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Wound haemorrhage</td>
<td>Uncommon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>Uncommon</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>Rare</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td>Uncommon</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Rare</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Uncommon</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Rare</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Nausea</td>
<td>Uncommon</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Rectal haemorrhage</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Haemorrhoidal haemorrhage</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrointestinal ulcer, including oesophageal ulcer</td>
<td>Rare</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrooesophagitis</td>
<td>Rare</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>Rare</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Rare</td>
<td>Uncommon</td>
<td>Rare</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic function abnormal/ Liver function Test abnormal</td>
<td>Common</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hepatic enzyme increased</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Not known</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin haemorrhage</td>
<td>Uncommon</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Description of selected adverse reactions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Bleeding reactions**

Due to the pharmacological mode of action, the use of Pradaxa may be associated with an increased risk of occult or overt bleeding from any tissue or organ. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia. In the clinical studies mucosal bleedings (e.g. gastrointestinal, genitourinary) were seen more frequently during long term Pradaxa treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit is of value to detect occult bleeding. The risk of bleedings may be increased in certain patient groups e.g. those patients with moderate renal impairment and/or on concomitant treatment affecting haemostasis or strong P-gp inhibitors (see section 4.4 Haemorrhagic risk). Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock.

Known bleeding complications such as compartment syndrome and acute renal failure due to hypoperfusion have been reported for Pradaxa. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient. A specific reversal agent for dabigatran, idarucizumab, is available in case of uncontrollable bleeding (see Section 4.9).

**Primary Prevention of Venous Thromboembolism in Orthopaedic Surgery**

The table 12 shows the number (%) of patients experiencing the adverse reaction bleeding during the treatment period in the VTE prevention in the two pivotal clinical trials, according to dose.

**Table 12: Number (%) of patients experiencing the adverse reaction bleeding**

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 150 mg once daily N (%)</th>
<th>Pradaxa 220 mg once daily N (%)</th>
<th>Enoxaparin N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>1,866 (100.0)</td>
<td>1,825 (100.0)</td>
<td>1,848 (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>
Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors

The table 13 shows bleeding events broken down to major and any bleeding in the pivotal study testing the prevention of thromboembolic stroke and systemic embolism in patients with atrial fibrillation.

Table 13: Bleeding events in a study testing the prevention of thromboembolic stroke and systemic embolism in patients with atrial fibrillation

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 110 mg twice daily</th>
<th>Pradaxa 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomized</td>
<td>6,015</td>
<td>6,076</td>
<td>6,022</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>347 (2.92 %)</td>
<td>409 (3.40 %)</td>
<td>426 (3.61 %)</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>27 (0.23 %)</td>
<td>39 (0.32 %)</td>
<td>91 (0.77 %)</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>134 (1.13 %)</td>
<td>192 (1.60 %)</td>
<td>128 (1.09 %)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>26 (0.22 %)</td>
<td>30 (0.25 %)</td>
<td>42 (0.36 %)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>1,566 (13.16 %)</td>
<td>1,787 (14.85 %)</td>
<td>1,931 (16.37 %)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>1,759 (14.78 %)</td>
<td>1,997 (16.60 %)</td>
<td>2,169 (18.39 %)</td>
</tr>
</tbody>
</table>

Subjects randomized to Pradaxa 110 mg twice daily or 150 mg twice daily had a significantly lower risk for life-threatening bleeds and intracranial bleeding compared to warfarin [p < 0.05]. Both dose strengths of Pradaxa had also a statistically significant lower total bleed rate. Subjects randomized to 110 mg Pradaxa twice daily had a significantly lower risk for major bleeds compared with warfarin (hazard ratio 0.81 [p=0.0027]). Subjects randomized to 150 mg Pradaxa twice daily had a significantly higher risk for major GI bleeds compared with warfarin (hazard ratio 1.48 [p=0.0005)]. This effect was seen primarily in patients ≤ 75 years.

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

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (DVT/PE treatment)

Table 14 shows bleeding events in the pooled pivotal studies RE-COVER and RE-COVER II testing the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). In the pooled studies the primary safety endpoints of major bleeding, major or clinically relevant bleeding and any bleeding were significantly lower than warfarin at a nominal alpha level of 5 %.

Table 14: Bleeding events in the studies RE-COVER and RE-COVER II testing the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 150 mg twice daily</th>
<th>Warfarin</th>
<th>Hazard ratio vs. warfarin (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients included in safety analysis</td>
<td>2,456</td>
<td>2,462</td>
<td></td>
</tr>
<tr>
<td>Major bleeding events</td>
<td>24 (1.0 %)</td>
<td>40 (1.6 %)</td>
<td>0.60 (0.36, 0.99)</td>
</tr>
<tr>
<td>Intracranial Bleeding</td>
<td>2 (0.1 %)</td>
<td>4 (0.2 %)</td>
<td>0.50 (0.09, 2.74)</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>10 (0.4 %)</td>
<td>12 (0.5 %)</td>
<td>0.83 (0.36, 1.93)</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>4 (0.2 %)</td>
<td>6 (0.2 %)</td>
<td>0.66 (0.19, 2.36)</td>
</tr>
</tbody>
</table>
Bleeding events for both treatments are counted from the first intake of Pradaxa or warfarin after the parenteral therapy has been discontinued (oral only treatment period). This includes all bleeding events, which occurred during Pradaxa therapy. All bleeding events which occurred during warfarin therapy are included except for those during the overlap period between warfarin and parenteral therapy.

Table 15 shows bleeding events in pivotal study RE-MEDY testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE). Some bleeding events (MBEs/CRBEs; any bleeding) were significantly lower at a nominal alpha level of 5% in patients receiving Pradaxa as compared with those receiving warfarin.

Table 15: Bleeding events in study RE-MEDY testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE)

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 150 mg twice daily</th>
<th>Warfarin</th>
<th>Hazard ratio vs warfarin (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated patients</td>
<td>1,430</td>
<td>1,426</td>
<td></td>
</tr>
<tr>
<td>Major bleeding events</td>
<td>13 (0.9 %)</td>
<td>25 (1.8 %)</td>
<td>0.54 (0.25, 1.16)</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>2 (0.1 %)</td>
<td>4 (0.3 %)</td>
<td>Not calculable*</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>4 (0.3%)</td>
<td>8 (0.5%)</td>
<td>Not calculable*</td>
</tr>
<tr>
<td>Life-threatening bleed</td>
<td>1 (0.1 %)</td>
<td>3 (0.2 %)</td>
<td>Not calculable*</td>
</tr>
<tr>
<td>Major bleeding event</td>
<td>80 (5.6 %)</td>
<td>145 (10.2 %)</td>
<td>0.55 (0.41, 0.72)</td>
</tr>
<tr>
<td>clinically relevant bleeds</td>
<td>145 (10.2 %)</td>
<td>373 (26.2 %)</td>
<td>0.71 (0.61, 0.83)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>278 (19.4 %)</td>
<td>373 (26.2 %)</td>
<td></td>
</tr>
<tr>
<td>Any GI bleeds</td>
<td>45 (3.1%)</td>
<td>32 (2.2 %)</td>
<td>1.39 (0.87, 2.20)</td>
</tr>
</tbody>
</table>

*HR not estimable as there is no event in either one cohort/treatment

Table 16 shows bleeding events in pivotal study RE-SONATE testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE). The rate of the combination of MBEs/CRBEs and the rate of any bleeding was significantly lower at a nominal alpha level of 5% in patients receiving placebo as compared with those receiving Pradaxa.

Table 16: Bleeding events in study RE-SONATE testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE)

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 150 mg twice daily</th>
<th>Placebo</th>
<th>Hazard ratio vs placebo (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated patients</td>
<td>684</td>
<td>659</td>
<td></td>
</tr>
<tr>
<td>Major bleeding events</td>
<td>2 (0.3 %)</td>
<td>0</td>
<td>Not calculable*</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0</td>
<td>0</td>
<td>Not calculable*</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>2 (0.3%)</td>
<td>0</td>
<td>Not</td>
</tr>
</tbody>
</table>
Life-threatening bleeds | 0 | 0 | calculable*  
Major bleeding event/clinical relevant bleeds | 36 (5.3%) | 13 (2.0%) | 2.69 (1.43, 5.07)  
Any bleeding | 72 (10.5%) | 40 (6.1%) | 1.77 (1.20, 2.61)  
Any GI bleeds | 5 (0.7%) | 2 (0.3%) | 2.38 (0.46, 12.27)  
*HR not estimable as there is no event in either one treatment

Paediatric population (DVT/PE)
In the clinical study 1160.88 in total, 9 adolescent patients (age 12 to <18 years) with diagnosis of primary VTE received an initial oral dose of dabigatran etexilate of 1.71 (±10%) mg/kg bodyweight. Based on dabigatran concentrations as determined by the diluted thrombin time test and clinical assessment, the dose was adjusted to the target dose of 2.14 (±10%) mg/kg bodyweight of dabigatran etexilate. On treatment 2 (22.1%) patients experienced mild related adverse events (gastroesophageal reflux / abdominal pain; abdominal discomfort) and 1 (11.1%) patient experienced a not related serious adverse event (recurrent VTE of the leg) in the post treatment period >3 days after stop of dabigatran etexilate.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose
Pradaxa doses 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 which 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. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. As protein binding is low, dabigatran can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies (see section 5.2).

Management of bleeding complications
In the event of haemorrhagic complications, Pradaxa treatment must be discontinued and the source of bleeding investigated. Depending on the clinical situation appropriate supportive treatment, such as surgical haemostasis and blood volume replacement, should be undertaken at the prescribers discretion. For situations when rapid reversal of the anticoagulant effect of Pradaxa is required the specific reversal agent (Praxbind, idarucizumab) antagonizing the pharmacodynamic effect of Pradaxa is available (see section 4.4).

Coagulation factor concentrates (activated or non-activated) or recombinant Factor VIIa may be taken into account. There is some experimental evidence to support the role of these medicinal products in reversing the anticoagulant effect of dabigatran, but data on their usefulness in clinical settings and also on the possible risk of rebound thromboembolism is very limited. Coagulation tests may become unreliable following administration of suggested coagulation factor concentrates. Caution should be exercised when interpreting these tests. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet medicinal products have been used. All symptomatic treatment should be given according to the physician's
judgement.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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 inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

Pharmacodynamic effects

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

There is a clear correlation between plasma dabigatran concentration and degree of anticoagulant effect based on phase II studies. Dabigatran prolongs the thrombin time (TT), ECT, and aPTT.

The calibrated quantitative diluted TT (dTT) test provides an estimation of dabigatran plasma concentration that can be compared to the expected dabigatran plasma concentrations. When the calibrated dTT assay delivers a dabigatran plasma concentration result at or below the limit of quantification, an additional coagulation assay such as TT, ECT or aPTT should be considered.

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

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

In general, it can be assumed that these measures of anti-coagulant activity may reflect dabigatran levels and can provide guidance for the assessment of bleeding risk, i.e. exceeding the 90th percentile of dabigatran trough levels or a coagulation assay such as aPTT measured at trough (for aPTT thresholds see section 4.4, table 5) is considered to be associated with an increased risk of bleeding.

Primary Prevention of Venous Thromboembolism in Orthopaedic Surgery

Steady state (after day 3) geometric mean dabigatran peak plasma concentration, measured around 2 hours after 220 mg dabigatran etexilate administration, was 70.8 ng/mL, with a range of 35.2-162 ng/mL (25th–75th percentile range). The dabigatran geometric mean trough concentration, measured at the end of the dosing interval (i.e. 24 hours after a 220 mg dabigatran dose), was on average 22.0 ng/mL, with a range of 13.0-35.7 ng/mL (25th-75th percentile range).
In a dedicated study exclusively in patients with moderate renal impairment (creatinine clearance, CrCL 30-50 mL/min) treated with dabigatran etexilate 150 mg QD, the dabigatran geometric mean trough concentration, measured at the end of the dosing interval, was on average 47.5 ng/mL, with a range of 29.6 - 72.2 ng/mL (25th-75th percentile range).

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

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

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

Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors (SPAF)

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

For patients with NVAF treated for prevention of stroke and systemic embolism with 150 mg dabigatran etexilate twice daily,

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

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (DVT/PE)

In patients treated for DVT and PE with 150 mg dabigatran etexilate twice daily, the dabigatran geometric mean trough concentration, measured within 10–16 hours after dose, at the end of the dosing interval (i.e. 12 hours after the 150 mg dabigatran evening dose), was 59.7 ng/ml, with a range of 38.6 - 94.5 ng/ml (25th-75th percentile range). For treatment of DVT and PE, with dabigatran etexilate 150 mg twice daily,

- the 90th percentile of dabigatran plasma concentrations measured at trough (10-16 hours after the previous dose) was about 146 ng/ml,
- an ECT at trough (10-16 hours after the previous dose), elevated approximately 2.3-fold compared to baseline refers to the observed 90th percentile of ECT prolongation of 74 seconds,
- the 90th percentile of aPTT at trough (10-16 hours after the previous dose) was 62 seconds, which would be 1.8-fold compared to baseline.

In patients treated for prevention of recurrent of DVT and PE with 150 mg dabigatran etexilate twice daily no pharmacokinetic data are available.

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Clinical efficacy and safety

Ethnic origin

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

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

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

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

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

Results of both studies showed that the antithrombotic effect of Pradaxa 220 mg and 150 mg were statistically non-inferior to that of enoxaparin on total VTE and all-cause mortality. The point estimate for incidence of Major VTE and VTE related mortality for the 150 mg dose was slightly worse than enoxaparin (table 17). Better results were seen with the 220 mg dose where the point estimate of Major VTE was slightly better than enoxaparin (table 17).

The clinical studies have been conducted in a patient population with a mean age > 65 years.

There were no differences in the phase 3 clinical studies for efficacy and safety data between men and women.

In the studied patient population of RE-MODEL and RE-NOVATE (5,539 patients treated), 51 % suffered from concomitant hypertension, 9 % from concomitant diabetes, 9 % from concomitant coronary artery disease and 20 % had a history of venous insufficiency. None of these diseases showed an impact on the effects of dabigatran on VTE-prevention or bleeding rates.

Data for the major VTE and VTE-related mortality endpoint were homogeneous with regards to the primary efficacy endpoint and are shown in table 17.

Data for the total VTE and all cause mortality endpoint are shown in table 18.

Data for adjudicated major bleeding endpoints are shown in table 19 below.
Table 17: 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>Pradaxa 220 mg once daily</th>
<th>Pradaxa 150 mg once daily</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 18: 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>Pradaxa 220 mg once daily</th>
<th>Pradaxa 150 mg once daily</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 enoxaparin</td>
<td>0.97</td>
<td>1.07</td>
<td></td>
</tr>
<tr>
<td>95 % CI</td>
<td>(0.82, 1.13)</td>
<td>(0.92, 1.25)</td>
<td></td>
</tr>
</tbody>
</table>

Table 19: Major bleeding events by treatment in the individual RE-MODEL and the RE-NOVATE studies.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pradaxa 220 mg once daily</th>
<th>Pradaxa 150 mg once daily</th>
<th>Enoxaparin 40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-NOVATE (hip)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated patients N</td>
<td>1,146</td>
<td>1,163</td>
<td>1,154</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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated patients N</td>
<td>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>

Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors

The clinical evidence for the efficacy of dabigatran etexilate is derived from the RE-LY study (Randomized Evaluation of Long-term anticoagulant therapy) a multi-centre, multi-national, randomized parallel group study of two blinded doses of dabigatran etexilate (110 mg and 150 mg twice daily) compared to open-label warfarin in patients with atrial fibrillation at moderate to high risk of stroke and systemic embolism. The primary objective in this study was to determine if dabigatran etexilate was non-inferior to warfarin in reducing the occurrence of the composite endpoint stroke and systemic embolism. Statistical superiority was also analysed.
In the RE-LY study, a total of 18,113 patients were randomized, with a mean age of 71.5 years and a mean CHADS\(_2\) score of 2.1. The patient population was 64 % male, 70 % Caucasian and 16 % Asian. For patients randomized to warfarin, the mean percentage of time in therapeutic range (TTR) (INR 2-3) was 64.4 % (median TTR 67 %).

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

Tables 20-22 display details of key results in the overall population:

**Table 20: Analysis of first occurrence of stroke or systemic embolism (primary endpoint) during the study period in RE-LY.**

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 110 mg twice daily</th>
<th>Pradaxa 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomized</td>
<td>6,015</td>
<td>6,076</td>
<td>6,022</td>
</tr>
<tr>
<td>Stroke and/or systemic embolism Incidences (%)</td>
<td>183 (1.54)</td>
<td>135 (1.12)</td>
<td>203 (1.72)</td>
</tr>
<tr>
<td>Hazard ratio over warfarin (95 % CI)</td>
<td>0.89 (0.73, 1.09)</td>
<td>0.65 (0.52, 0.81)</td>
<td></td>
</tr>
<tr>
<td>p value superiority</td>
<td>p=0.2721</td>
<td>p=0.0001</td>
<td></td>
</tr>
</tbody>
</table>

% refers to yearly event rate

**Table 21: Analysis of first occurrence of ischemic or haemorrhagic strokes during the study period in RE-LY.**

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 110 mg twice daily</th>
<th>Pradaxa 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomized</td>
<td>6,015</td>
<td>6,076</td>
<td>6,022</td>
</tr>
<tr>
<td>Stroke Incidences (%)</td>
<td>171 (1.44)</td>
<td>123 (1.02)</td>
<td>187 (1.59)</td>
</tr>
<tr>
<td>Hazard ratio vs. warfarin (95 % CI)</td>
<td>0.91 (0.74, 1.12)</td>
<td>0.64 (0.51, 0.81)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.3553</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Systemic embolism Incidences (%)</td>
<td>15 (0.13)</td>
<td>13 (0.11)</td>
<td>21 (0.18)</td>
</tr>
<tr>
<td>Hazard ratio vs. warfarin (95 % CI)</td>
<td>0.71 (0.37, 1.38)</td>
<td>0.61 (0.30, 1.21)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.3099</td>
<td>0.1582</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke Incidences (%)</td>
<td>152 (1.28)</td>
<td>104 (0.86)</td>
<td>134 (1.14)</td>
</tr>
<tr>
<td>Hazard ratio vs. warfarin (95 % CI)</td>
<td>1.13 (0.89, 1.42)</td>
<td>0.76 (0.59, 0.98)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.3138</td>
<td>0.0351</td>
<td></td>
</tr>
<tr>
<td>Haemorrhagic stroke Incidences (%)</td>
<td>14 (0.12)</td>
<td>12 (0.10)</td>
<td>45 (0.38)</td>
</tr>
<tr>
<td>Hazard ratio vs. warfarin (95 % CI)</td>
<td>0.31 (0.17, 0.56)</td>
<td>0.26 (0.14, 0.49)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0001</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>———</td>
<td>———</td>
<td>———</td>
<td></td>
</tr>
<tr>
<td>% refers to yearly event rate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 22: Analysis of all cause and cardiovascular survival during the study period in RE-LY.**

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

% refers to yearly event rate

Tables 23-25 display results of the primary efficacy and safety endpoint in relevant sub-populations:

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

**Table 23: Hazard Ratio and 95 % CI for stroke/systemic embolism by subgroups**

| Endpoint | Pradaxa 110 mg twice daily vs. Warfarin | Pradaxa 150 mg twice daily vs. warfarin |
|———|———|———|
| Age (years) | | |
| < 65 | 1.10 (0.64, 1.87) | 0.51 (0.26, 0.98) |
| 65 ≤ and < 75 | 0.86 (0.62, 1.19) | 0.67 (0.47, 0.95) |
| ≥ 75 | 0.88 (0.66, 1.17) | 0.68 (0.50, 0.92) |
| ≥ 80 | 0.68 (0.44, 1.05) | 0.67 (0.44, 1.02) |
| CrCL(mL/min) | | |
| 30 ≤ and < 50 | 0.89 (0.61, 1.31) | 0.48 (0.31, 0.76) |
| 50 ≤ and < 80 | 0.91 (0.68, 1.20) | 0.65 (0.47, 0.88) |
| ≥ 80 | 0.81 (0.51, 1.28) | 0.69 (0.43, 1.12) |

For the primary safety endpoint of major bleeding there was an interaction of treatment effect and age. The relative risk of bleeding with dabigatran compared to warfarin increased with age. Relative risk was highest in patients ≥ 75 years. The concomitant use of antiplatelets ASA or clopidogrel approximately doubles MBE rates with both dabigatran etexilate and warfarin. There was no significant interaction of treatment effects with the subgroups of renal function and CHADS2 score.
Table 24: Hazard Ratio and 95 % CI for major bleeds by subgroups

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Pradaxa 110 mg twice daily vs. Warfarin</th>
<th>Pradaxa 150 mg twice daily vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>0.32 (0.18, 0.57)</td>
<td>0.35 (0.20, 0.61)</td>
</tr>
<tr>
<td>65 ≤ and &lt; 75</td>
<td>0.71 (0.56, 0.89)</td>
<td>0.82 (0.66, 1.03)</td>
</tr>
<tr>
<td>≥ 75</td>
<td>1.01 (0.84, 1.23)</td>
<td>1.19 (0.99, 1.43)</td>
</tr>
<tr>
<td>≥ 80</td>
<td>1.14 (0.86, 1.51)</td>
<td>1.35 (1.03, 1.76)</td>
</tr>
<tr>
<td>CrCL(ml/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 ≤ and &lt; 50</td>
<td>1.02 (0.79, 1.32)</td>
<td>0.94 (0.73, 1.22)</td>
</tr>
<tr>
<td>50 ≤ and &lt; 80</td>
<td>0.75 (0.61, 0.92)</td>
<td>0.90 (0.74, 1.09)</td>
</tr>
<tr>
<td>≥ 80</td>
<td>0.59 (0.43, 0.82)</td>
<td>0.87 (0.65, 1.17)</td>
</tr>
<tr>
<td>ASA use</td>
<td>0.84 (0.69, 1.03)</td>
<td>0.97 (0.79, 1.18)</td>
</tr>
<tr>
<td>Clopidogrel use</td>
<td>0.89 (0.55, 1.45)</td>
<td>0.92 (0.57, 1.48)</td>
</tr>
</tbody>
</table>

RELY-ABLE (Long term multi-center extension of dabigatran treatment in patients with atrial fibrillation who completed the RE-LY trial)

The RE-LY extension study (RELY-ABLE) provided additional safety information for a cohort of patients which continued the same dose of dabigatran etexilate as assigned in the RE-LY trial. Patients were eligible for the RELY-ABLE trial if they had not permanently discontinued study medication at the time of their final RE-LY study visit. Enrolled patients continued to receive the same double-blind dabigatran etexilate dose randomly allocated in RE-LY, for up to 43 months of follow up after RE-LY (total mean follow-up RE-LY + RELY-ABLE, 4.5 years). There were 5897 patients enrolled, representing 49 % of patients originally randomly assigned to receive dabigatran etexilate in RE-LY and 86 % of RELY-ABLE–eligible patients.

During the additional 2.5 years of treatment in RELY-ABLE, with a maximum exposure of over 6 years (total exposure in RELY + RELY-ABLE), the long-term safety profile of dabigatran etexilate was confirmed for both test doses 110 mg b.i.d. and 150 mg b.i.d.. No new safety findings were observed.

The rates of outcome events including, major bleed and other bleeding events were consistent with those seen in RE-LY.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE treatment)

The efficacy and safety was investigated in two multi-center, randomised, double blind, parallel-group, replicate studies RE-COVER and RE-COVER II. These studies compared dabigatran etexilate (150 mg bid) with warfarin (target INR 2.0-3.0) in patients with acute DVT and/or PE. The primary objective of these studies was to determine if dabigatran etexilate was non-inferior to warfarin in reducing the occurrence of the primary endpoint which was the composite of recurrent symptomatic DVT and/or PE and related deaths within the 6 month treatment period.

In the pooled RE-COVER and RE-COVER II studies, a total of 5,153 patients were randomised and 5,107 were treated.

The duration of treatment with fixed dose of dabigatran was 174.0 days without coagulation monitoring. For patients randomized to warfarin, the median time in therapeutic range (INR 2.0 to 3.0) was 60.6 %.

The trials, demonstrated that treatment with dabigatran etexilate 150 mg twice daily was non-inferior to the treatment with warfarin (non-inferiority margin for RE-COVER, and RE-COVER II: 3.6 for risk difference and 2.75 for hazard ratio).
Table 25: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the pooled studies RE-COVER and RE-COVER II

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated patients</td>
<td>2,553</td>
<td>2,554</td>
</tr>
<tr>
<td>Recurrent symptomatic VTE and VTE-related death</td>
<td>68 (2.7%)</td>
<td>62 (2.4%)</td>
</tr>
<tr>
<td>Hazard ratio vs warfarin (95% confidence interval)</td>
<td>1.09 (0.77, 1.54)</td>
<td></td>
</tr>
<tr>
<td>Secondary efficacy endpoints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent symptomatic VTE and all-cause deaths</td>
<td>109 (4.3%)</td>
<td>104 (4.1%)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>3.52, 5.13</td>
<td>3.34, 4.91</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>45 (1.8%)</td>
<td>39 (1.5%)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>1.29, 2.35</td>
<td>1.09, 2.08</td>
</tr>
<tr>
<td>Symptomatic PE</td>
<td>27 (1.1%)</td>
<td>26 (1.0%)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.70, 1.54</td>
<td>0.67, 1.49</td>
</tr>
<tr>
<td>VTE-related deaths</td>
<td>4 (0.2%)</td>
<td>3 (0.1%)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.04, 0.40</td>
<td>0.02, 0.34</td>
</tr>
<tr>
<td>All-cause deaths</td>
<td>51 (2.0%)</td>
<td>52 (2.0%)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>1.49, 2.62</td>
<td>1.52, 2.66</td>
</tr>
</tbody>
</table>

Prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE prevention)

Two randomized, parallel group, double-blind studies were performed in patients previously treated with anticoagulation therapy. RE-MEDY, warfarin controlled study, enrolled patients already treated for 3 to 12 months with the need for further anticoagulant treatment and RE-SONATE, the placebo controlled study, enrolled patients already treated for 6 to 18 months with Vitamin K inhibitors.

The objective of the RE-MEDY study was to compare the safety and efficacy of oral dabigatran etexilate (150 mg bid) to warfarin (target INR 2.0-3.0) for the long-term treatment and prevention of recurrent, symptomatic DVT and/or PE. A total of 2,866 patients were randomized and 2,856 patients were treated. Duration of dabigatran etexilate treatment ranged from 6 to 36 months (median 534.0 days). For patients randomized to warfarin, the median time in therapeutic range (INR 2.0-3.0) was 64.9 %.

RE-MEDY demonstrated that treatment with dabigatran etexilate 150 mg twice daily was non-inferior to warfarin (non-inferiority margin: 2.85 for hazard ratio and 2.8 for risk difference).
Table 26: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the RE-MEDY study

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated patients</td>
<td>1430</td>
<td>1426</td>
</tr>
<tr>
<td>Recurrent symptomatic VTE and VTE-related death</td>
<td>26 (1.8 %)</td>
<td>18 (1.3 %)</td>
</tr>
<tr>
<td>Hazard ratio vs warfarin</td>
<td>1.44 (0.78, 2.64)</td>
<td></td>
</tr>
<tr>
<td>non-inferiority margin</td>
<td>2.85</td>
<td></td>
</tr>
<tr>
<td>Patients with event at 18 months</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>Cumulative risk at 18 months (%)</td>
<td>1.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Risk difference vs. warfarin (%)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>95% confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-inferiority margin</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Secondary efficacy endpoints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent symptomatic VTE and all-cause deaths</td>
<td>42 (2.9 %)</td>
<td>36 (2.5 %)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>2.12, 3.95</td>
<td>1.77, 3.48</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>17 (1.2 %)</td>
<td>13 (0.9 %)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.69, 1.90</td>
<td>0.49, 1.55</td>
</tr>
<tr>
<td>Symptomatic PE</td>
<td>10 (0.7 %)</td>
<td>5 (0.4 %)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.34, 1.28</td>
<td>0.11, 0.82</td>
</tr>
<tr>
<td>VTE-related deaths</td>
<td>1 (0.1 %)</td>
<td>1 (0.1 %)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.00, 0.39</td>
<td>0.00, 0.39</td>
</tr>
<tr>
<td>All-cause deaths</td>
<td>17 (1.2 %)</td>
<td>19 (1.3 %)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.69, 1.90</td>
<td>0.80, 2.07</td>
</tr>
</tbody>
</table>

The objective of the RE-SONATE study was to evaluate superiority of dabigatran etexilate versus placebo for the prevention of recurrent symptomatic DVT and/or PE in patients who had already completed 6 to 18 months of treatment with VKA. The intended therapy was 6 months dabigatran etexilate 150 mg twice daily without need for monitoring.

RE-SONATE demonstrated dabigatran etexilate was superior to placebo for the prevention of recurrent symptomatic DVT/PE events including unexplained deaths, with a risk reduction from 5.6 % to 0.4 % (relative risk reduction 92 % based on hazard ratio ) during the treatment period (p<0.0001).

All secondary and sensitivity analyses of the primary endpoint and all secondary endpoints showed superiority of dabigatran etexilate over placebo.

The study included observational follow-up for 12 months after the conclusion of treatment. After discontinuation of study medication the effect was maintained until the end of the follow-up, indicating that the initial treatment effect of dabigatran etexilate was sustained. No rebound effect was observed. At the end of the follow-up VTE events in patients treated with dabigatran etexilate was 6.9 % vs. 10.7 % among the placebo group (hazard ratio 0.61 (95% CI 0.42, 0.88), p=0.0082).
Table 27: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the RE-SONATE study.

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 150 mg twice daily</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated patients</td>
<td>681</td>
<td>662</td>
</tr>
<tr>
<td>Recurrent symptomatic VTE and related deaths</td>
<td>3 (0.4 %)</td>
<td>37 (5.6 %)</td>
</tr>
<tr>
<td>Hazard Ratio vs placebo (95% confidence interval)</td>
<td>0.08 (0.02, 0.25)</td>
<td></td>
</tr>
<tr>
<td>p-value for superiority</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Secondary efficacy endpoints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent symptomatic VTE and all-cause deaths</td>
<td>3 (0.4 %)</td>
<td>37 (5.6 %)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.09, 1.28</td>
<td>3.97, 7.62</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>2 (0.3 %)</td>
<td>23 (3.5 %)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.04, 1.06</td>
<td>2.21, 5.17</td>
</tr>
<tr>
<td>Symptomatic PE</td>
<td>1 (0.1 %)</td>
<td>14 (2.1 %)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.00, 0.82</td>
<td>1.16, 3.52</td>
</tr>
<tr>
<td>VTE-related deaths</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.00, 0.54</td>
<td>0.00, 0.56</td>
</tr>
<tr>
<td>Unexplained deaths</td>
<td>0 (0)</td>
<td>2 (0.3 %)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.00, 0.54</td>
<td>0.04, 1.09</td>
</tr>
<tr>
<td>All-cause deaths</td>
<td>0 (0)</td>
<td>2 (0.3 %)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.00, 0.54</td>
<td>0.04, 1.09</td>
</tr>
</tbody>
</table>

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

A phase II study examined dabigatran etexilate and warfarin in a total of 252 patients with recent mechanical valve replacement surgery (i.e. within the current hospital stay) and in patients who received a mechanical heart valve replacement more than three months ago. More thromboembolic events (mainly strokes and symptomatic/asymptomatic prosthetic valve thrombosis) and more bleeding events were observed with dabigatran etexilate than with warfarin. In the early post-operative patients, major bleeding manifested predominantly as haemorrhagic pericardial effusions, specifically in patients who started dabigatran etexilate early (i.e. on Day 3) after heart valve replacement surgery (see section 4.3).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Pradaxa in all subsets of the paediatric population for the granted indications (see section 4.2 for information on paediatric use).

The pharmacokinetics and pharmacodynamics of dabigatran etexilate administered twice daily for three consecutive days (total 6 doses) at the end of standard anticoagulant therapy were assessed in an open-label safety and tolerability study in 9 stable adolescents (12 to < 18 years). All patients received an initial oral dose of 1.71 (± 10%) mg/kg of dabigatran etexilate (80 % of the adult dose of 150 mg/70 kg adjusted for the patient’s weight). Based on dabigatran concentrations and clinical assessment, the dose was subsequently modified to a target dose of 2.14 (± 10 %) mg/kg of dabigatran etexilate (100 % of the adult dose adjusted for the patient’s weight). In this small number of adolescents, dabigatran etexilate capsules were apparently tolerated with only three mild and transient
gastrointestinal adverse events reported by two patients. According to the relatively low exposure, coagulation at 72 hrs (presumed dabigatran trough level at steady state or close to steady state conditions) was only slightly prolonged with aPTT at maximum 1.60 fold, ECT 1.86 fold, and Hemoclot® TT (Anti-FIIa) 1.36 fold, respectively. Dabigatran plasma concentrations observed at 72 hrs were relatively low, between 32.9 ng/mL and 97.2 ng/mL at final doses between 100 mg and 150 mg (gMean dose normalized total dabigatran plasma concentration of 0.493 ng/mL/mg).

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<sub>max</sub> 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.

C<sub>max</sub> and AUC were dose proportional.

The oral bioavailability may be increased by 75 % after a single dose and 37 % at steady state 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 (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.

Biotransformation

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
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.

**Elimination**

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 28.

**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 28: 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>

Additionally, dabigatran exposure (at trough and peak) was assessed in a prospective open label randomized pharmacokinetic study in NVAF patients with severe renal impairment (defined as creatinine clearance [CrCl] 15-30 mL/min) receiving dabigatran etexilate 75 mg twice daily. This regimen resulted in a geometric mean trough concentration of 155 ng/ml (gCV of 76.9 %), measured immediately before administration of the next dose and in a geometric mean peak concentration of 202 ng/ml (gCV of 70.6 %) measured two hours after the administration of the last dose.

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

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

The median CrCL in the RE-COVER study was 100.4 mL/min. 21.7 % of patients had mild renal impairment (CrCL > 50 - < 80 mL/min) and 4.5% of patients had a moderate renal impairment (CrCL between 30 and 50 mL/min). Patients with mild and moderate renal impairment had at steady state an
average 1.8-fold and 3.6-fold higher pre-dose dabigatran plasma concentrations compared with patients with CrCL > 80 mL/min, respectively. Similar values for CrCL were found in RE-COVER II.

The median CrCL in the RE-MEDY and RE-SONATE studies were 99.0 mL/min and 99.7 mL/min, respectively. 22.9 % and 22.5 % of the patients had a CrCL > 50-< 80 mL/min, and 4.1 % and 4.8 % had a CrCL between 30 and 50 mL/min in in the RE-MEDY and RE-SONATE studies.

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

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

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

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

**Pharmacokinetic interactions**

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 repeated 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.

Dabigatran, the active moiety of dabigatran etexilate mesilate, is persistent in the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

**Capsule content**
- Tartaric acid
- Acacia
- Hypermellose
- Dimeticone 350
- Talc
- Hydroxypropylcellulose

**Capsule shell**
- Carrageenan
- Potassium chloride
- Titanium dioxide
- Indigo carmine (E132)
- Hypermellose

**Black printing ink**
- Shellac
- Iron oxide black (E172)
- Potassium hydroxide

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 10 x 1, 30 x 1 or 60 x 1 hard capsules in perforated aluminium unit dose blisters. Multipack containing 3 packs of 60 x 1 hard capsules (180 hard capsules) in perforated aluminium unit dose blisters. Multipack containing 2 packs of 50 x 1 hard capsules (100 hard capsules) in perforated aluminium unit dose blisters. Carton containing 6 blister strips (60 x 1) in perforated aluminium unit dose white blisters.

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:

- One individual blister should be teared off from the blister card along the perforated line.
- The backing foil should be peeled off and the capsule can be removed.
- 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, the following instructions should be observed:

- The cap opens by pushing and turning.
- After taking the capsule out, the cap should be returned on the bottle right away and the bottle should be tightly closed.

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

7. MARKETING AUTHORIZATION HOLDER

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

8. MARKETING AUTHORIZATION NUMBER(S)

EU/1/08/442/005
EU/1/08/442/006
EU/1/08/442/007
EU/1/08/442/008
EU/1/08/442/014
EU/1/08/442/015
EU/1/08/442/018

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorisation: 18 March 2008
Date of latest renewal: 17 January 2013
10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.
1. **NAME OF THE MEDICINAL PRODUCT**

Pradaxa 150 mg hard capsules

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

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

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Hard capsule.

Capsules with light blue, opaque cap and white, opaque body of size 0 filled with yellowish pellets. The cap is imprinted with the Boehringer Ingelheim company symbol, the body with “R150”.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults

4.2 **Posology and method of administration**

**Posology**

*Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors (SPAF)*

*Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE)*

The recommended doses of Pradaxa in the indications SPAF, DVT and PE are shown in table 1.
**Table 1: Dose recommendations for SPAF, DVT and PE**

<table>
<thead>
<tr>
<th>Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors (SPAF)</th>
<th>300 mg Pradaxa taken as one 150 mg capsule twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT, and PE in adults (DVT/PE)</td>
<td>300 mg Pradaxa taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days</td>
</tr>
<tr>
<td><strong>Dose reduction recommended</strong></td>
<td></td>
</tr>
<tr>
<td>Patients aged ≥80 years</td>
<td>daily dose of 220 mg Pradaxa taken as one 110 mg capsule twice daily</td>
</tr>
<tr>
<td>Patients who receive concomitant verapamil</td>
<td></td>
</tr>
<tr>
<td><strong>Dose reduction for consideration</strong></td>
<td></td>
</tr>
<tr>
<td>Patients between 75-80 years</td>
<td></td>
</tr>
<tr>
<td>Patients with moderate renal impairment (CrCL 30-50 mL/min)</td>
<td>daily dose of Pradaxa of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding</td>
</tr>
<tr>
<td>Patients with gastritis, esophagitis or gastroesophageal reflux</td>
<td></td>
</tr>
<tr>
<td>Other patients at increased risk of bleeding</td>
<td></td>
</tr>
</tbody>
</table>

For DVT/PE the recommendation for the use of Pradaxa 220 mg taken as one 110 mg capsule twice daily is based on pharmacokinetic and pharmacodynamic analyses and has not been studied in this clinical setting. See further down and sections 4.4, 4.5, 5.1 and 5.2.

In case of intolerability to Pradaxa, patients should be instructed to immediately consult their treating physician in order to be switched to alternate acceptable treatment options for prevention of stroke and systemic embolism associated with atrial fibrillation or for DVT/PE.

**Assessment of renal function prior to and during Pradaxa treatment**

In all patients and especially in the elderly (>75 years), as renal impairment may be frequent in this age group:

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

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

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

The method to be used to estimate renal function (CrCL in mL/min) is the Cockcroft-Gault method.
**Duration of use**

The duration of use of Pradaxa in the indications SPAF, DVT and PE are shown in table 2.

**Table 2: Duration of use for SPAF and DVT/PE**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Duration of use</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPAF</td>
<td>Therapy should be continued long term.</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4). Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.</td>
</tr>
</tbody>
</table>

**Missed dose**

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

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

**Discontinuation of Pradaxa**

Pradaxa treatment should not be discontinued without medical advice. Patients should be instructed to contact the treating physician if they develop gastrointestinal symptoms such as dyspepsia (see section 4.8).

**Switching**

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

Parenteral anticoagulants to Pradaxa:
The parenteral anticoagulant should be discontinued and Pradaxa should be started 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous Unfractionated Heparin (UFH)) (see section 4.5).

Pradaxa treatment to Vitamin K antagonists (VKA):
The starting time of the VKA should be adjusted based on CrCL as follows:
- CrCL ≥ 50 mL/min, VKA should be started 3 days before discontinuing Pradaxa
- CrCL ≥ 30-< 50 mL/min, VKA should be started 2 days before discontinuing Pradaxa

Because Pradaxa can impact the International Normalized Ratio (INR), the INR will better reflect VKA’s effect only after Pradaxa has been stopped for at least 2 days. Until then, INR values should be interpreted with caution.

VKA to Pradaxa:
The VKA should be stopped. Pradaxa can be given as soon as the INR is < 2.0.

**Cardioversion**

Patients can stay on Pradaxa while being cardioverted.
Catheter ablation for atrial fibrillation (SPAF)

Catheter ablation can be conducted in patients on 150 mg twice daily Pradaxa treatment. Pradaxa treatment does not need to be interrupted (see section 5.1).

Special populations

Elderly

For dose modifications in this population see table 1 above.

Patients at risk of bleeding

Patients with an increased bleeding risk (see sections 4.4, 4.5, 5.1 and 5.2) should be closely monitored clinically (looking for signs of bleeding or anaemia). Dose adjustment should be decided at the discretion of the physician, following assessment of the potential benefit and risk to an individual patient (see table 1 above). A coagulation test (see section 4.4) may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. When excessive dabigatran exposure is identified in patients at high risk of bleeding, a reduced dose of 220 mg taken as one 110 mg capsule twice daily is recommended. When clinically relevant bleeding occurs, treatment should be interrupted.

For subjects with gastritis, esophagitis, or gastroesophageal reflux, a dose reduction may be considered due to the elevated risk of major gastro-intestinal bleeding (see table 1 above and section 4.4).

Renal impairment

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

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

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

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

Dose reductions are recommended for patients who receive concomitantly verapamil (see table 1 above and sections 4.4 and 4.5). In this situation Pradaxa and verapamil should be taken at the same time.

Weight

No dose adjustment is necessary (see section 5.2), but close clinical surveillance is recommended in patients with a body weight < 50 kg (see section 4.4).

Gender

No dose adjustment is necessary (see section 5.2).
**Paediatric population**

There is no relevant use of Pradaxa in the paediatric population for the indication of prevention of stroke and systemic embolism in patients with NVAF.

For the indication DVT/PE, the safety and efficacy of Pradaxa in children from birth to less than 18 years of age have not yet been established. Currently available data are described in section 4.8 and 5.1, but no recommendation on a posology can be made.

**Method of administration**

Pradaxa is for oral use. The capsules can be taken with or without food. Pradaxa should be swallowed as a whole with a glass of water, to facilitate delivery to the stomach. 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
- Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5)
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with the following strong P-gp inhibitors: systemic ketoconazole, cyclosporine, itraconazole and dronedarone (see section 4.5)
- Prosthetic heart valves requiring anticoagulant treatment (see section 5.1).

**4.4 Special warnings and precautions for use**

**Haemorrhagic risk**

Pradaxa should be used with caution in conditions with an increased risk of bleeding or with concomitant use of medicinal products affecting haemostasis by inhibition of platelet aggregation. Bleeding can occur at any site during therapy with Pradaxa. An unexplained fall in haemoglobin and/or haematocrit or blood pressure should lead to a search for a bleeding site.

For situations of life-threatening or uncontrolled bleeding, when rapid reversal of the anticoagulation effect of dabigatran is required, the specific reversal agent (Praxbind, idarucizumab) is available (see section 4.9).

In clinical trials, Pradaxa was associated with higher rates of major gastrointestinal (GI) bleeding. An increased risk was seen in the elderly (≥ 75 years) for the 150 mg twice daily dose regimen. Further risk factors (see also table 3) comprise co-medication with platelet aggregation inhibitors such as clopidogrel and acetylsalicylic acid (ASA) or non steroidal antiinflammatory drugs (NSAID), as well as the presence of esophagitis, gastritis or gastroesophageal reflux.
Risk factors

Table 3 summarises factors which may increase the haemorrhagic risk.

Table 3: Risk 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>• Strong P-gp inhibitors (see section 4.3 and 4.5)</td>
</tr>
<tr>
<td></td>
<td>• Mild to moderate P-gp inhibitor co-medication (e.g. amiodarone, verapamil, quinidine and ticagrelor; see section 4.5)</td>
</tr>
<tr>
<td></td>
<td>Minor:</td>
</tr>
<tr>
<td></td>
<td>• Low body weight (&lt; 50 kg)</td>
</tr>
<tr>
<td>Pharmacodynamic interactions (see section 4.5)</td>
<td>• ASA and other platelet aggregation inhibitors such as clopidogrel</td>
</tr>
<tr>
<td></td>
<td>• NSAID</td>
</tr>
<tr>
<td></td>
<td>• SSRIs or SNRIs</td>
</tr>
<tr>
<td></td>
<td>• Other medicinal products which may impair haemostasis</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>• Recent biopsy, major trauma</td>
</tr>
<tr>
<td></td>
<td>• Bacterial endocarditis</td>
</tr>
<tr>
<td></td>
<td>• Esophagitis, gastritis or gastroesophageal reflux</td>
</tr>
</tbody>
</table>

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

Precautions and management of the haemorrhagic risk

For the management of bleeding complications, see also section 4.9.

Benefit-risk assessment

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

Close clinical surveillance

Close observation for signs of bleeding or anaemia is recommended throughout the treatment period, especially if risk factors are combined (see table 3 above). Particular caution should be exercised when Pradaxa is co-administered with verapamil, amiodarone, quinidine or clarithromycin (P-gp inhibitors) and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment (see section 4.5).

Close observation for signs of bleeding is recommended in patients concomitantly treated with NSAIDs (see section 4.5).
Discontinuation of Pradaxa

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

When severe bleedings occur, treatment must be discontinued, the source of bleeding investigated and use of the specific reversal agent Praxbind (idarucizumab) may be considered (see section 4.9 Management of bleeding complications).

Dose reduction

A dose reduction should be either considered or is recommended as indicated in section 4.2.

Use of proton-pump inhibitors

The administration of a proton-pump inhibitor (PPI) can be considered to prevent GI bleeding.

Laboratory coagulation parameters

Although Pradaxa does not in general require routine anticoagulant monitoring, the measurement of dabigatran related anticoagulation may be helpful to detect excessive high exposure to dabigatran in the presence of additional risk factors.

Diluted thrombin time (dTT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information, but results should be interpreted with caution due to inter-test variability (see section 5.1). The International Normalised Ratio (INR) test is unreliable in patients on Pradaxa and false positive INR elevations have been reported. Therefore, INR tests should not be performed.

Table 4 shows coagulation test thresholds at trough that may be associated with an increased risk of bleeding (see section 5.1).

Table 4: Coagulation test thresholds at trough that may be associated with an increased risk of bleeding.

<table>
<thead>
<tr>
<th>Test (trough value)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>dTT [ng/mL]</td>
<td>SPAF and DVT/PE</td>
</tr>
<tr>
<td>ECT [x-fold upper limit of normal]</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>aPTT [x-fold upper limit of normal]</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>INR</td>
<td>Should not be performed</td>
</tr>
</tbody>
</table>

Use of fibrinolytic medicinal products for the treatment of acute ischemic stroke

The use of fibrinolytic medicinal products for the treatment of acute ischemic stroke may be considered if the patient presents with a dTT, ECT or aPTT not exceeding the upper limit of normal (ULN) according to the local reference range.

Surgery and interventions

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

Patients can stay on Pradaxa while being cardioverted. Pradaxa treatment (150 mg twice daily) does not need to be interrupted in patients undergoing catheter ablation for atrial fibrillation (see section 4.2).

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.

**Emergency surgery or urgent procedures**

Pradaxa should be temporarily discontinued. When rapid reversal of the anticoagulation effect is required the specific reversal agent (Praxbind, idarucizumab) to Pradaxa is available.

Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Pradaxa treatment can be re-initiated 24 hours after administration of Praxbind (idarucizumab), if the patient is clinically stable and adequate haemostasis has been achieved.

**Subacute surgery/interventions**

Pradaxa should be temporarily discontinued. A surgery / intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed the risk of bleeding may be increased. This risk of bleeding should be weighed against the urgency of intervention.

**Elective surgery**

If possible, Pradaxa should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete haemostasis may be required consider stopping Pradaxa 2-4 days before surgery.

Table 5 summarises discontinuation rules before invasive or surgical procedures.

**Table 5: 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>Pradaxa should be stopped 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>

**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 Pradaxa. These patients require frequent observation for neurological signs and symptoms of spinal or epidural haematoma.

**Postoperative phase**

Pradaxa should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established.

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

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

Hepatic impairment

Patients with elevated liver enzymes > 2 ULN were excluded in the main trials. No treatment experience is available for this subpopulation of patients, and therefore the use of Pradaxa is not recommended for this population. Hepatic impairment or liver disease expected to have any impact on survival is contraindicated (see section 4.3).

Interaction with P-gp inducers

Concomitant administration of P-gp inducers is expected to result in decreased dabigatran plasma concentrations, and should be avoided (see sections 4.5 and 5.2).

Myocardial Infarction (MI)

In the phase III study RE-LY (SPAF, see section 5.1) the overall rate of MI was 0.82, 0.81, and 0.64 % / year for dabigatran etexilate 110 mg twice daily, dabigatran etexilate 150 mg twice daily and warfarin, respectively, an increase in relative risk for dabigatran of 29 % and 27 % compared to warfarin. Irrespective of therapy, the highest absolute risk of MI was seen in the following subgroups, with similar relative risk: patients with previous MI, patients ≥ 65 years with either diabetes or coronary artery disease, patients with left ventricular ejection fraction < 40 %, and patients with moderate renal dysfunction. Furthermore a higher risk of MI was seen in patients concomitantly taking ASA plus clopidogrel or clopidogrel alone.

In the three active controlled DVT/PE phase III studies, a higher rate of MI was reported in patients who received dabigatran etexilate than in those who received warfarin: 0.4% vs. 0.2% in the short-term RE-COVER and RE-COVER II studies; and 0.8% vs. 0.1% in the long-term RE-MEDY trial. The increase was statistically significant in this study (p=0.022).

In the RE-SONATE study, which compared dabigatran etexilate to placebo, the rate of MI was 0.1% for patients who received dabigatran etexilate and 0.2% for patients who received placebo

Active Cancer Patients (DVT/PE)

The efficacy and safety have not been established for DVT/PE patients with active cancer.

4.5 Interaction with other medicinal products and other forms of interaction

Transporter interactions

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors (see table 6) 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. Dose reductions may be required in combination with some P-gp inhibitors (see sections 4.2, 4.3, 4.4 and 5.1).

Table 6: Transporter interactions

<table>
<thead>
<tr>
<th>P-gp inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant use contraindicated (see section 4.3)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td><strong>Ketoconazole</strong></td>
</tr>
<tr>
<td><strong>Dronedarone</strong></td>
</tr>
<tr>
<td><strong>Itraconazole, cyclosporine</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concomitant use not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tacrolimus</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cautions to be exercised in case concomitant use (see sections 4.2 and 4.4)</th>
</tr>
</thead>
</table>
| **Verapamil** | When dabigatran etexilate (150 mg) was co-administered with oral verapamil, the \(C_{\text{max}}\) and AUC of dabigatran were increased but the magnitude of this change differs depending on timing of administration and formulation of verapamil (see sections 4.2 and 4.4).  

The greatest elevation of dabigatran exposure was observed with the first dose of an immediate release formulation of verapamil administered one hour prior to the dabigatran etexilate intake (increase of \(C_{\text{max}}\) by about 2.8-fold and AUC by about 2.5-fold). The effect was progressively decreased with administration of an extended release formulation (increase of \(C_{\text{max}}\) by about 1.9-fold and AUC by about 1.7-fold) or administration of multiple doses of verapamil (increase of \(C_{\text{max}}\) by about 1.6-fold and AUC by about 1.5-fold).  

There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increase of \(C_{\text{max}}\) by about 1.1-fold and AUC by about 1.2-fold). This is explained by completed dabigatran absorption after 2 hours. |
| **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 \(C_{\text{max}}\) were increased by about 1.6-fold and 1.5-fold, respectively. In view of the long half-life of amiodarone the potential for an interaction may exist for weeks after discontinuation of amiodarone (see sections 4.2 and 4.4). |
| **Quinidine** | Quinidine was given as 200 mg dose every 2nd hour up to a total dose of 1,000 mg. Dabigatran etexilate was given twice daily over 3 consecutive days, on the 3rd day either with or without quinidine. Dabigatran AUC\(_{\text{τ,ss}}\) and \(C_{\text{max,ss}}\) were increased on average by 1.53-fold and 1.56-fold, respectively with concomitant quinidine (see sections 4.2 and 4.4). |
| **Clarithromycin** | When clarithromycin (500 mg twice daily) was administered together with dabigatran etexilate in healthy volunteers, increase of AUC by about 1.19-fold and \(C_{\text{max}}\) by about 1.15-fold was observed. |
| **Ticagrelor** | When a single dose of 75 mg dabigatran etexilate was coadministered simultaneously with a loading dose of 180 mg ticagrelor, the dabigatran AUC and \(C_{\text{max}}\) were increased by 1.73-fold and 1.95-fold, respectively. After multiple doses |
of ticagrelor 90 mg b.i.d. the increase of dabigatran exposure is 1.56-fold and 1.46-fold for $C_{\text{max}}$ and AUC, respectively.

Concomitant administration of a loading dose of 180 mg ticagrelor and 110 mg dabigatran etexilate (in steady state) increased the dabigatran AUC$_{\text{τ,ss}}$ and $C_{\text{max,ss}}$ by 1.49-fold and 1.65-fold, respectively, compared with dabigatran etexilate given alone. When a loading dose of 180 mg ticagrelor was given 2 hours after 110 mg dabigatran etexilate (in steady state), the increase of dabigatran AUC$_{\text{τ,ss}}$ and $C_{\text{max,ss}}$ was reduced to 1.27-fold and 1.23-fold, respectively, compared with dabigatran etexilate given alone. This staggered intake is the recommended administration for start of ticagrelor with a loading dose.

Concomitant administration of 90 mg ticagrelor b.i.d. (maintenance dose) with 110 mg dabigatran etexilate increased the adjusted dabigatran AUC$_{\text{τ,ss}}$ and $C_{\text{max,ss}}$ 1.26-fold and 1.29-fold, respectively, compared with dabigatran etexilate given alone.

Posaconazole

Posaconazole also inhibits P-gp to some extent but has not been clinically studied. Caution should be exercised when Pradaxa is co-administered with posaconazole.

### P-gp inducers

**Concomitant use should be avoided.**

- e.g. rifampicin, St. John’s wort (Hypericum perforatum), carbamazepine, or phenytoin

Concomitant administration is expected to result in decreased dabigatran concentrations.

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.

### Protease inhibitors such as ritonavir

**Concomitant use not recommended**

- e.g. ritonavir and its combinations with other protease inhibitors

These 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 clinically relevant changes on dabigatran exposure have been observed.

### Anticoagulants and antiplatelet aggregation medicinal products

There is no or only limited experience with the following treatments which may increase the risk of bleeding when used concomitantly with Pradaxa: anticoagulants such as unfractionated heparin (UFH), low molecular weight heparins (LMWH), and heparin derivatives (fondaparinux, desirudin), thrombolytic medicinal products, and vitamin K antagonists, rivaroxaban or other oral anticoagulants.
(see section 4.3), and antiplatelet aggregation medicinal products such as GPIIb/IIIa receptor antagonists, ticlopidine, prasugrel, ticagrelor, dextran, and sulfipyrazone (see section 4.4).

From the data collected in the phase III study RE-LY (see section 5.1) it was observed that the concomitant use of other oral or parenteral anticoagulants increases major bleeding rates with both dabigatran etexilate and warfarin by approximately 2.5-fold, mainly related to situations when switching from one anticoagulant to another (see section 4.3). Furthermore, concomitant use of antiplatelets, ASA or clopidogrel approximately doubled major bleeding rates with both dabigatran etexilate and warfarin (see section 4.4).

UFH can be administered at doses necessary to maintain a patent central venous or arterial catheter (see section 4.3).

Table 7: Interactions with anticoagulants and antiplatelet aggregation medicinal products

<table>
<thead>
<tr>
<th>NSAIDs</th>
<th>NSAIDs given for short-term analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use in the RE-LY study, NSAIDs increased the risk of bleeding by approximately 50% on both dabigatran etexilate and warfarin.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>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(<em>{T,R}) and C(</em>{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(<em>{T,R}) and C(</em>{max,ss}) were increased by about 30-40% (see section 4.4).</td>
</tr>
<tr>
<td>ASA</td>
<td>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).</td>
</tr>
<tr>
<td>LMWH</td>
<td>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.</td>
</tr>
</tbody>
</table>

Other interactions

Table 8: Other interactions

<table>
<thead>
<tr>
<th>Selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs, SNRIs</td>
</tr>
<tr>
<td>SSRIs and SNRIs increased the risk of bleeding in RE-LY in all treatment groups,</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substances influencing gastric pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pantoprazole</td>
</tr>
<tr>
<td>When Pradaxa was co-administered with pantoprazole, a decrease in the dabigatran AUC 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.</td>
</tr>
</tbody>
</table>
Ranitidine administration together with Pradaxa had no clinically relevant effect on the extent of absorption of dabigatran.

Interactions linked to dabigatran etexilate and dabigatran metabolic profile

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

\textbf{4.6 Fertility, pregnancy and lactation}

Women of childbearing potential

Women of childbearing potential should avoid pregnancy during treatment with Pradaxa.

\textbf{Pregnancy}

There is limited amount of 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.

Pradaxa should not be used during pregnancy unless clearly necessary.

\textbf{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.

\textbf{Fertility}

No human data available.

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

\textbf{4.7 Effects on ability to drive and use machines}

Pradaxa has no or negligible influence on the ability to drive and use machines.

\textbf{4.8 Undesirable effects}

\textbf{Summary of the safety profile}

The safety of Pradaxa has been evaluated in a pivotal study investigating the prevention of stroke and systemic embolism in patients with atrial fibrillation, in two active controlled DVT/PE treatment trials and in one active controlled DVT/PE prevention trial. In these four phase III trials, 16,709 patients were exposed to Pradaxa (see Table 9).
Table 9: Number of patients studied, maximum daily dose in phase III studies

<table>
<thead>
<tr>
<th>Indication</th>
<th>Number of patients treated with Pradaxa</th>
<th>Maximum daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke and systemic embolism prevention in patients with atrial fibrillation</td>
<td>6,059 / 5,983</td>
<td>300 mg / 220 mg</td>
</tr>
<tr>
<td>DVT/PE treatment (RE-COVER, RE-COVER II)</td>
<td>2,553</td>
<td>300 mg</td>
</tr>
<tr>
<td>DVT/PE prevention (RE-MEDY, RE-SONATE)</td>
<td>2,114</td>
<td>300 mg</td>
</tr>
</tbody>
</table>

In total, 22% of patients with atrial fibrillation treated for the prevention of stroke and systemic embolism (long-term treatment for up to 3 years), 14% of patients treated for DVT/PE and 15% of patients treated for DVT/PE prevention experienced adverse reactions.

The most commonly reported events are bleedings occurring in approximately 16.6% in patients with atrial fibrillation treated long-term for the prevention of stroke and systemic embolism and in 14.4% of patients treated for DVT/PE. Furthermore, bleeding occurred in 19.4% of patients in the DVT/PE prevention trial RE-MEDY and in 10.5% of patients in the DVT/PE trial RE-SONATE.

Since the patient population treated in the three indications are not comparable and bleeding events are distributed over several System Organ Classes (SOC), a summary description of major and any bleeding are broken down by indication and are provided in tables 11-14 below.

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

Tabulated list of adverse reactions

Table 10 shows the adverse reactions identified from the study in prevention of thromboembolic stroke and systemic embolism in patients with atrial fibrillation, the studies in DVT/PE treatment and in DVT/PE prevention. They are ranked under headings of System Organ Class (SOC) and frequency using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 10: Adverse reactions

<table>
<thead>
<tr>
<th>SOC / Preferred term.</th>
<th>Stroke and systemic embolism prevention in patients with atrial fibrillation</th>
<th>DVT/PE treatment and DVT/PE prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Haemoglobin decreased</td>
<td>Uncommon</td>
<td>Not known</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Uncommon</td>
<td>Rare</td>
</tr>
<tr>
<td>Haematocrit decreased</td>
<td>Rare</td>
<td>Not known</td>
</tr>
<tr>
<td>Immune system disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Rash</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Condition</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>--------</td>
<td>----------</td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Angioedema</td>
<td>Rare</td>
<td>Rare</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>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>Uncommon</td>
<td>Rare</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>Respiratory, thoracic and mediastinal disorders</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>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Nausea</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Rectal haemorrhage</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Gastrorrhoidal haemorrhage</td>
<td>Uncommon</td>
<td>Uncommon</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>Rare</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic function abnormal/ Liver function Test abnormal</td>
<td>Uncommon</td>
<td>Uncommon</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 enzyme increased</td>
<td>Rare</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>Rare</td>
<td>Not known</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin haemorrhage</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemarthrosis</td>
<td>Rare</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genitourological haemorrhage, including haematuria</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>General disorders and administration site conditions</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>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic haemorrhage</td>
<td>Rare</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Incision site haemorrhage</td>
<td>Rare</td>
<td>Rare</td>
</tr>
</tbody>
</table>
Description of selected adverse reactions

Bleeding reactions

Due to the pharmacological mode of action, the use of Pradaxa may be associated with an increased risk of occult or overt bleeding from any tissue or organ. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia. In the clinical studies mucosal bleedings (e.g. gastrointestinal, genitourinary) were seen more frequently during long term Pradaxa treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit is of value to detect occult bleeding. The risk of bleedings may be increased in certain patient groups e.g. those patients with moderate renal impairment and/or on concomitant treatment affecting haemostasis or strong P-gp inhibitors (see section 4.4 Haemorrhagic risk). Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock.

Known bleeding complications such as compartment syndrome and acute renal failure due to hypoperfusion have been reported for Pradaxa. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient. A specific reversal agent for dabigatran, idarucizumab, is available in case of uncontrollable bleeding (see Section 4.9).

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

The table 11 shows bleeding events broken down to major and any bleeding in the pivotal study testing the prevention of thromboembolic stroke and systemic embolism in patients with atrial fibrillation.

Table 11: Bleeding events in a study testing the prevention of thromboembolic stroke and systemic embolism in patients with atrial fibrillation

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 110 mg twice daily</th>
<th>Pradaxa 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomized</td>
<td>6,015</td>
<td>6,076</td>
<td>6,022</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>347 (2.92 %)</td>
<td>409 (3.40 %)</td>
<td>426 (3.61 %)</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>27 (0.23 %)</td>
<td>39 (0.32 %)</td>
<td>91 (0.77 %)</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>134 (1.13 %)</td>
<td>192 (1.60 %)</td>
<td>128 (1.09 %)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>26 (0.22 %)</td>
<td>30 (0.25 %)</td>
<td>42 (0.36 %)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>1,566 (13.16 %)</td>
<td>1,787 (14.85 %)</td>
<td>1,931 (16.37 %)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>1,759 (14.78 %)</td>
<td>1,997 (16.60 %)</td>
<td>2,169 (18.39 %)</td>
</tr>
</tbody>
</table>

Subjects randomized to Pradaxa 110 mg twice daily or 150 mg twice daily had a significantly lower risk for life-threatening bleeds and intracranial bleeding compared to warfarin [p < 0.05]. Both dose strengths of Pradaxa had also a statistically significant lower total bleed rate. Subjects randomized to 110 mg Pradaxa twice daily had a significantly lower risk for major bleeds compared with warfarin (hazard ratio 0.81 [p=0.0027]). Subjects randomized to 150 mg Pradaxa twice daily had a significantly higher risk for major GI bleeds compared with warfarin (hazard ratio 1.48 [p=0.0005]). This effect was seen primarily in patients ≥ 75 years.

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

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (DVT/PE) treatment

76
Table 12 shows bleeding events in the pooled pivotal studies RE-COVER and RE-COVER II testing the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). In the pooled studies the primary safety endpoints of major bleeding, major or clinically relevant bleeding and any bleeding were significantly lower than warfarin at a nominal alpha level of 5%.

**Table 12: Bleeding events in the studies RE-COVER and RE-COVER II testing the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)**

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 150 mg twice daily</th>
<th>Warfarin</th>
<th>Hazard ratio vs. warfarin (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients included in safety analysis</td>
<td>2,456</td>
<td>2,462</td>
<td></td>
</tr>
<tr>
<td>Major bleeding events</td>
<td>24 (1.0%)</td>
<td>40 (1.6%)</td>
<td>0.60 (0.36, 0.99)</td>
</tr>
<tr>
<td>Intracranial Bleeding</td>
<td>2 (0.1%)</td>
<td>4 (0.2%)</td>
<td>0.50 (0.09, 2.74)</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>10 (0.4%)</td>
<td>12 (0.5%)</td>
<td>0.83 (0.36, 1.93)</td>
</tr>
<tr>
<td>Life-threatening bleed</td>
<td>4 (0.2%)</td>
<td>6 (0.2%)</td>
<td>0.66 (0.19, 2.36)</td>
</tr>
<tr>
<td>Major bleeding events/clinically relevant bleeds</td>
<td>109 (4.4%)</td>
<td>189 (7.7%)</td>
<td>0.56 (0.45, 0.71)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>354 (14.4%)</td>
<td>503 (20.4%)</td>
<td>0.67 (0.59, 0.77)</td>
</tr>
<tr>
<td>Any GI bleeding</td>
<td>70 (2.9%)</td>
<td>55 (2.2%)</td>
<td>1.27 (0.90, 1.82)</td>
</tr>
</tbody>
</table>

Bleeding events for both treatments are counted from the first intake of Pradaxa or warfarin after the parenteral therapy has been discontinued (oral only treatment period). This includes all bleeding events, which occurred during Pradaxa therapy. All bleeding events which occurred during warfarin therapy are included except for those during the overlap period between warfarin and parenteral therapy.

Table 13 shows bleeding events in pivotal study RE-MEDY testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE). Some bleeding events (MBEs/CRBEs; any bleeding) were significantly lower at a nominal alpha level of 5% in patients receiving Pradaxa as compared with those receiving warfarin.

**Table 13: Bleeding events in study RE-MEDY testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE)**

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 150 mg twice daily</th>
<th>Warfarin</th>
<th>Hazard ratio vs. warfarin (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated patients</td>
<td>1,430</td>
<td>1,426</td>
<td></td>
</tr>
<tr>
<td>Major bleeding events</td>
<td>13 (0.9%)</td>
<td>25 (1.8%)</td>
<td>0.54 (0.25, 1.16)</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>2 (0.1%)</td>
<td>4 (0.3%)</td>
<td>Not calculable*</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>4 (0.3%)</td>
<td>8 (0.5%)</td>
<td>Not calculable*</td>
</tr>
<tr>
<td>Life-threatening bleed</td>
<td>1 (0.1%)</td>
<td>3 (0.2%)</td>
<td>Not calculable*</td>
</tr>
<tr>
<td>Major bleeding events/clinically relevant bleeds</td>
<td>80 (5.6%)</td>
<td>145 (10.2%)</td>
<td>0.55 (0.41, 0.72)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>278 (19.4%)</td>
<td>373 (26.2%)</td>
<td>0.71 (0.61, 0.83)</td>
</tr>
<tr>
<td>Any GI bleeds</td>
<td>45 (3.1%)</td>
<td>32 (2.2%)</td>
<td>1.39 (0.87, 2.20)</td>
</tr>
</tbody>
</table>
Table 14 shows bleeding events in pivotal study RE-SONATE testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE). The rate of the combination of MBEs/CRBEs and the rate of any bleeding was significantly lower at a nominal alpha level of 5% in patients receiving placebo as compared with those receiving Pradaxa.

**Table 14: Bleeding events in study RE-SONATE testing prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE)**

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 150 mg twice daily</th>
<th>Placebo</th>
<th>Hazard ratio vs placebo (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated patients</td>
<td>684</td>
<td>659</td>
<td></td>
</tr>
<tr>
<td>Major bleeding events</td>
<td>2 (0.3%)</td>
<td>0</td>
<td>Not calculable*</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0</td>
<td>0</td>
<td>Not calculable*</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>2 (0.3%)</td>
<td>0</td>
<td>Not calculable*</td>
</tr>
<tr>
<td>Life-threatening bleeds</td>
<td>0</td>
<td>0</td>
<td>Not calculable*</td>
</tr>
<tr>
<td>Major bleeding event/clinical relevant bleeds</td>
<td>36 (5.3%)</td>
<td>13 (2.0%)</td>
<td>2.69 (1.43, 5.07)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>72 (10.5%)</td>
<td>40 (6.1%)</td>
<td>1.77 (1.20, 2.61)</td>
</tr>
<tr>
<td>Any GI bleeds</td>
<td>5 (0.7%)</td>
<td>2 (0.3%)</td>
<td>2.38 (0.46, 12.27)</td>
</tr>
</tbody>
</table>

*HR not estimable as there is no event in either one treatment

**Paediatric population (DVT/PE)**

In the clinical study 1160.88 in total, 9 adolescent patients (age 12 to < 18 years) with diagnosis of primary VTE received an initial oral dose of dabigatran etexilate of 1.71 (± 10 %) mg/kg bodyweight. Based on dabigatran concentrations as determined by the diluted thrombin time test and clinical assessment, the dose was adjusted to the target dose of 2.14 (± 10%) mg/kg bodyweight of dabigatran etexilate. On treatment 2 (22.1 %) patients experienced mild related adverse events (gastrooesophageal reflux / abdominal pain; abdominal discomfort) and 1 (11.1 %) patient experienced a not related serious adverse event (recurrent VTE of the leg) in the post treatment period > 3 days after stop of dabigatran etexilate.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

**4.9 Overdose**

Pradaxa doses 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. Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. As protein binding is low,
dabigatran can be dialysed; there is limited clinical experience to demonstrate the utility of this approach in clinical studies (see section 5.2).

Management of bleeding complications

In the event of haemorrhagic complications, Pradaxa treatment must be discontinued and the source of bleeding investigated. Depending on the clinical situation appropriate supportive treatment, such as surgical haemostasis and blood volume replacement, should be undertaken at the prescriber’s discretion.

For situations when rapid reversal of the anticoagulant effects of Pradaxa is required the specific reversal agent (Praxbind, idarucizumab) antagonizing the pharmacodynamic effect of Pradaxa is available (see section 4.4).

Coagulation factor concentrates (activated or non-activated) or recombinant Factor VIIa may be taken into account. There is some experimental evidence to support the role of these medicinal products in reversing the anticoagulant effect of dabigatran, but data on their usefulness in clinical settings and also on the possible risk of rebound thromboembolism is very limited. Coagulation tests may become unreliable following administration of suggested coagulation factor concentrates. Caution should be exercised when interpreting these tests. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long acting antiplatelet medicinal products have been used. All symptomatic treatment should be given according to the physician's judgement.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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 inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

Pharmacodynamic effects

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

There is a clear correlation between plasma dabigatran concentration and degree of anticoagulant effect based on phase II studies. Dabigatran prolongs the thrombin time (TT), ECT, and aPTT.

The calibrated quantitative diluted TT (dTT) test provides an estimation of dabigatran plasma concentration that can be compared to the expected dabigatran plasma concentrations. When the calibrated dTT assay delivers a dabigatran plasma concentration result at or below the limit of quantification, an additional coagulation assay such as TT, ECT or aPTT should be considered.
The ECT can provide a direct measure of the activity of direct thrombin inhibitors.

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

In general, it can be assumed that these measures of anti-coagulant activity may reflect dabigatran levels and can provide guidance for the assessment of bleeding risk, i.e. exceeding the 90th percentile of dabigatran trough levels or a coagulation assay such as aPTT measured at trough (for aPTT thresholds see section 4.4, table 4) is considered to be associated with an increased risk of bleeding.

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

For patients with NVAF treated for prevention of stroke and systemic embolism with 150 mg dabigatran etexilate twice daily,

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

In patients treated for DVT and PE with 150 mg dabigatran etexilate twice daily, the dabigatran geometric mean trough concentration, measured within 10–16 hours after dose, at the end of the dosing interval (i.e. 12 hours after the 150 mg dabigatran evening dose), was 59.7 ng/ml, with a range of 38.6 - 94.5 ng/ml (25th-75th percentile range). For treatment of DVT and PE, with dabigatran etexilate 150 mg twice daily,

- the 90th percentile of dabigatran plasma concentrations measured at trough (10-16 hours after the previous dose) was about 146 ng/ml,
- an ECT at trough (10-16 hours after the previous dose), elevated approximately 2.3-fold compared to baseline refers to the observed 90th percentile of ECT prolongation of 74 seconds,
- the 90th percentile of aPTT at trough (10-16 hours after the previous dose) was 62 seconds, which would be 1.8-fold compared to baseline.

In patients treated for prevention of recurrent of DVT and PE with 150 mg dabigatran etexilate twice daily no pharmacokinetic data are available.

Clinical efficacy and safety

Ethnic origin

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

Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors

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

In the RE-LY study, a total of 18,113 patients were randomized, with a mean age of 71.5 years and a mean CHADS$_2$ score of 2.1. The patient population was 64% male, 70% Caucasian and 16% Asian. For patients randomized to warfarin, the mean percentage within time in therapeutic range (TTR) (INR 2-3) was 64.4% (median TTR 67%).

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

Tables 15-17 display details of key results in the overall population:

**Table 15**: Analysis of first occurrence of stroke or systemic embolism (primary endpoint) during the study period in RE-LY.

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 110 mg twice daily</th>
<th>Pradaxa 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomized</td>
<td>6,015</td>
<td>6,076</td>
<td>6,022</td>
</tr>
<tr>
<td>Stroke and/or systemic embolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidences (%)</td>
<td>183 (1.54)</td>
<td>135 (1.12)</td>
<td>203 (1.72)</td>
</tr>
<tr>
<td>Hazard ratio over warfarin (95% CI)</td>
<td>0.89 (0.73, 1.09)</td>
<td>0.65 (0.52, 0.81)</td>
<td></td>
</tr>
<tr>
<td>p value superiority</td>
<td>p=0.2721</td>
<td>p=0.0001</td>
<td></td>
</tr>
</tbody>
</table>

% refers to yearly event rate

**Table 16**: Analysis of first occurrence of ischemic or haemorrhagic strokes during the study period in RE-LY.

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 110 mg twice daily</th>
<th>Pradaxa 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomized</td>
<td>6,015</td>
<td>6,076</td>
<td>6,022</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidences (%)</td>
<td>171 (1.44)</td>
<td>123 (1.02)</td>
<td>187 (1.59)</td>
</tr>
<tr>
<td>Hazard ratio vs. warfarin (95% CI)</td>
<td>0.91 (0.74, 1.12)</td>
<td>0.64 (0.51, 0.81)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.3553</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Systemic embolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidences (%)</td>
<td>15 (0.13)</td>
<td>13 (0.11)</td>
<td>21 (0.18)</td>
</tr>
<tr>
<td>Hazard ratio vs. warfarin (95% CI)</td>
<td>0.71 (0.37, 1.38)</td>
<td>0.61 (0.30, 1.21)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.3099</td>
<td>0.1582</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidences (%)</td>
<td>152 (1.28)</td>
<td>104 (0.86)</td>
<td>134 (1.14)</td>
</tr>
<tr>
<td>Hazard ratio vs.</td>
<td>1.13 (0.89, 1.42)</td>
<td>0.76 (0.59, 0.98)</td>
<td></td>
</tr>
</tbody>
</table>
warfarin (95 % CI) | p-value | p-value |
--- | --- | --- |
Haemorrhagic stroke | | |
Incidences (%) | 14 (0.12) | 12 (0.10) | 45 (0.38) |
Hazard ratio vs. warfarin (95 % CI) | 0.31 (0.17, 0.56) | 0.26 (0.14, 0.49) |
p-value | 0.0001 | < 0.0001 |

% refers to yearly event rate

Table 17: Analysis of all cause and cardiovascular survival during the study period in RE-LY.

<table>
<thead>
<tr>
<th>Subjects randomized</th>
<th>Pradaxa 110 mg twice daily</th>
<th>Pradaxa 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidences (%)</td>
<td>446 (3.75)</td>
<td>438 (3.64)</td>
<td>487 (4.13)</td>
</tr>
<tr>
<td>Hazard ratio vs. warfarin (95 % CI)</td>
<td>0.91 (0.80, 1.03)</td>
<td>0.88 (0.77, 1.00)</td>
<td></td>
</tr>
</tbody>
</table>
p-value | 0.1308 | 0.0517 |
| Vascular mortality | | | |
| Incidences (%) | 289 (2.43) | 274 (2.28) | 317 (2.69) |
| Hazard ratio vs. warfarin (95 % CI) | 0.90 (0.77, 1.06) | 0.85 (0.72, 0.99) |
p-value | 0.2081 | 0.0430 |

% refers to yearly event rate

Tables 18-19 display results of the primary efficacy and safety endpoint in relevant sub-populations:

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

Table 18: Hazard Ratio and 95 % CI for stroke/systemic embolism by subgroups

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Pradaxa 110 mg twice daily vs. warfarin</th>
<th>Pradaxa 150 mg twice daily vs. warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>1.10 (0.64, 1.87)</td>
<td>0.51 (0.26, 0.98)</td>
</tr>
<tr>
<td>65 ≤ and &lt; 75</td>
<td>0.86 (0.62, 1.19)</td>
<td>0.67 (0.47, 0.95)</td>
</tr>
<tr>
<td>≥ 75</td>
<td>0.88 (0.66, 1.17)</td>
<td>0.68 (0.50, 0.92)</td>
</tr>
<tr>
<td>≥ 80</td>
<td>0.68 (0.44, 1.05)</td>
<td>0.67 (0.44, 1.02)</td>
</tr>
<tr>
<td>CrCl(mL/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 ≤ and &lt; 50</td>
<td>0.89 (0.61, 1.31)</td>
<td>0.48 (0.31, 0.76)</td>
</tr>
<tr>
<td>50 ≤ and &lt; 80</td>
<td>0.91 (0.68, 1.20)</td>
<td>0.65 (0.47, 0.88)</td>
</tr>
<tr>
<td>≥ 80</td>
<td>0.81 (0.51, 1.28)</td>
<td>0.69 (0.43, 1.12)</td>
</tr>
</tbody>
</table>

For the primary safety endpoint of major bleeding there was an interaction of treatment effect and age. The relative risk of bleeding with dabigatran compared to warfarin increased with age. Relative risk was highest in patients ≥ 75 years. The concomitant use of antiplatelets ASA or clopidogrel approximately doubles MBE rates with both dabigatran and warfarin. There was no significant interaction of treatment effects with the subgroups of renal function and CHADS2 score.
Table 19: Hazard Ratio and 95 % CI for major bleeds by subgroups

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Pradaxa 110 mg twice daily vs. warfarin</th>
<th>Pradaxa 150 mg twice daily vs. warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>0.32 (0.18, 0.57)</td>
<td>0.35 (0.20, 0.61)</td>
</tr>
<tr>
<td>65 ≤ and &lt; 75</td>
<td>0.71 (0.56, 0.89)</td>
<td>0.82 (0.66, 1.03)</td>
</tr>
<tr>
<td>≥ 75</td>
<td>1.01 (0.84, 1.23)</td>
<td>1.19 (0.99, 1.43)</td>
</tr>
<tr>
<td>≥ 80</td>
<td>1.14 (0.86, 1.51)</td>
<td>1.35 (1.03, 1.76)</td>
</tr>
<tr>
<td>CrCL (mL/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 ≤ and &lt; 50</td>
<td>1.02 (0.79, 1.32)</td>
<td>0.94 (0.73, 1.22)</td>
</tr>
<tr>
<td>50 ≤ and &lt; 80</td>
<td>0.75 (0.61, 0.92)</td>
<td>0.90 (0.74, 1.09)</td>
</tr>
<tr>
<td>≥ 80</td>
<td>0.59 (0.43, 0.82)</td>
<td>0.87 (0.65, 1.17)</td>
</tr>
<tr>
<td>ASA use</td>
<td>0.84 (0.69, 1.03)</td>
<td>0.97 (0.79, 1.18)</td>
</tr>
<tr>
<td>Clopidogrel use</td>
<td>0.89 (0.55, 1.45)</td>
<td>0.92 (0.57, 1.48)</td>
</tr>
</tbody>
</table>

RELY-ABLE (Long term multi-center extension of dabigatran treatment in patients with atrial fibrillation who completed the RE-LY trial)

The RE-LY extension study (RELY-ABLE) provided additional safety information for a cohort of patients which continued the same dose of dabigatran etexilate as assigned in the RE-LY trial. Patients were eligible for the RELY-ABLE trial if they had not permanently discontinued study medication at the time of their final RE-LY study visit. Enrolled patients continued to receive the same double-blind dabigatran etexilate dose randomly allocated in RE-LY, for up to 43 months of follow up after RE-LY (total mean follow-up RE-LY + RELY-ABLE, 4.5 years). There were 5897 patients enrolled, representing 49 % of patients originally randomly assigned to receive dabigatran etexilate in RE-LY and 86 % of RELY-ABLE-eligible patients.

During the additional 2.5 years of treatment in RELY-ABLE, with a maximum exposure of over 6 years (total exposure in RELY + RELY-ABLE), the long-term safety profile of dabigatran etexilate was confirmed for both test doses 110 mg b.i.d. and 150 mg b.i.d.. No new safety findings were observed.

The rates of outcome events including, major bleed and other bleeding events were consistent with those seen in RE-LY.

Patients undergoing catheter ablation for atrial fibrillation

A prospective, randomized, open-label, multicenter, exploratory study with blinded, centrally adjudicated endpoint evaluation (RE-CIRCUIT) was conducted in 704 patients who were under stable anticoagulant treatment. The study compared 150 mg twice daily uninterrupted dabigatran etexilate with uninterrupted INR-adjusted warfarin in catheter ablation of paroxysmal or persistent atrial fibrillation. Of the 704 enrolled patients, 317 underwent atrial fibrillation ablation on uninterrupted dabigatran and 318 underwent atrial fibrillation ablation on uninterrupted warfarin. All patients underwent a Trans-oesophageal Echocardiography (TEE) prior to catheter ablation. The primary outcome (adjudicated major bleeding according to ISTH criteria) occurred in 5 (1.6 %) patients in the dabigatran etexilate group and 22 (6.9 %) patients in the warfarin group (risk difference −5.3%; 95% CI −8.4, −2.2; P=0.0009). There was no stroke/systemic embolism/TIA (composite) event in the dabigatran etexilate arm, and one event (TIA) in the warfarin arm from the time of ablation and until 8 weeks post-ablation. This exploratory study showed that dabigatran etexilate was associated with a significant reduction in MBE rate compared with INR-adjusted warfarin in the setting of ablation.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE treatment)

The efficacy and safety was investigated in two multi-center, randomised, double blind, parallel-group, replicate studies RE-COVER and RE-COVER II. These studies compared dabigatran etexilate (150 mg bid) with warfarin (target INR 2.0-3.0) in patients with acute DVT and/or PE. The primary objective of these studies was to determine if dabigatran etexilate was non-inferior to warfarin in
reducing the occurrence of the primary endpoint which was the composite of recurrent symptomatic DVT and/or PE and related deaths within the 6 month treatment period.

In the pooled RE-COVER and RE-COVER II studies, a total of 5,153 patients were randomised and 5,107 were treated.

The duration of treatment with fixed dose of dabigatran was 174.0 days without coagulation monitoring. For patients randomized to warfarin, the median time in therapeutic range (INR 2.0 to 3.0) was 60.6 %.

The trials, demonstrated that treatment with dabigatran etexilate 150 mg twice daily was non-inferior to the treatment with warfarin (non-inferiority margin for RE-COVER and RE-COVER II: 3.6 for risk difference and 2.75 for hazard ratio).

**Table 20: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the pooled studies RE-COVER and RE-COVER II**

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated patients</td>
<td>2,553</td>
<td>2,554</td>
</tr>
<tr>
<td>Recurrent symptomatic VTE and VTE-related death</td>
<td>68 (2.7%)</td>
<td>62 (2.4%)</td>
</tr>
<tr>
<td>Hazard ratio vs warfarin (95% confidence interval)</td>
<td>1.09 (0.77, 1.54)</td>
<td></td>
</tr>
<tr>
<td>Secondary efficacy endpoints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent symptomatic VTE and all-cause deaths</td>
<td>109 (4.3%)</td>
<td>104 (4.1%)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>3.52, 5.13</td>
<td>3.34, 4.91</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>45 (1.8%)</td>
<td>39 (1.5%)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>1.29, 2.35</td>
<td>1.09, 2.08</td>
</tr>
<tr>
<td>Symptomatic PE</td>
<td>27 (1.1%)</td>
<td>26 (1.0%)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.70, 1.54</td>
<td>0.67, 1.49</td>
</tr>
<tr>
<td>VTE-related deaths</td>
<td>4 (0.2%)</td>
<td>3 (0.1%)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.04, 0.40</td>
<td>0.02, 0.34</td>
</tr>
<tr>
<td>All-cause deaths</td>
<td>51 (2.0%)</td>
<td>52 (2.0%)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>1.49, 2.62</td>
<td>1.52, 2.66</td>
</tr>
</tbody>
</table>

Prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults (DVT/PE prevention)

Two randomized, parallel group, double-blind studies were performed in patients previously treated with anticoagulation therapy. RE-MEDY, warfarin controlled study, enrolled patients already treated for 3 to 12 months with the need for further anticoagulant treatment and RE-SONATE, the placebo controlled study, enrolled patients already treated for 6 to 18 months with Vitamin K inhibitors.
The objective of the RE-MEDY study was to compare the safety and efficacy of oral dabigatran etexilate (150 mg bid) to warfarin (target INR 2.0-3.0) for the long-term treatment and prevention of recurrent, symptomatic DVT and/or PE. A total of 2,866 patients were randomized and 2,856 patients were treated. Duration of dabigatran etexilate treatment ranged from 6 to 36 months (median 534.0 days). For patients randomized to warfarin, the median time in therapeutic range (INR 2.0-3.0) was 64.9 %.

RE-MEDY demonstrated that treatment with dabigatran etexilate 150 mg twice daily was non-inferior to warfarin (non-inferiority margin: 2.85 for hazard ratio and 2.8 for risk difference).

**Table 21: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the RE-MEDY study**

<table>
<thead>
<tr>
<th>Treated patients</th>
<th>Pradaxa 150 mg twice daily</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent symptomatic VTE and VTE-related death</td>
<td>26 (1.8 %)</td>
<td>18 (1.3 %)</td>
</tr>
<tr>
<td>Hazard ratio vs warfarin</td>
<td>1.44</td>
<td>(0.78, 2.64)</td>
</tr>
<tr>
<td>(95% confidence interval)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-inferiority margin</td>
<td>2.85</td>
<td></td>
</tr>
<tr>
<td>Patients with event at 18 months</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>Cumulative risk at 18 months (%)</td>
<td>1.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Risk difference vs. warfarin (%)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>95% confidence interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-inferiority margin</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Secondary efficacy endpoints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent symptomatic VTE and all-cause deaths</td>
<td>42 (2.9 %)</td>
<td>36 (2.5 %)</td>
</tr>
<tr>
<td>95 % confidence interval</td>
<td>2.12, 3.95</td>
<td>1.77, 3.48</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>17 (1.2 %)</td>
<td>13 (0.9 %)</td>
</tr>
<tr>
<td>95 % confidence interval</td>
<td>0.69, 1.90</td>
<td>0.49, 1.55</td>
</tr>
<tr>
<td>Symptomatic PE</td>
<td>10 (0.7 %)</td>
<td>5 (0.4 %)</td>
</tr>
<tr>
<td>95 % confidence interval</td>
<td>0.34, 1.28</td>
<td>0.11, 0.82</td>
</tr>
<tr>
<td>VTE-related deaths</td>
<td>1 (0.1 %)</td>
<td>1 (0.1 %)</td>
</tr>
<tr>
<td>95 % confidence interval</td>
<td>0.00, 0.39</td>
<td>0.00, 0.39</td>
</tr>
<tr>
<td>All-cause deaths</td>
<td>17 (1.2 %)</td>
<td>19 (1.3 %)</td>
</tr>
<tr>
<td>95 % confidence interval</td>
<td>0.69, 1.90</td>
<td>0.80, 2.07</td>
</tr>
</tbody>
</table>

The objective of the RE-SONATE study was to evaluate superiority of dabigatran etexilate versus placebo for the prevention of recurrent symptomatic DVT and/or PE in patients who had already completed 6 to 18 months of treatment with VKA. The intended therapy was 6 months dabigatran etexilate 150 mg twice daily without need for monitoring.

RE-SONATE demonstrated dabigatran etexilate was superior to placebo for the prevention of recurrent symptomatic DVT/PE events including unexplained deaths, with a risk reduction from 5.6 % to 0.4 % (relative risk reduction 92 % based on hazard ratio) during the treatment period (p<0.0001). All secondary and sensitivity analyses of the primary endpoint and all secondary endpoints showed superiority of dabigatran etexilate over placebo.

The study included observational follow-up for 12 months after the conclusion of treatment. After discontinuation of study medication the effect was maintained until the end of the follow-up, indicating that the initial treatment effect of dabigatran etexilate was sustained. No rebound effect was
observed. At the end of the follow-up VTE events in patients treated with dabigatran etexilate was 6.9 % vs. 10.7 % among the placebo group (hazard ratio 0.61 (95% CI 0.42, 0.88), p=0.0082).

Table 22: Analysis of the primary and secondary efficacy endpoints (VTE is a composite of DVT and/or PE) until the end of post-treatment period for the RE-SONATE study.

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa 150 mg twice daily</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated patients</td>
<td>681</td>
<td>662</td>
</tr>
<tr>
<td>Recurrent symptomatic VTE and related deaths</td>
<td>3 (0.4 %)</td>
<td>37 (5.6 %)</td>
</tr>
<tr>
<td>Hazard Ratio vs placebo (95% confidence interval)</td>
<td>0.08 (0.02, 0.25)</td>
<td></td>
</tr>
<tr>
<td>p-value for superiority</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Secondary efficacy endpoints</td>
<td>3 (0.4 %)</td>
<td>37 (5.6 %)</td>
</tr>
<tr>
<td>Recurrent symptomatic VTE and all-cause deaths</td>
<td>3 (0.4 %)</td>
<td>37 (5.6 %)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.09, 1.28</td>
<td>3.97, 7.62</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>2 (0.3 %)</td>
<td>23 (3.5 %)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.04, 1.06</td>
<td>2.21, 5.17</td>
</tr>
<tr>
<td>Symptomatic PE</td>
<td>1 (0.1 %)</td>
<td>14 (2.1 %)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.00, 0.82</td>
<td>1.16, 3.52</td>
</tr>
<tr>
<td>VTE-related deaths</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.00, 0.54</td>
<td>0.00, 0.56</td>
</tr>
<tr>
<td>Unexplained deaths</td>
<td>0 (0)</td>
<td>2 (0.3 %)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.00, 0.54</td>
<td>0.04, 1.09</td>
</tr>
<tr>
<td>All-cause deaths</td>
<td>0 (0)</td>
<td>2 (0.3 %)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.00, 0.54</td>
<td>0.04, 1.09</td>
</tr>
</tbody>
</table>

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

A phase II study examined dabigatran etexilate and warfarin in a total of 252 patients with recent mechanical valve replacement surgery (i.e. within the current hospital stay) and in patients who received a mechanical heart valve replacement more than three months ago. More thromboembolic events (mainly strokes and symptomatic/asymptomatic prosthetic valve thrombosis) and more bleeding events were observed with dabigatran etexilate than with warfarin. In the early post-operative patients, major bleeding manifested predominantly as haemorrhagic pericardial effusions, specifically in patients who started dabigatran etexilate early (i.e. on Day 3) after heart valve replacement surgery (see section 4.3).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Pradaxa in all subsets of the paediatric population for the granted indications (see section 4.2 for information on paediatric use).

The pharmacokinetics and pharmacodynamics of dabigatran etexilate administered twice daily for three consecutive days (total 6 doses) at the end of standard anticoagulant therapy were assessed in an open-label safety and tolerability study in 9 stable adolescents (12 to < 18 years). All patients received an initial oral dose of 1.71 (± 10 %) mg/kg of dabigatran etexilate (80 % of the adult dose of 150 mg/70 kg adjusted for the patient’s weight). Based on dabigatran concentrations and clinical assessment, the dose was subsequently modified to a target dose of 2.14 (± 10 %) mg/kg of dabigatran.
etexilate (100% of the adult dose adjusted for the patient’s weight). In this small number of
adolescents, dabigatran etexilate capsules were apparently tolerated with only three mild and transient
gastrointestinal adverse events reported by two patients. According to the relatively low exposure,
coagulation at 72 hrs (presumed dabigatran trough level at steady state or close to steady state
conditions) was only slightly prolonged with aPTT at maximum 1.60 fold, ECT 1.86 fold, and
Hemoclot® TT (Anti-FIIa) 1.36 fold, respectively. Dabigatran plasma concentrations observed at
72 hrs were relatively low, between 32.9 ng/mL and 97.2 ng/mL at final doses between 100 mg and
150 mg (gMean dose normalized total dabigatran plasma concentration of 0.493 ng/mL/mg).

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

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

C\text{max} and AUC were dose proportional.

The oral bioavailability may be increased by 75% after a single dose and 37% at steady state
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 (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.

Biotransformation

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.

**Elimination**

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 23.

**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 23: 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>

Additionally, dabigatran exposure (at trough and peak) was assessed in a prospective open label randomized pharmacokinetic study in NVAF patients with severe renal impairment (defined as creatinine clearance [CrCl] 15-30 mL/min) receiving dabigatran etexilate 75 mg twice daily. This regimen resulted in a geometric mean trough concentration of 155 ng/ml (gCV of 76.9 %), measured immediately before administration of the next dose and in a geometric mean peak concentration of 202 ng/ml (gCV of 70.6 %) measured two hours after the administration of the last dose.

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

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

The median CrCL in the RE-COVER study was 100.4 mL/min. 21.7 % of patients had mild renal impairment (CrCL > 50 - < 80 mL/min) and 4.5% of patients had a moderate renal impairment (CrCL
between 30 and 50 mL/min). Patients with mild and moderate renal impairment had at steady state an average 1.8-fold and 3.6-fold higher pre-dosedabigatran plasma concentrations compared with patients with CrCL > 80 mL/min, respectively. Similar values for CrCL were found in RE-COVER II.

The median CrCL in the RE-MEDY and RE-SONATE studies were 99.0 mL/min and 99.7 mL/min, respectively. 22.9 % and 22.5 % of the patients had a CrCL > 50-< 80 mL/min, and 4.1 % and 4.8 % had a CrCL between 30 and 50 mL/min in in the RE-MEDY and RE-SONATE studies.

**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<sub>max</sub> 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 impairment**
No change in dabigatran exposure was seen in 12 subjects with moderate hepatic insufficiency (Child Pugh B) compared to 12 controls (see sections 4.2 and 4.4).

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

**Gender**
In atrial fibrillation patients females had on average 30 % higher trough and post-dose concentrations. No dose adjustment is recommended (see section 4.2).

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

**Pharmacokinetic interactions**

*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 repeated 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.

Dabigatran, the active moiety of dabigatran etexilate mesilate, is persistent in the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<table>
<thead>
<tr>
<th>Capsule content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tartaric acid</td>
</tr>
<tr>
<td>Acacia</td>
</tr>
<tr>
<td>Hypromellose</td>
</tr>
<tr>
<td>Dimeticone 350</td>
</tr>
<tr>
<td>Talc</td>
</tr>
<tr>
<td>Hydroxypropylcellulose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Capsule shell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrageenan</td>
</tr>
<tr>
<td>Potassium chloride</td>
</tr>
<tr>
<td>Titanium dioxide</td>
</tr>
<tr>
<td>Indigo carmine (E132)</td>
</tr>
<tr>
<td>Hypromellose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Black printing ink</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shellac</td>
</tr>
<tr>
<td>Iron oxide black (E172)</td>
</tr>
<tr>
<td>Potassium hydroxide</td>
</tr>
</tbody>
</table>

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 10 x 1, 30 x 1 or 60 x 1 hard capsules in perforated aluminium unit dose blisters.
Multipack containing 3 packs of 60 x 1 hard capsules (180 hard capsules) in perforated aluminium unit dose blisters.
Multipack containing 2 packs of 50 x 1 hard capsules (100 hard capsules) in perforated aluminium unit dose blisters.  
Carton containing 6 blister strips (60 x 1) in perforated aluminium unit dose white blisters.  
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:  
  • One individual blister should be teared off from the blister card along the perforated line.  
  • The backing foil should be peeled off and the capsule can be removed.  
  • 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, the following instructions should be observed:  
  • The cap opens by pushing and turning.  
  • After taking the capsule out, the cap should be returned on the bottle right away and the bottle should be tightly closed.  
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHOURISATION HOLDER  
Boehringer Ingelheim International GmbH  
Binger Str. 173  
D-55216 Ingelheim am Rhein  
Germany  

8. MARKETING AUTHORISATION NUMBER(S)  
EU/1/08/442/009  
EU/1/08/442/010  
EU/1/08/442/011  
EU/1/08/442/012  
EU/1/08/442/013  
EU/1/08/442/016  
EU/1/08/442/019  

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHOURISATION  
Date of first authorisation: 18 March 2008  
Date of latest renewal: 17 January 2013  

10. DATE OF REVISION OF THE TEXT  
Detailed information on this medicinal product is available on the website of the European Medicines Agency 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

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
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

Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Strasse 65
D-88397 Biberach an der Riss
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union references dates (EURD list) provided for under Artical 107c(7) of Directive 1002/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- Additional risk minimisation measures

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 all therapeutic indications prior to launch 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
- Information on medicinal products that are contraindicated or which should be used with caution due to an increased risk of bleeding and/or increased dabigatran exposure
- Contraindication for patients with prosthetic heart valves requiring anticoagulant treatment
- 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 about all medicines they are currently taking
  - 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 MAH shall also provide a patient alert card in each medication pack, the text of which is included in Annex III.
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

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

Swallow whole, do not chew or break the capsule.
Read the package leaflet before use.
Oral use.
Patient alert card inside.

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

### 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

### 12. MARKETING AUTHORISATION NUMBER(S)

- EU/1/08/442/001 10 x 1 capsules
- EU/1/08/442/002 30 x 1 capsules
- EU/1/08/442/003 60 x 1 capsules
- EU/1/08/442/017 60 x 1 capsules

### 13. BATCH NUMBER

Lot

### 14. GENERAL CLASSIFICATION FOR SUPPLY

### 15. INSTRUCTIONS ON USE

### 16. INFORMATION IN BRAILLE

Pradaxa 75 mg

### 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.
<table>
<thead>
<tr>
<th>Column</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC</td>
<td></td>
</tr>
<tr>
<td>SN</td>
<td></td>
</tr>
<tr>
<td>NN</td>
<td></td>
</tr>
<tr>
<td>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>FOLDING BOX FOR BLISTER for 110 mg</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</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>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 x 1 hard capsule</td>
</tr>
<tr>
<td>30 x 1 hard capsule</td>
</tr>
<tr>
<td>60 x 1 hard capsule</td>
</tr>
</tbody>
</table>

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/005 10 x 1 capsules
EU/1/08/442/006 30 x 1 capsules
EU/1/08/442/007 60 x 1 capsules
EU/1/08/442/018 60 x 1 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 110 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.
18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
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

4. PHARMACEUTICAL FORM AND CONTENTS

60x1 hard capsules. Component of a multipack, can’t be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow whole, do not chew or break the capsule.
Read the package leaflet before use.
Oral use.
Patient alert card inside.

   1
   Tear-off

   2
   Peel-off

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

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

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 110 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
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

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 180 (3 packs of 60×1) hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATON HOLDER

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

12. MARKETING AUTHORIZATION NUMBER(S)

EU/1/08/442/014

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 110 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**MULTIPACK OF 100 (2 PACKS OF 50 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**

4. **PHARMACEUTICAL FORM AND CONTENTS**

   50x1 hard capsules. Component of a multipack, can’t be sold separately.

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

   Swallow whole, do not chew or break the capsule.
   Read the package leaflet before use.
   Oral use.
   Patient alert card inside.

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

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/1/08/442/015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 110 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACK OF 100 (2 PACKS OF 50 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

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 100 (2 packs of 50x1) hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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/1/08/442/015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 110 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
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

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

Swallow whole, do not chew or break the capsule.
Read the package leaflet before use.
Oral use.
Patient alert card inside.

Tear-off

Peel-off

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/009 10 x 1 capsules
EU/1/08/442/01030 x 1 capsules
EU/1/08/442/011 60 x 1 capsules
EU/1/08/442/019 60 x 1 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.
18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

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

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 150 mg hard capsules
dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60x1 hard capsules. Component of a multipack, can’t be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow whole, do not chew or break the capsule.
Read the package leaflet before use.
Oral use.
Patient alert card inside.

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

### 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

### 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/012

### 13. BATCH NUMBER

Lot

### 14. GENERAL CLASSIFICATION FOR SUPPLY

### 15. INSTRUCTIONS ON USE

### 16. INFORMATION IN BRAILLE

Pradaxa 150 mg

### 17. UNIQUE IDENTIFIER – 2D BARCODE

### 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
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

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 180 (3 packs of 60x1) hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIPACK OF 100 (2 PACKS OF 50 HARD-CAPSULES) – WITHOUT BLUE BOX – 150 mg HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 150 mg hard capsules
dabigatran etexilate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

50x1 hard capsules. Component of a multipack, can’t be sold seperatly.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Swallow whole, do not chew or break the capsule.
Read the package leaflet before use.
Oral use.
Patient alert card inside.

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

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/1/08/442/016

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Pradaxa 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>OUTER WRAPPER LABEL ON MULTIPACK OF 100 (2 PACKS OF 50 HARD CAPSULES) WRAPPED IN TRANSPARENT FOIL – INCLUDING THE BLUE BOX – 150 mg HARD CAPSULES</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multipack: 100 (2 packs of 50x1) hard capsules.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Store in the original package in order to protect from moisture.</td>
</tr>
</tbody>
</table>
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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/1/08/442/016

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Pradaxa 150 mg

17. **UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

18. **UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLISTER FOR 75 mg</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
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<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>
MINIMUM PARTICULARS TO APPEAR ON WHITE BLISTERS OR STRIPS

BLISTER FOR 75 mg

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 75 mg hard capsules
dabigatran etexilate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

็ด Peel back
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLISTER FOR 110 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradaxa 110 mg hard capsules</td>
</tr>
<tr>
<td>dabigatran etexilate</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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</tbody>
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<table>
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<tr>
<th>3. EXPIRY DATE</th>
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<tr>
<td>EXP</td>
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<tr>
<th>4. BATCH NUMBER</th>
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<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>
<tr>
<td>MINIMUM PARTICULARS TO APPEAR ON WHITE BLISTERS OR STRIPS</td>
</tr>
<tr>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td>BLISTER FOR 110 mg</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Pradaxa 110 mg hard capsules
dabigatran etexilate

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

Boehringer Ingelheim (logo)

3. **EXPIRY DATE**

EXP

4. **BATCH NUMBER**

Lot

5. **OTHER**

👉 Peel back
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR 150 mg

1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 150 mg hard capsules
dabigatran etexilate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Peel back
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON WHITE BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLISTER FOR 150 mg</td>
</tr>
</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 etexilate</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>
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<tr>
<th>3. EXPIRY DATE</th>
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</thead>
<tbody>
<tr>
<td>EXP</td>
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</table>

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

### 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

### 4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

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

Swallow whole, do not chew or break the capsule.
Read the package leaflet before use.
Oral use.
Patient alert card inside.

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

Keep out of the sight and reach of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

### 8. EXPIRY DATE

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

### 9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed. Store in the original package in order to protect from moisture.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
### 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>
</tr>
</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>
</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>Swallow whole, do not chew or break the capsule.</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Oral use.</td>
</tr>
<tr>
<td>Patient alert card inside.</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 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>
</tr>
</tbody>
</table>
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/442/008

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

15. **INSTRUCTIONS ON USE**

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

16. **INFORMATION IN BRAILLE**

2D barcode carrying the unique identifier included.

17. **UNIQUE IDENTIFIER – 2D BARCODE**

18. **UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:
SN:
NN:
# PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING.

**FOLDING BOX AND LABEL FOR BOTTLE** for 150 mg

## 1. NAME OF THE MEDICINAL PRODUCT

Pradaxa 150 mg hard capsules
dabigatran etexilate

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

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

Swallow whole, do not chew or break the capsule.
Read the package leaflet before use.
Oral use.
Patient alert card inside.

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

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

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

## 9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed. Store in the original package in order to protect from moisture.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/442/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
B. PACKAGE LEAFLET
**Package leaflet: Information for the patient**

**Pradaxa 75 mg hard capsules**

dabigatran etexilate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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. See section 4.

What is 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

Pradaxa contains the active substance dabigatran etexilate and belongs to a group of medicines called anticoagulants. It works by blocking a substance in the body which is involved in blood clot formation.

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

2. What you need to know before you take Pradaxa

Do not take Pradaxa

- if you are allergic to dabigatran etexilate 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 (e.g., stomach ulcer, injury or bleeding in the brain, recent surgery of the brain or eyes).
- if you have an increased tendency to bleed. This may be inborn, of unknown cause or due to other medicines.
- if you are taking medicines to prevent blood clotting (e.g. warfarin, rivaroxaban, apixaban or heparin), except when changing anticoagulant treatment or while having a venous or arterial line and you get heparin through this line to keep it open.
- 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 oral cyclosporine, a medicine to prevent organ rejection after transplantation.
- if you are taking dronedarone, a medicine used to treat abnormal heart beat.
- if you have received an artificial heart valve which requires permanent blood thinning.
Warnings and precautions

Talk to your doctor before taking Pradaxa. You may also need to talk to your doctor during treatment with Pradaxa if you experience symptoms or if you have to undergo surgery.

Tell your doctor if you have or have had any medical conditions or illnesses, in particular any of those included in the following list:

- if you have an increased bleeding risk, such as:
  ▪ 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. See 'Other medicines and Pradaxa' below.
  ▪ if you are taking anti-inflammatory medicines such as diclofenac, ibuprofen, piroxicam.
  ▪ if you are suffering from an infection of the heart (bacterial endocarditis).
  ▪ if you know you have impaired kidney function, or you are suffering from dehydration (symptoms include feeling thirsty and passing reduced amounts of dark-coloured (concentrated) urine).
  ▪ if you are older than 75 years.
  ▪ if you weigh 50 kg or less.

- if you have had a heart attack or if you have been diagnosed with conditions that increase the risk to develop a heart attack.

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

Take special care with Pradaxa

- if you need to have an operation:
  In this case Pradaxa will need to be stopped temporarily due to an increased bleeding risk during and shortly after an operation. It is very important to take Pradaxa before and after the operation exactly at the times you have been told by your doctor.

- if an operation involves a catheter or injection into your spinal column (e.g. for epidural or spinal anaesthesia or pain reduction):
  ▪ it is very important to take Pradaxa before and after the operation exactly at the times you have been told by your doctor.
  ▪ tell your doctor immediately if you get numbness or weakness of your legs or problems with your bowel or bladder after the end of anaesthesia, because urgent care is necessary.

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

Children and adolescents

Pradaxa is not recommended in children and adolescents below 18 years old.
Other medicines and Pradaxa

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. In particular you should tell your doctor before taking Pradaxa, if you are taking one of the medicines listed below:

- Medicines to reduce blood clotting (e.g. warfarin, phenprocoumon, acenocoumarol, heparin, clopidogrel, prasugrel, ticagrelor, rivaroxaban, acetylsalicylic acid)
- Medicines to treat fungal infections (e.g. ketoconazole, itraconazole), unless they are only applied to the skin
- Medicines to treat abnormal heart beats (e.g. amiodarone, dronedarone, quinidine, verapamil). If you are taking amiodarone, quinidine or verapamil containing medicines, your doctor will tell you to use a reduced dose of Pradaxa. See also section 3.
- Medicines to prevent organ rejection after transplantation (e.g. tacrolimus, cyclosporine)
- Anti-inflammatory and pain reliever medicines (e.g. acetylsalicylic acid, ibuprofen, diclofenac)
- St. John’s wort, a herbal medicine for depression
- Antidepressant medicines called selective serotonin re-uptake inhibitors or serotonin-norepinephrine re-uptake inhibitors
- Rifampicin or clarithromycin (two antibiotics)
- Anti-viral medicines for AIDS (e.g. ritonavir)
- Certain medicines for treatment of epilepsy (e.g. carbamazepine, phenytoin)

Pregnancy and breast-feeding

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

Pradaxa has no known effects on the ability to drive or use machines.

3. How to take Pradaxa

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

The recommended dose 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.

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.
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 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 28-35 days.

How to take Pradaxa

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

Instructions for opening the blisters

The following pictogram illustrates how to take Pradaxa capsules out of the blister

1. Tear off one individual blister from the blister card along the perforated line

2. Peel off the backing foil and remove the capsule.

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

Instructions for the bottle

- Push and turn for opening.
- After removing the capsule, place the cap back on the bottle and tightly close the bottle right away after you take your dose.

Change of anticoagulant treatment

Without specific guidance from your doctor do not change your anticoagulant treatment.

If you take more Pradaxa than you should

Taking too much Pradaxa increases the risk of bleeding. Contact your doctor immediately if you have taken too many Pradaxa capsules. Specific treatment options are available.

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 a forgotten dose.
If you stop taking Pradaxa

Take Pradaxa exactly as prescribed. Do not stop taking Pradaxa without talking to your doctor first, because the risk of developing a blood clot could be higher if you stop treatment too early. Contact your doctor if you experience indigestion after taking Pradaxa.

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.

Pradaxa affects blood clotting, so most side effects are related to signs such as bruising or bleeding. Major or severe bleeding may occur, these constitute the most serious side effects and, regardless of location, may become disabling, life-threatening or even lead to death. In some cases these bleedings may not be obvious.

If you experience any bleeding event that does not stop by itself or if you experience signs of excessive bleeding (exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling) consult your doctor immediately. Your doctor may decide to keep you under closer observation or change your medicine.

Tell your doctor immediately, if you experience a serious allergic reaction which causes difficulty in breathing or dizziness.

Possible side effects are listed below, grouped by how likely they are to happen.

Common (may affect up to 1 in 10 people):
- A fall in the amount of haemoglobin in the blood (the substance in the red blood cells)
- Unusual laboratory test results on liver function

Uncommon (may affect up to 1 in 100 people):
- Bleeding may happen from the nose, into the stomach or bowel, from penis/vagina or urinary tract (incl. blood in the urine that stains the urine pink or red), from piles, from the rectum, under the skin, into a joint, from or after an injury or after an operation
- Haematoma formation or bruising occurring after an operation
- Blood detected in the stools by a laboratory test
- A fall in the number of red cells in the blood
- A decrease in the proportion of red cells in the blood
- Allergic reaction
- Vomiting
- Frequent loose or liquid bowel movements
- Feeling sick
- Wound secretion (liquid exuding from the surgical wound)
- Liver enzymes increased
- Yellowing of the skin or whites of the eyes, caused by liver or blood problems

Rare (may affect up to 1 in 1,000 people):
- Bleeding
- Bleeding may happen in the brain, from a surgical incision, from the site of entry of an injection or 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
- Coughing of blood or blood stained sputum
- A fall in the number of platelets in the blood
- A fall in the number of red cells in the blood after an operation
- Serious allergic reaction which causes difficulty in breathing or dizziness
- Serious allergic reaction which causes swelling of the face or throat
- Skin rash notable for dark red, raised, itchy bumps caused by an allergic reaction
- Sudden change of the skin which affects its colour and appearance
- Itching
- Ulcer in the stomach or bowel (incl. ulcer in the gullet)
- Inflammation of the gullet and stomach
- Reflux of gastric juice into the gullet
- Belly ache or stomach ache
- Indigestion
- Difficulty in swallowing
- Fluid exiting a wound
- Fluid exiting a wound after an operation

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

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this 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 after “EXP”. 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. 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. Each hard capsule contains 75 mg dabigatran etexilate (as mesylate).

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

- The capsule shell contains carrageenan, potassium chloride, titanium dioxide, and hypromellose.

- The black printing ink contains shellac, iron oxide black and potassium hydroxide.
**What Pradaxa looks like and contents of the pack**

Pradaxa 75 mg are hard capsules with an opaque, white cap and an opaque, white body. The Boehringer Ingelheim logo is printed on the cap and “R75” on the body of the capsule.

Pradaxa is available in packs containing 10 x 1, 30 x 1 or 60 x 1 capsules in aluminium perforated unit dose blisters. Furthermore, Pradaxa is available in packs containing 60 x 1 capsules in aluminium perforated unit dose white 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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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/
Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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. See section 4.

What is 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
Pradaxa contains the active substance dabigatran etexilate and belongs to a group of medicines called anticoagulants. It works by blocking a substance in the body which is involved in blood clot formation.

Pradaxa is used in adults to:
- prevent the formation of blood clots in the veins after knee or hip replacement surgery.
- prevent blood clots in the brain (stroke) and other blood vessels in the body if you have a form of irregular heart rhythm called nonvalvular atrial fibrillation and at least one additional risk factor.
- treat blood clots in the veins of your legs and lungs and to prevent blood clots from re-occuring in the vein of your legs and lungs.

2. What you need to know before you take Pradaxa
Do not take Pradaxa
- if you are allergic to dabigatran etexilate 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 (e.g., stomach ulcer, injury or bleeding in the brain, recent surgery of the brain or eyes).
- if you have an increased tendency to bleed. This may be inborn, of unknown cause or due to other medicines.
- if you are taking medicines to prevent blood clotting (e.g. warfarin, rivaroxaban, apixaban or heparin), except when changing anticoagulant treatment or while having a venous or arterial line and you get heparin through this line to keep it open.
- 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 oral cyclosporine, a medicine to prevent organ rejection after transplantation.
- if you are taking dronedarone, a medicine used to treat abnormal heart beat.
- if you have received an artificial heart valve which requires permanent blood thinning.

Warnings and precautions

Talk to your doctor before taking Pradaxa. You may also need to talk to your doctor during treatment with Pradaxa if you experience symptoms or if you have to undergo surgery.

Tell your doctor if you have or have had any medical conditions or illnesses, in particular any of those included in the following list:

- if you have an increased bleeding risk, such as:
  ▪ 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. See 'Other medicines and Pradaxa' below.
  ▪ if you are taking anti-inflammatory medicines such as diclofenac, ibuprofen, piroxicam.
  ▪ if you are suffering from an infection of the heart (bacterial endocarditis).
  ▪ if you know you have impaired kidney function, or you are suffering from dehydration (symptoms include feeling thirsty and passing reduced amounts of dark-coloured (concentrated) urine).
  ▪ if you are older than 75 years.
  ▪ if you weigh 50 kg or less.

- if you have had a heart attack or if you have been diagnosed with conditions that increase the risk to develop a heart attack.

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

Take special care with Pradaxa

- if you need to have an operation:
  In this case Pradaxa will need to be stopped temporarily due to an increased bleeding risk during and shortly after an operation. It is very important to take Pradaxa before and after the operation exactly at the times you have been told by your doctor.

- if an operation involves a catheter or injection into your spinal column (e.g. for epidural or spinal anaesthesia or pain reduction):
  ▪ it is very important to take Pradaxa before and after the operation exactly at the times you have been told by your doctor.
  ▪ tell your doctor immediately if you get numbness or weakness of your legs or problems with your bowel or bladder after the end of anaesthesia, because urgent care is necessary.

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

Pradaxa is not recommended in children and adolescents below 18 years old.

Other medicines and Pradaxa

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. **In particular you should tell your doctor before taking Pradaxa, if you are taking one of the medicines listed below:**

- Medicines to reduce blood clotting (e.g. warfarin, phenprocoumon, acenocoumarol, heparin, clopidogrel, prasugrel, ticagrelor, rivaroxaban, acetylsalicylic acid)
- Medicines to treat fungal infections (e.g. ketoconazole, itraconazole), unless they are only applied to the skin
- Medicines to treat abnormal heart beats (e.g. amiodarone, dronedarone, quinidine, verapamil). If you are taking amiodarone, quinidine or verapamil containing medicines, your doctor may tell you to use a reduced dose of Pradaxa depending on the condition for which Pradaxa is prescribed to you. See section 3.
- Medicines to prevent organ rejection after transplantation (e.g. tacrolimus, cyclosporine)
- Anti-inflammatory and pain reliever medicines (e.g. acetylsalicylic acid, ibuprofen, diclofenac)
- St. John’s wort, a herbal medicine for depression
- Antidepressant medicines called selective serotonin re-uptake inhibitors or serotonin-norepinephrine re-uptake inhibitors
- Rifampicin or clarithromycin (two antibiotics)
- Anti-viral medicines for AIDS (e.g. ritonavir)
- Certain medicines for treatment of epilepsy (e.g. carbamazepine, phenytoin)

Pregnancy and breast-feeding

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

Pradaxa has no known effects on the ability to drive or use machines.

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.

**Take Pradaxa as recommended for the following conditions:**

Prevention of blood clot formation after knee or hip replacement surgery

The recommended dose 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.

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

*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 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 28-35 days.

Prevention of brain or body vessel obstruction by blood clot formation developing after abnormal heart beats and Treatment of blood clots in the veins of your legs and lungs including prevention of blood clots from re-occuring in the vein of your legs and lungs

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

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

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

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

**How to take Pradaxa**

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

**Instructions for opening the blisters**

The following pictogram illustrates how to take Pradaxa capsules out of the blister

1. Tear off one individual blister from the blister card along the perforated line

2. Peel off the backing foil and remove the capsule.
• Do not push the capsules through the blister foil.
• Do not peel off the blister foil until a capsule is required.

**Instructions for the bottle**

• Push and turn for opening.
• After removing the capsule, place the cap back on the bottle and tightly close the bottle right away after you take your dose.

**Change of anticoagulant treatment**

Without specific guidance from your doctor do not change your anticoagulant treatment.

**If you take more Pradaxa than you should**

Taking too much Pradaxa increases the risk of bleeding. Contact your doctor immediately if you have taken too many Pradaxa capsules. Specific treatment options are available.

**If you forget to take Pradaxa**

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

**Prevention of brain or body vessel obstruction by blood clot formation developing after abnormal heart beats and treatment of blood clots in the veins of your legs and lungs including prevention of blood clots from re-occurring in the vein of your legs and lungs**
A forgotten dose can still be taken up to 6 hours prior to the next due dose.
A missed dose should be omitted if the remaining time is below 6 hours prior to the next due dose. Do not take a double dose to make up for a forgotten dose.

**If you stop taking Pradaxa**

Take Pradaxa exactly as prescribed. Do not stop taking Pradaxa without talking to your doctor first, because the risk of developing a blood clot could be higher if you stop treatment too early. Contact your doctor if you experience indigestion after taking Pradaxa.

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.

Pradaxa affects blood clotting, so most side effects are related to signs such as bruising or bleeding. Major or severe bleeding may occur, these constitute the most serious side effects and, regardless of location, may become disabling, life-threatening or even lead to death. In some cases these bleedings may not be obvious.

If you experience any bleeding event that does not stop by itself or if you experience signs of excessive bleeding (exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling) consult your doctor immediately. Your doctor may decide to keep you under closer observation or change your medicine.

Tell your doctor immediately, if you experience a serious allergic reaction which causes difficulty in breathing or dizziness.
Possible side effects are listed below, grouped by how likely they are to happen.

**Prevention of blood clot formation after knee or hip replacement surgery**

Common (may affect up to 1 in 10 people):
- A fall in the amount of haemoglobin in the blood (the substance in the red blood cells)
- Unusual laboratory test results on liver function

Uncommon (may affect up to 1 in 100 people):
- Bleeding may happen from the nose, into the stomach or bowel, from penis/vagina or urinary tract (incl. blood in the urine that stains the urine pink or red), from piles, from the rectum, under the skin, into a joint, from or after an injury or after an operation
- Haematoma formation or bruising occurring after an operation
- Blood detected in the stools by a laboratory test
- A fall in the number of red cells in the blood
- A decrease in the proportion of red cells in the blood
- Allergic reaction
- Vomiting
- Frequent loose or liquid bowel movements
- Feeling sick
- Wound secretion (liquid exuding from the surgical wound)
- Liver enzymes increased
- Yellowing of the skin or whites of the eyes, caused by liver or blood problems

Rare (may affect up to 1 in 1,000 people):
- Bleeding
- Bleeding may happen in the brain, from a surgical incision, from the site of entry of an injection or 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
- Coughing of blood or blood stained sputum
- A fall in the number of platelets in the blood
- A fall in the number of red cells in the blood after an operation
- Serious allergic reaction which causes difficulty in breathing or dizziness
- Serious allergic reaction which causes swelling of the face or throat
- Skin rash notable for dark red, raised, itchy bumps caused by an allergic reaction
- Sudden change of the skin which affects its colour and appearance
- Itching
- Ulcer in the stomach or bowel (incl. ulcer in the gullet)
- Inflammation of the gullet and stomach
- Reflux of gastric juice into the gullet
- Belly ache or stomach ache
- Indigestion
- Difficulty in swallowing
- Fluid exiting a wound
- Fluid exiting a wound after an operation

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

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

Common (may affect up to 1 in 10 people):
- Bleeding may happen from the nose, into the stomach or bowel, from penis/vagina or urinary tract (incl. blood in the urine that stains the urine pink or red), or under the skin
- A fall in the number of red cells in the blood
- Belly ache or stomach ache
- Indigestion
- Frequent loose or liquid bowel movements
- Feeling sick

Uncommon (may affect up to 1 in 100 people):
- Bleeding
- Bleeding may happen from piles, from the rectum, or in the brain.
- Haematoma formation
- Coughing of blood or blood stained sputum
- A fall in the number of platelets in the blood
- A fall in the amount of haemoglobin in the blood (the substance in the red blood cells)
- Allergic reaction
- Sudden change of the skin which affects its colour and appearance
- Itching
- Ulcer in the stomach or bowel (incl. ulcer in the gullet)
- Inflammation of the gullet and stomach
- Reflux of gastric juice into the gullet
- Vomiting
- Difficulty in swallowing
- Unusual laboratory test results on liver function

Rare (may affect up to 1 in 1,000 people):
- Bleeding may happen into a joint, from a surgical incision, from an injury, or from the site of entry of an injection or from the site of entry of a catheter into a vein
- Serious allergic reaction which causes difficulty in breathing or dizziness
- Serious allergic reaction which causes swelling of the face or throat
- Skin rash notable for dark red, raised, itchy bumps caused by an allergic reaction
- A decrease in the proportion of red cells in the blood
- Liver enzymes increased
- Yellowing of the skin or whites of the eyes, caused by liver or blood problems

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

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

Treatment of blood clots in the veins of your legs and lungs including prevention of blood clots from re-occurring in the veins of your legs and/or lungs

Common (may affect up to 1 in 10 people):
- Bleeding may happen from the nose, into the stomach or bowel, from the rectum, from penis/vagina or urinary tract (incl. blood in the urine that stains the urine pink or red), or under the skin
- Indigestion

Uncommon (may affect up to 1 in 100 people):
- Bleeding
- Bleeding may happen into a joint or from an injury
- Bleeding may happen from piles
- A fall in the number of red cells in the blood
- Haematoma formation
- Coughing of blood or blood stained sputum
- Allergic reaction
- Sudden change of the skin which affects its colour and appearance
- Itching
- Ulcer in the stomach or bowel
- Inflammation of the gullet and stomach
- Reflux of gastric juice into the gullet
- Feeling sick
- Vomiting
- Belly ache or stomach ache
- Frequent loose or liquid bowel movements
- Unusual laboratory test results on liver function
- Liver enzymes increased

Rare (may affect up to 1 in 1,000 people):
- Bleeding may happen, from a surgical incision, or from the site of entry of an injection or from the site of entry of a catheter into a vein or from the brain
- A fall in the number of platelets in the blood
- Serious allergic reaction which causes difficulty in breathing or dizziness
- Serious allergic reaction which causes swelling of the face or throat
- Skin rash notable for dark red, raised, itchy bumps caused by an allergic reaction
- Difficulty in swallowing
- A decrease in the proportion of red cells in the blood

Not known (frequency cannot be estimated from the available data):
- Difficulty in breathing or wheezing
- A fall in the amount of haemoglobin in the blood (the substance in the red blood cells)
- A fall in the number of red cells in the blood
- Yellowing of the skin or whites of the eyes, caused by liver or blood problems

In the trial program the rate of heart attacks with Pradaxa was higher than with warfarin. The overall occurrence was low. No imbalance in the rate of heart attacks was observed in patients treated with dabigatran versus patients treated with placebo.

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this 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 after “EXP”. 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. 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. Each hard capsule contains 110 mg dabigatran etexilate (as mesylate).

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

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

- The black printing ink contains shellac, iron oxide black and potassium hydroxide.

What Pradaxa looks like and contents of the pack

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

Pradaxa is available in packs containing 10 x 1, 30 x 1 or 60 x 1 capsules, a multipack containing 3 packs of 60 x 1 hard capsules (180 hard capsules) or a multipack containing 2 packs of 50 x 1 hard capsules (100 hard capsules) in aluminium perforated unit dose blisters. Furthermore, Pradaxa is available in packs containing 60 x 1 capsules in aluminium perforated unit dose white blisters.

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

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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

Manufacturer

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

and

Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Strasse 65
D-88397 Biberach an der Riss
Germany
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/
Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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. See section 4.

What is 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

Pradaxa contains the active substance dabigatran etexilate and belongs to a group of medicines called anticoagulants. It works by blocking a substance in the body which is involved in blood clot formation.

Pradaxa is used in adults to:

- prevent blood clots in the brain (stroke) and other blood vessels in the body if you have a form of irregular heart rhythm called nonvalvular atrial fibrillation and at least one additional risk factor.

- treat blood clots in the veins of your legs and lungs and to prevent blood clots from re-occurring in the vein of your legs and lungs.

2. What you need to know before you take Pradaxa

Do not take Pradaxa

- if you are allergic to dabigatran etexilate 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 (e.g., stomach ulcer, injury or bleeding in the brain, recent surgery of the brain or eyes).
- if you have an increased tendency to bleed. This may be inborn, of unknown cause or due to other medicines.
- if you are taking medicines to prevent blood clotting (e.g., warfarin, rivaroxaban, apixaban or heparin), except when changing anticoagulant treatment or while having a venous or arterial line and you get heparin through this line to keep it open.

- 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 oral cyclosporine, a medicine to prevent organ rejection after transplantation.
- if you are taking dronedarone, a medicine used to treat abnormal heart beat.
- if you have received an artificial heart valve which requires permanent blood thinning.

**Warnings and precautions**

Talk to your doctor before taking Pradaxa. You may also need to talk to your doctor during treatment with Pradaxa if you experience symptoms or if you have to undergo surgery.

**Tell your doctor** if you have or have had any medical conditions or illnesses, in particular any of those included in the following list:

- if you have an increased bleeding risk, such as:
  - 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. See 'Other medicines and Pradaxa' below.
  - if you are taking anti-inflammatory medicines such as diclofenac, ibuprofen, piroxicam.
  - if you are suffering from an infection of the heart (bacterial endocarditis).
  - if you know you have impaired kidney function, or you are suffering from dehydration (symptoms include feeling thirsty and passing reduced amounts of dark-coloured (concentrated) urine).
  - if you are older than 75 years.
  - if you weigh 50 kg or less.

- if you have had a heart attack or if you have been diagnosed with conditions that increase the risk to develop a heart attack.

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

**Take special care with Pradaxa**

- if you need to have an operation:
  In this case Pradaxa will need to be stopped temporarily due to an increased bleeding risk during and shortly after an operation. It is very important to take Pradaxa before and after the operation exactly at the times you have been told by your doctor.

- if an operation involves a catheter or injection into your spinal column (e.g. for epidural or spinal anaesthesia or pain reduction):
  - it is very important to take Pradaxa before and after the operation exactly at the times you have been told by your doctor.
  - tell your doctor immediately if you get numbness or weakness of your legs or problems with your bowel or bladder after the end of anaesthesia, because urgent care is necessary.

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

**Children and adolescents**

Pradaxa is not recommended in children and adolescents below 18 years old.
Other medicines and Pradaxa

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. In particular you should tell your doctor before taking Pradaxa, if you are taking one of the medicines listed below:

- Medicines to reduce blood clotting (e.g. warfarin, phenprocoumon, acenocoumarol, heparin, clopidogrel, prasugrel, ticagrelor, rivaroxaban, acetylsalicylic acid)
- Medicines to treat fungal infections (e.g. ketoconazole, itraconazole), unless they are only applied to the skin
- Medicines to treat abnormal heart beats (e.g. amiodarone, dronedarone, quinidine, verapamil).
  If you are taking verapamil containing medicines, your doctor will tell you to use a reduced dose of Pradaxa. See section 3.
- Medicines to prevent organ rejection after transplantation (e.g. tacrolimus, cyclosporine)
- Anti-inflammatory and pain reliever medicines (e.g. acetylsalicylic acid, ibuprofen, diclofenac)
- St. John’s wort, a herbal medicine for depression
- Antidepressant medicines called selective serotonin re-uptake inhibitors or serotonin-norepinephrine re-uptake inhibitors
- Rifampicin or clarithromycin (two antibiotics)
- Anti-viral medicines for AIDS (e.g. ritonavir)
- Certain medicines for treatment of epilepsy (e.g. carbamazepine, phenytoin)

Pregnancy and breast-feeding

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

Pradaxa has no known effects on the ability to drive or use machines.

3. How to take Pradaxa

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

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

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

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

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

How to take Pradaxa

Pradaxa can be taken with or without food. The capsule should be swallowed whole with a glass of water, to ensure delivery to the stomach. Do not break, chew, or empty the pellets from the capsule since this may increase the risk of bleeding.
Instructions for opening the blisters

The following pictogram illustrates how to take Pradaxa capsules out of the blister

1. Tear off one individual blister from the blister card along the perforated line.

2. Peel off the backing foil and remove the capsule.

• Do not push the capsules through the blister foil.
• Do not peel off the blister foil until a capsule is required.

Instructions for the bottle

• Push and turn for opening.
• After removing the capsule, place the cap back on the bottle and tightly close the bottle right away after you take your dose.

Change of anticoagulant treatment

Without specific guidance from your doctor do not change your anticoagulant treatment.

If you take more Pradaxa than you should

Taking too much Pradaxa increases the risk of bleeding. Contact your doctor immediately if you have taken too many Pradaxa capsules. Specific treatment options are available.

If you forget to take Pradaxa

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

If you stop taking Pradaxa

Take Pradaxa exactly as prescribed. Do not stop taking Pradaxa without talking to your doctor first, because the risk of developing a blood clot could be higher if you stop treatment too early. Contact your doctor if you experience indigestion after taking Pradaxa.

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.

Pradaxa affects blood clotting, so most side effects are related to signs such as bruising or bleeding. Major or severe bleeding may occur, these constitute the most serious side effects and, regardless of location, may become disabling, life-threatening or even lead to death. In some cases these bleedings may not be obvious.

If you experience any bleeding event that does not stop by itself or if you experience signs of excessive bleeding (exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling) consult your doctor immediately. Your doctor may decide to keep you under closer observation or change your medicine.

Tell your doctor immediately, if you experience a serious allergic reaction which causes difficulty in breathing or dizziness.

Possible side effects are listed below, grouped by how likely they are to happen.

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

Common (may affect up to 1 in 10 people):
- Bleeding may happen from the nose, into the stomach or bowel, from penis/vagina or urinary tract (incl. blood in the urine that stains the urine pink or red), or under the skin
- A fall in the number of red cells in the blood
- Belly ache or stomach ache
- Indigestion
- Frequent loose or liquid bowel movements
- Feeling sick

Uncommon (may affect up to 1 in 100 people):
- Bleeding
- Bleeding may happen from piles, from the rectum, or in the brain.
- Haematoma formation
- Coughing of blood or blood stained sputum
- A fall in the number of platelets in the blood
- A fall in the amount of haemoglobin in the blood (the substance in the red blood cells)
- Allergic reaction
- Sudden change of the skin which affects its colour or appearance
- Itching
- Ulcer in the stomach or bowel (incl. ulcer in the gullet)
- Inflammation of the gullet and stomach
- Reflux of gastric juice into the gullet
- Vomiting
- Difficulty in swallowing
- Unusual laboratory test results on liver function

Rare (may affect up to 1 in 1,000 people):
- Bleeding may happen into a joint, from a surgical incision, from an injury, from the site of entry of an injection or from the site of entry of a catheter into a vein
- Serious allergic reaction which causes difficulty in breathing or dizziness
- Serious allergic reaction which causes swelling of the face or throat
- Skin rash notable for dark red, raised, itchy bumps caused by an allergic reaction
- A decrease in the proportion of red cells in the blood
- Liver enzymes increased
- Yellowing of the skin or whites of the eyes, caused by liver or blood problems
Not known (frequency cannot be estimated from the available data):

- Difficulty in breathing or wheezing

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

Treatment of blood clots in the veins of your legs and lungs including prevention of blood clots from re-occurring in the veins of your legs and/or lungs

Common (may affect up to 1 in 10 people):
- Bleeding may happen from the nose, into the stomach or bowel, from the rectum, from penis/vagina or urinary tract (incl. blood in the urine that stains the urine pink or red), or under the skin
- Indigestion

Uncommon (may affect up to 1 in 100 people):
- Bleeding
- Bleeding may happen into a joint or from an injury
- A fall in the number of red cells in the blood
- Haematoma formation
- Coughing of blood or blood stained sputum
- Allergic reaction
- Sudden change of the skin which affects its colour and appearance
- Itching
- Ulcer in the stomach or bowel
- Inflammation of the gullet and stomach
- Reflux of gastric juice into the gullet
- Feeling sick
- Vomiting
- Belly ache or stomach ache
- Frequent loose or liquid bowel movements
- Unusual laboratory test results on liver function
- Liver enzymes increased

Rare (may affect up to 1 in 1,000 people):
- Bleeding may happen, from a surgical incision, or from the site of entry of an injection or from the site of entry of a catheter into a vein or from the brain
- A fall in the number of platelets in the blood
- Serious allergic reaction which causes difficulty in breathing or dizziness
- Serious allergic reaction which causes swelling of the face or throat
- Skin rash notable for dark red, raised, itchy bumps caused by an allergic reaction
- Difficulty in swallowing
- A decrease in the proportion of red cells in the blood

Not known (frequency cannot be estimated from the available data):
- Difficulty in breathing or wheezing
- A fall in the amount of haemoglobin in the blood (the substance in the red blood cells)
- A fall in the number of red cells in the blood
- Yellowing of the skin or whites of the eyes, caused by liver or blood problems

In the trial program the rate of heart attacks with Pradaxa was higher than with warfarin. The overall occurrence was low. No imbalance in the rate of heart attacks was observed in patients treated with dabigatran versus patients treated with placebo.
Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this 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 after “EXP”. The expiry date refers to the last day of that month.

Blisters: 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. 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. Each hard capsule contains 150 mg dabigatran etexilate (as mesylate).

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

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

- The black printing ink contains shellac, iron oxide black and potassium hydroxide.

What Pradaxa looks like and contents of the pack

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

Pradaxa is available in packs containing 10 x 1, 30 x 1 or 60 x 1 capsules, a multipack containing 3 packs of 60 x 1 hard capsules (180 hard capsules) or a multipack containing 2 packs of 50 x 1 hard capsules (100 hard capsules) in aluminium perforated unit dose blisters. Furthermore, Pradaxa is available in packs containing 60 x 1 capsules in aluminium perforated unit dose white blisters.

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

Not all pack sizes may be marketed.
Marketing Authorisation Holder

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
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Manufacturer

Boehringer Ingelheim Pharma GmbH & Co. KG
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and

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For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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http://www.ema.europa.eu/
Dear Patient,

Your doctor has initiated treatment with Pradaxa®. In order to use Pradaxa® safely, please consider the important information inside. As this patient alert card contains important information about your treatment, please carry this card with you at all times to inform healthcare professionals about your intake of Pradaxa®.

Pradaxa® Information for Patients

About your treatment
- Pradaxa® thins the blood, which prevents you from getting dangerous blood clots.
- Follow your doctor’s instructions when taking Pradaxa®. Never skip a dose or stop the intake of Pradaxa® without talking to your doctor.
- Inform your doctor about all medicines you are currently taking.
- Inform your doctor about your intake of Pradaxa® before any surgery/invasive procedure.
- Pradaxa® can be taken with or without food. Swallow the capsule whole with a glass of water. Do not break, chew, or empty the pellets from the capsule.

When to seek medical advice
- Taking Pradaxa® may increase the risk of bleeding. Speak to your doctor immediately if you experience any of the following possible signs and symptoms of bleeding: swelling, discomfort, unusual pain or headache, dizziness, paleness, weakness, unusual bruising, nosebleeds, bleeding of gums, unusual long bleeding cuts, abnormal menstrual flow or vaginal bleeding, blood in your urine which may be pink or brown, red/black stools, coughing up blood, vomiting blood or coffee ground like material.
- If you fall or injure yourself, especially if you hit your head, urgently seek medical advice.
- Do not stop intake of Pradaxa® without talking to your doctor, if you experience heartburn, nausea, vomiting, stomach discomfort, bloating or upper abdominal pain.

Pradaxa® Information for Healthcare Professionals

- Pradaxa® is an oral anticoagulant (direct thrombin inhibitor).
- Pradaxa® may need to be stopped in advance of surgical or other invasive procedures.
- In case of major bleeding events, Pradaxa® must be stopped immediately.
- A specific reversal agent (Praxbind®) is available (please refer to the Summary of Product Characteristics of Pradaxa® and Praxbind®).
- Pradaxa® is mainly eliminated by the kidneys; adequate diuresis must be maintained. Pradaxa® is dialyzable.
Please complete this section or ask your doctor to do it.

Patient Information

Name of the patient

____________________________________

Date of birth

____________________________________

Indication for anticoagulation

____________________________________

Dose of Pradaxa®
ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. **NAME OF THE MEDICINAL PRODUCT**

Praxbind 2.5 g/50 mL solution for injection/infusion

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each mL of solution for injection/infusion contains 50 mg idarucizumab.

Each vial contains 2.5 g idarucizumab in 50 mL.

Idarucizumab is produced by recombinant DNA technology in Chinese Hamster Ovary cells.

**Excipients with known effect:**
Each 50 mL vial contains 2 g sorbitol and 25 mg sodium (see section 4.4).

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Solution for injection/infusion

Clear to slightly opalescent, colourless to slightly yellow solution.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Praxbind is a specific reversal agent for dabigatran and is indicated in adult patients treated with Pradaxa (dabigatran etexilate) when rapid reversal of its anticoagulant effects is required:

- For emergency surgery/urgent procedures
- In life-threatening or uncontrolled bleeding.

4.2 **Posology and method of administration**

Restricted to hospital use only.

**Posology**

The recommended dose of Praxbind is 5 g (2x2.5 g/50 mL).
In a subset of patients, recurrence of plasma concentrations of unbound dabigatran and concomitant prolongation of clotting tests have occurred up to 24 hours after administration of idarucizumab (see section 5.1).

Administration of a second 5 g dose of Praxbind may be considered in the following situations:
- recurrence of clinically relevant bleeding together with prolonged clotting times, or
- if potential re-bleeding would be life-threatening and prolonged clotting times are observed, or
- patients require a second emergency surgery/urgent procedure and have prolonged clotting times.

Relevant coagulation parameters are activated Partial Thromboplastin Time (aPTT), diluted Thrombin Time (dTT) or Ecarin Clotting Time (ECT) (see section 5.1).

A maximum daily dose has not been investigated.

**Restarting Antithrombotic Therapy**

Pradaxa (dabigatran etexilate) treatment can be re-initiated 24 hours after administration of Praxbind, if the patient is clinically stable and adequate haemostasis has been achieved.

After administration of Praxbind, other antithrombotic therapy (e.g. low-molecular weight heparin) can be started at any time, if the patient is clinically stable and adequate haemostasis has been achieved.

Absence of antithrombotic therapy exposes patients to the thrombotic risk of their underlying disease or condition.

**Patients with renal impairment**

No dose adjustment is required in renally impaired patients. Renal impairment did not impact the reversal effect of idarucizumab.

**Patients with hepatic impairment**

No dose adjustment is required in hepatically impaired patients (see section 5.2).

**Elderly**

No dose adjustment is required in elderly patients aged 65 years and above (see section 5.2).

**Paediatric population**

The safety and efficacy of Praxbind in children below the age of 18 years have not yet been established. No data are available.

**Method of administration**

Intravenous use.

Praxbind (2x2.5 g/50 mL) is administered intravenously as two consecutive infusions over 5 to 10 minutes each or as a bolus injection.

For additional instructions for use and handling see section 6.6.

**4.3 Contraindications**

None.
4.4 Special warnings and precautions for use

Idarucizumab binds specifically to dabigatran and reverses its anticoagulant effect. It will not reverse the effects of other anticoagulants (see section 5.1).

Praxbind treatment can be used in conjunction with standard supportive measures, which should be considered as medically appropriate.

Hypersensitivity

The risk of using Praxbind in patients with known hypersensitivity (e.g. anaphylactoid reaction) to idarucizumab or to any of the excipients needs to be weighed cautiously against the potential benefit of such an emergency treatment. If an anaphylactic reaction or other serious allergic reaction occurs, administration of Praxbind should be discontinued immediately and appropriate therapy initiated.

Hereditary fructose intolerance

The recommended dose of Praxbind contains 4 g sorbitol as an excipient. In patients with hereditary fructose intolerance, parenteral administration of sorbitol has been associated with reports of hypoglycemia, hypophosphatemia, metabolic acidosis, increase in uric acid, acute liver failure with breakdown of excretory and synthetic function, and death. Therefore, in patients with hereditary fructose intolerance the risk of treatment with Praxbind must be weighed against the potential benefit of such an emergency treatment. If Praxbind is administered in these patients, intensified medical care during Praxbind exposure and within 24 hours of exposure is required.

Thromboembolic Events

Patients being treated with dabigatran have underlying disease states that predispose them to thromboembolic events. Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. To reduce this risk, resumption of anticoagulant therapy should be considered as soon as medically appropriate (see section 4.2).

Urinary protein testing

Praxbind causes transient proteinuria as a physiologic reaction to renal protein overflow after bolus/short term application of 5g idarucizumab intravenously (see section 5.2). The transient proteinuria is not indicative of renal damage, which should be taken into account for urine testing.

Sodium content

This medicinal product contains 2.2 mmol (or 50 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies with Praxbind and other medicinal products have been performed. Based on the pharmacokinetic properties and the high specificity in binding to dabigatran, clinically relevant interactions with other medicinal products are considered unlikely.

Preclinical investigations with idarucizumab have shown no interactions with
- volume expanders.
- coagulation factor concentrates, such as prothrombin complex concentrates (PCCs, e.g. 3 factor and 4 factor), activated PCCs (aPCCs) and recombinant factor VIIa.
- other anticoagulants (e.g. thrombin inhibitors other than dabigatran, Factor Xa inhibitors including low-molecular weight heparin, vitamin K-antagonists, heparin). Thus idarucizumab will not reverse the effects of other anticoagulants.
4.6  Fertility, pregnancy and lactation

Pregnancy

There are no data for the use of Praxbind in pregnant women. Reproductive and developmental toxicity studies have not been performed, given the nature and the intended clinical use of the medicinal product. Praxbind may be used during pregnancy, if the expected clinical benefit outweighs the potential risks.

Breast-feeding

It is unknown whether idarucizumab is excreted in human milk.

Fertility

There are no data on the effect of Praxbind on fertility (see section 5.3).

4.7  Effects on ability to drive and use machines

Not relevant.

4.8  Undesirable effects

The safety of Praxbind has been evaluated in 224 healthy subjects as well as 123 patients in an ongoing phase III trial, who had uncontrolled bleeding or required emergency surgery or procedures and were under treatment with Pradaxa (dabigatran etexilate).

No adverse reactions have been identified.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9  Overdose

There is no clinical experience with overdoses of Praxbind.

The highest single dose of Praxbind studied in healthy subjects was 8 g. No safety signals have been identified in this group.

5.  PHARMACOLOGICAL PROPERTIES

5.1  Pharmacodynamic properties

Pharmacotherapeutic group: all other therapeutic products, antidotes, ATC code: V03AB37

Mechanism of action

Idarucizumab is a specific reversal agent for dabigatran. It is a humanized monoclonal antibody fragment (Fab) that binds to dabigatran with very high affinity, approximately 300-fold more potent than the binding affinity of dabigatran for thrombin. The idarucizumab-dabigatran complex is characterised by a rapid on-rate and extremely slow off-rate resulting in a very stable complex. Idarucizumab potently and specifically binds to dabigatran and its metabolites and neutralises their anticoagulant effect.
Clinical efficacy and safety

Three randomised, double-blind, placebo-controlled Phase I studies in 283 subjects (224 treated with idarucizumab) were conducted to assess the safety, efficacy, tolerability, pharmacokinetics and pharmacodynamics of idarucizumab, given alone or after administration of dabigatran etexilate. The investigated population consisted of healthy subjects and subjects exhibiting specific population characteristics covering age, body weight, race, sex and renal impairment. In these studies the doses of idarucizumab ranged from 20 mg to 8 g and the infusion times ranged from 5 minutes to 1 hour.

Representative values for pharmacokinetic and pharmacodynamics parameters were established on the basis of healthy subjects aged 45-64 years receiving 5 g idarucizumab (see sections 5.1 and 5.2).

A prospective, open-label, non-randomized, uncontrolled study (RE-VERSE AD) is currently ongoing to investigate the treatment of adult patients who presented with dabigatran-related life-threatening or uncontrolled bleeding (Group A) or who required emergency surgery or urgent procedures (Group B). The primary endpoint was the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after the administration of idarucizumab, based on central laboratory determination of dilute thrombin time (dTT) or ecarin clotting time (ECT). A key secondary endpoint is the restoration of haemostasis.

An interim analysis of RE-VERSE AD included data for 123 patients: 66 patients with serious bleeding (Group A) and 57 requiring an urgent procedure (Group B). Approximately half of the patients in each group were male. The median age was 77 years and the median creatinine clearance was 61 mL/min. Approximately 68% of patients in Group A and 63% of patients in Group B had been treated with dabigatran 110 mg twice daily. Results of central laboratory evaluations were available for a subset of 90 patients (51 in Group A, 39 in Group B).

Most patients (>89%), in both Groups A and B, achieved complete reversal of the anticoagulant effect of dabigatran as measured by dTT or ECT in the first 4 hours after administration of 5 g idarucizumab. Reversal effects were evident immediately after administration.
Figure 1 – Reversal of dabigatran-induced clotting time prolongation determined by dTT in 90 patients from the RE-VERSE AD study.
Restoration of haemostasis was achieved in 91% of evaluable patients who had serious bleeding and normal haemostasis was observed in 92% of patients who required an urgent procedure.

Of the total 123 patients, 26 patients died; each of these deaths could be attributed either as a complication of the index event or associated with co-morbidities. Thrombotic events were reported in 5 patients, none of which were on antithrombotic therapy at the time of the event, and in each of these cases, the thrombotic event could be attributed to the underlying medical condition of the patient. Mild symptoms of potential hypersensitivity (pyrexia, bronchospasm, hyperventilation, rash or pruritus) were reported. A causal relationship to idarucizumab could not be established. Further adverse events, reported in greater than or equal to 5% of patients, were hypokalemia (9/123; 7%), delirium (9/123; 7%), constipation (8/123; 7%), pyrexia (7/123; 6%), pneumonia (7/123; 6%).

**Pharmacodynamic effects**

The pharmacodynamics of idarucizumab after administration of dabigatran etexilate were investigated in 141 subjects in Phase I studies, of which data for a representative subgroup of 6 healthy subjects aged 45 to 64 years receiving a dose of 5 g as intravenous infusion are presented. The median peak dabigatran exposure in the investigated healthy subjects was in the range of a twice daily administration of 150 mg dabigatran etexilate in patients.
Effect of idarucizumab on the exposure and anticoagulant activity of dabigatran

Immediately after the administration of idarucizumab, the plasma concentrations of unbound dabigatran were reduced by more than 99%, resulting in levels with no anticoagulant activity.

The majority of the patients showed sustained reversal of dabigatran plasma concentrations up to 12 hours (>90%). In a subset of patients, recurrence of plasma levels of unbound dabigatran and concomitant elevation of clotting tests was observed, possibly due to re-distribution of dabigatran from the periphery. This occurred 2-24 hours after administration of idarucizumab mainly at timepoints ≥12 hours.

Figure 3 – Plasma-levels of unbound dabigatran in the representative group of healthy subjects (administration of idarucizumab or placebo at 0 h)

Dabigatran prolongs the clotting time of coagulation markers such as diluted Thrombin Time (dTTh), Thrombin Time (TT), activated Partial Thromboplastin Time (aPTT) and Ecarin Clotting Time (ECT), which provide an approximate indication of the anticoagulation intensity. A value in the normal range after administration of idarucizumab indicates that a patient is no longer anticoagulated. A value above the normal range may reflect residual active dabigatran or other clinical conditions e.g., presence of other drugs or transfusion coagulopathy. These tests were used to assess the anticoagulant effect of dabigatran. A complete and sustained reversal of dabigatran-induced clotting time prolongation was observed immediately after the idarucizumab infusion, lasting over the entire observation period of at least 24 h.
Figure 4 – Reversal of dabigatran-induced clotting time prolongation determined by dTT in the representative group of healthy subjects (administration of idarucizumab or placebo at 0 h)

Figure 5 – Reversal of dabigatran-induced clotting time prolongation determined by ECT in the representative group of healthy subjects (administration of idarucizumab or placebo at 0 h)
Thrombin generation parameters

Dabigatran exerts pronounced effects on parameters of the endogenous thrombin potential (ETP). Idarucizumab treatment normalised both thrombin lag time ratio and time to peak ratio to baseline levels as determined 0.5 to 12 hours after the end of the idarucizumab infusion. Idarucizumab alone has shown no procoagulant effect measured as ETP. This suggests that idarucizumab has no prothrombotic effect.

Re-administration of dabigatran etexilate

24 hours after the idarucizumab infusion, re-administration of dabigatran etexilate resulted in expected anticoagulant activity.

Immunogenicity

Serum samples from 283 subjects (224 treated with idarucizumab) were tested for antibodies to idarucizumab before and after treatment.

Pre-existing antibodies with cross-reactivity to idarucizumab were detected in approximately 13 % (36/283) of the subjects. No impact on the pharmacokinetics or the reversal effect of idarucizumab or hypersensitivity reactions were observed in these subjects.

Treatment-emergent anti-idarucizumab antibodies with low titers were observed in 4 % (9/224) of the subjects suggesting a low immunogenic potential of idarucizumab. In a subgroup of 6 subjects, idarucizumab was administered a second time, two months after the first administration. No anti-idarucizumab antibodies were detected in these subjects prior to the second administration. In one subject, treatment-emergent anti-idarucizumab antibodies were detected after the second administration.

Preclinical pharmacodynamics

A trauma model in pigs was performed using a blunt liver injury after dosing with dabigatran to achieve supratherapeutic concentrations of about 10-fold of human plasma levels. Idarucizumab effectively and rapidly reversed the life-threatening bleeding within 15 min after the injection. All pigs survived at idarucizumab doses of approximately 2.5 and 5 g. Without idarucizumab, the mortality in the anticoagulated group was 100 %.

The European Medicines Agency has deferred the obligation to submit the results of studies with Praxbind in one or more subsets of the paediatric population in the prevention and treatment of dabigatran associated haemorrhage (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of idarucizumab were investigated in 224 subjects in Phase I studies, of which data for a representative subgroup of 6 healthy subjects aged 45 to 64 years receiving a dose of 5 g as intravenous infusion are presented.

Distribution

Idarucizumab exhibited multiphasic disposition kinetics and limited extravascular distribution. Following the intravenous infusion of a 5 g dose, the geometric mean volume of distribution at steady state (V_{ss}) was 8.9 L (geometric coefficient of variation (gCV) 24.8 %).

Biotransformation

Several pathways have been described that may contribute to the metabolism of antibodies. All of these pathways involve biodegradation of the antibody to smaller molecules, i.e. small peptides or amino acids, which are then reabsorbed and incorporated in the general protein synthesis.
Elimination

Idarucizumab was rapidly eliminated with a total clearance of 47.0 mL/min (gCV 18.4 %), an initial half-life of 47 minutes (gCV 11.4 %) and a terminal half-life of 10.3 h (gCV 18.9 %). After intravenous administration of 5 g idarucizumab, 32.1 % (gCV 60.0 %) of the dose was recovered in urine within a collection period of 6 hours and less than 1 % in the following 18 hours. The remaining part of the dose is assumed to be eliminated via protein catabolism, mainly in the kidney. After treatment with idarucizumab proteinuria has been observed. The transient proteinuria is a physiologic reaction to renal protein overflow after bolus/short term application of 5g idarucizumab intravenously. The transient proteinuria usually peaked about 4 h after idarucizumab administration and normalised within 12-24 hours. In single cases the transient proteinuria persisted for more than 24 hours.

Patients with renal impairment

In Phase I studies Praxbind has been investigated in subjects with a creatinine clearance ranging from 44 to 213 mL/min. Subjects with a creatinine clearance below 44 mL/min have not been studied in Phase I. Depending on the degree of renal impairment the total clearance was reduced compared to healthy subjects, leading to an increased exposure of idarucizumab.

Based on pharmacokinetic data from 68 patients with different degrees of renal function (median creatinine clearance 19.2 - 126 mL/min) it is estimated that mean idarucizumab exposure (AUC0–24h) increases by 26% in patients with mild (CrCl 60-90 mL/min), by 78% in moderate (30-60 mL/min) and by 199% in severe (0-30 mL/min) renal impairment. Since dabigatran is also excreted primarily via the kidneys, increases in the exposure to dabigatran are also seen with worsening renal function.

Based on these data and the extent of reversal of the anticoagulant effect of dabigatran in patients, renal impairment does not appear to impact the reversal effect of idarucizumab, although the conclusion for patients with severe renal impairment is drawn from only a small subset of patients.

Patients with hepatic impairment

Praxbind has not been studied in patients with hepatic impairment. Antibody fragments are known to be eliminated mainly by proteolytic catabolism in the kidney. An impact of hepatic impairment on the pharmacokinetics of idarucizumab is not expected.

Older people/Sex/Race

Based on population pharmacokinetic analyses, sex, age, and race do not have a clinically meaningful effect on the pharmacokinetics of idarucizumab.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on repeated dose toxicity studies of up to four weeks in rats and two weeks in monkeys. Safety pharmacology studies have demonstrated no effects on the respiratory, central nervous or cardiovascular system.

Studies to evaluate the mutagenic and carcinogenic potential of idarucizumab have not been performed. Based on its mechanism of action and the characteristics of proteins no carcinogenic or genotoxic effects are anticipated.

Studies to assess the potential reproductive effects of idarucizumab have not been performed. No treatment-related effects have been identified in reproductive tissues of either sex during repeat dose intravenous toxicity studies of up to four weeks in the rat and two weeks in monkeys. Additionally, no idarucizumab binding to human reproductive tissues was observed in a tissue cross-reactivity study. Therefore, preclinical results do not suggest a risk to fertility or embryo-fetal development.
No local irritation of the blood vessel was observed after i.v. or paravenous administration of idarucizumab. The idarucizumab formulation did not produce haemolysis of human whole blood in vitro.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sodium acetate trihydrate
acetic acid
sorbitol
polysorbate 20
water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

After opening the vial, chemical and physical in-use stability of idarucizumab has been demonstrated for 6 hours at room temperature.

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product shall be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C).

Do not freeze.

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

Prior to use, the unopened vial may be kept at room temperature (up to 30 °C) for up to 48 hours, if stored in the original package in order to protect from light. The solution should not be exposed to light for more than 6 hours (in unopened vial and/or in-use).

For storage conditions after opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

50 mL solution in a glass vial (type I glass), with a butyl rubber stopper, an aluminium cap and a label with integrated hanger.

Pack size of 2 vials.

6.6 Special precautions for disposal and other handling

Parenteral medicinal products such as Praxbind should be inspected visually for particulate matter and discoloration prior to administration.
Praxbind must not be mixed with other medicinal products. A pre-existing intravenous line may be used for administration of Praxbind. The line must be flushed with sodium chloride 9 mg/ml (0.9 %) solution for injection prior to and at the end of infusion. No other infusion should be administered in parallel via the same intravenous access.

Praxbind is for single-use only and does not contain preservatives (see section 6.3).

No incompatibilities between Praxbind and polyvinyl chloride, polyethylene or polyurethane infusion sets or polypropylene syringes have been observed.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1056/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 November 2015

10. DATE OF REVISION OF THE TEXT

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

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Straße 65
88397 Biberach an der Riss
GERMANY

Name and address of the manufacturer responsible for batch release

Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Straße 65
88397 Biberach an der Riss
GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX

1. **NAME OF THE MEDICINAL PRODUCT**

   Praxbind 2.5 g/50 mL solution for injection/infusion
   Idarucizumab

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   Each vial of 50 mL contains 2.5 g idarucizumab.

3. **LIST OF EXCIPIENTS**

   Excipients: Sodium acetate trihydrate, acetic acid, sorbitol, polysorbate 20, water for injection.

4. **PHARMACEUTICAL FORM AND CONTENTS**

   Solution for injection/infusion
   2 vials of 50 mL each

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

   Intravenous use
   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**

   For single use only.

8. **EXPIRY DATE**

   EXP

9. **SPECIAL STORAGE CONDITIONS**

   Store in a refrigerator. Do not freeze.
   Store in the original package in order to protect from light.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORIZATIONAL NUMBER(S)

EU/1/15/1056/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number} [product code]
SN: {number} [serial number]
NN: {number} [national reimbursement number or other national number identifying the medicinal product]
19. OTHER – Printing on inside of lid

- The enclosed package leaflet contains additional information for healthcare professionals
- The recommended dose of Praxbind is 5 g (2x2.5 g/50 mL)
- Intravenous administration as two consecutive infusions over 5 to 10 min each or as bolus injections
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<thead>
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<th>PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING</th>
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<td>Vial label</td>
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<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
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</thead>
<tbody>
<tr>
<td>For single use only.</td>
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</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
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<tbody>
<tr>
<td>EXP</td>
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<table>
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<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
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<tbody>
<tr>
<td>Store in a refrigerator. Do not freeze.</td>
</tr>
<tr>
<td>Store in the original package in order to protect from light.</td>
</tr>
</tbody>
</table>
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

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/1/15/1056/001

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Justification for not including Braille accepted

17. **UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included

18. **UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC: {number} [product code]
SN: {number} [serial number]
NN: {number} [national reimbursement number or other national number identifying the medicinal product]
B. PACKAGE LEAFLET
Praxbind is a reversal agent specific for dabigatran (Pradaxa), a blood thinner medicine that blocks a substance in the body, which is involved in blood clot formation. Praxbind is used to rapidly trap dabigatran in order to inactivate its effect. Praxbind contains the active substance idarucizumab.

Praxbind is used in adults in emergency situations where your doctor decides that rapid inactivation of the effect of Pradaxa is required

- For emergency surgery/urgent procedures
- In life-threatening or uncontrolled bleeding.

This medicine will only remove dabigatran from your body. It will not remove other medicines used to prevent the formation of blood clots.
After dabigatran has been removed from your body, you are not protected from the formation of blood clots. Your doctor will continue treating you with medicines used to prevent the formation of blood clots as soon as your medical condition allows.

**Children and adolescents**

There is no information on the use of Praxbind in children.

**Other medicines and Praxbind**

Tell your doctor if you are taking, have recently taken or might take any other medicines.

This medicine has been designed to only bind to dabigatran. It is unlikely that Praxbind will influence the effect of other medicines or that other medicines will influence Praxbind.

**Pregnancy and breast-feeding**

Tell your doctor, if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby.

There is no information on the effects of this medicine in pregnant or breast-feeding women. Praxbind does not affect any functions in the body as such, so your doctor may decide to give you this medicine, if the expected benefits outweigh any potential risks.

**Praxbind contains sodium**

This medicine contains 50 mg sodium per dose. You need to take this into account if you are on a controlled sodium diet.

3. **How to use Praxbind**

This medicine is for hospital use only.

The recommended dose is 5 g (2 vials of 50 mL).

In rare cases you may still have too much dabigatran in your blood after a first dose of Praxbind and your doctor may decide to give you a second 5 g dose in specific situations.

Your doctor or nurse will give you this medicine by injection or infusion into a vein.

After you have received Praxbind, your doctor will decide on the continuation of your treatment to prevent blood clot formation. Pradaxa can be given again 24 hours after Praxbind administration.

Detailed instructions for your doctor or nurse on how to administer Praxbind can be found at the end of this package leaflet (see 'Handling instructions').

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

4. **Possible side effects**

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

Until now, no side effects have been indentified.
**Reporting of side effects**

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. **How to store Praxbind**

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 vial and the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C-8 °C).

Do not freeze.

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

Once opened, Praxbind is intended for immediate use.

6. **Contents of the pack and other information**

**What Praxbind contains**
- The active substance is idarucizumab.
- The other ingredients are sodium acetate trihydrate, acetic acid, sorbitol, polysorbate 20 and water for injection.

**What Praxbind looks like and contents of the pack**

Praxbind solution for injection/infusion is a clear to slightly opalescent, colourless to slightly yellow solution supplied in a glass vial closed with a butyl rubber stopper and an aluminium cap.

Each pack contains two vials.

**Marketing Authorisation Holder**

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**Manufacturer**

Boehringer Ingelheim Pharma GmbH & Co. KG
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in MM/YYYY.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.
The following information is intended for healthcare professionals only:

Praxbind binds specifically to dabigatran and reverses its anticoagulant effect. It will not reverse the effects of other anticoagulants.

Praxbind treatment can be used in conjunction with standard supportive measures, which should be considered as medically appropriate.

The recommended dose of Praxbind contains 4 g sorbitol as an excipient. In patients with hereditary fructose intolerance there is a risk for serious adverse reactions, which must be weighed against the benefit of an emergency treatment with Praxbind. If Praxbind is administered in these patients, intensified medical care during Praxbind exposure and within 24 hours of exposure is required.

**Dosage and administration:**

The recommended dose of Praxbind is 5 g (2x2.5 g/50 mL).

Administration of a second 5 g dose of Praxbind may be considered in the following situations:

- recurrence of clinically relevant bleeding together with prolonged clotting times, or
- if potential re-bleeding would be life-threatening and prolonged clotting times are observed, or
- patients require a second emergency surgery/urgent procedure and have prolonged clotting times.

Relevant coagulation parameters are activated Partial Thromboplastin Time (aPTT), diluted Thrombin Time (dTT) or Ecarin Clotting Time (ECT).

A maximum daily dose has not been investigated.

Praxbind (2x2.5 g/50 mL) is administered intravenously, as two consecutive infusions over 5 to 10 minutes each or as a bolus injection.

Patients being treated with dabigatran have underlying disease states that predispose them to thromboembolic events. Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. To reduce this risk, resumption of anticoagulant therapy should be considered as soon as medically appropriate.

Pradaxa (dabigatran etexilate) treatment can be re-initiated 24 hours after administration of Praxbind, if the patient is clinically stable and adequate haemostasis has been achieved.

After administration of Praxbind, other antithrombotic therapy (e.g. low-molecular weight heparin) can be started at any time, if the patient is clinically stable and adequate haemostasis has been achieved.

**Handling instructions:**

Praxbind must not be mixed with other medicinal products. A pre-existing intravenous line may be used for administration of Praxbind. The line must be flushed with sodium chloride 9 mg/ml (0.9 %) solution for injection prior to and at the end of infusion. No other infusion should be administered in parallel via the same intravenous access.

Praxbind is for single-use only and does not contain preservatives.

Prior to use, the unopened vial may be kept at room temperature (up to 30 °C) for up to 48 hours, if stored in the original package in order to protect from light. After opening the vial, chemical and physical in-use stability of idarucizumab has been demonstrated for 6 hours at room temperature. The solution should not be exposed to light for more than 6 hours (in unopened vial and/or in-use).

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product shall be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.
No incompatibilities between Praxbind and polyvinyl chloride, polyethylene or polyurethane infusion sets or polypropylene syringes have been observed.